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## The German Multicentre Study on Multiple Chemical Sensitivity (MCS)

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### Abstract

In this multicentre study on multiple chemical sensitivity (MCS) 291 consecutive environmental medicine (EM) outpatients were examined in several environmental medicine outpatient centres/units throughout Germany in 2000/2003. Of the EM outpatients, 89 were male (30.6%) and 202 were female (69.4%), aged 22–80 (mean 48 years, S.D. = 12 years). The sample was representative for university-based environmental outpatient departments and represented a cross-sectional study design with an integrated clinical-based case-control comparison (MCS vs. non-MCS). Three classifications of MCS were used: self-reported MCS (sMCS), clinically diagnosed MCS (cMCS), and formalised computer-assisted MCS with two variants (f1MCS, f2MCS). Data were collected by means of an environmental medicine questionnaire, psychosocial questionnaires, the German version of the Composite International Diagnostic Interview (CIDI), and a medical baseline documentation, as well as special examinations in partial projects on olfaction and genetic susceptibility markers.

The hypothesis guided evaluation of the project showed that the patients' heterogenic health complaints did not indicate a characteristic set of symptoms for MCS. No systematic connection could be observed between complaints and the triggers implicated, nor was there any evidence for a genetic predisposition, or obvious disturbances of the olfactory system. The standardised psychiatric diagnostics applying CIDI demonstrated that the EM patients in general and the subgroup with MCS in particular suffered more often from mental disorders compared to an age and

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gender matched sample of the general population and that in most patients these disorders commenced many years before environment-related health complaints.

Our results do not support the assumption of a toxicogenic-somatic basis of the MCS phenomenon. In contrast, numerous indicators for the relevance of behavioural accentuations, psychic alterations or psychosomatic impairments were found in the group of EM-outpatients with subjective “environmental illness”.

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## Introduction

### An overview on the German MCS-Multicentre Study

The German MCS Research Network was constituted in 1999 and conducted the multicentre study on MCS under the direction of the Robert Koch Institute, sponsored by the Federal Environmental Agency of Germany. The Research Network consisted of 6 study centres, all of which were environmental medicine outpatient units, listed in [Box 1](#). Consecutive out-

patients were examined and data were collected in the year 2000 and, after a break of 2 years, in the first half of 2003. The second phase of data acquisition was used to add further patients to the sample since not enough patients were recruited in 2000. Two research reports on the study results have been published in German ([Eis et al., 2003a, 2005a](#)).

A subproject, named “MCS and susceptibility”, was carried out in collaboration with the Department of Clinical Pharmacology of the University of Göttingen. In this module a subsample of patients was tested for

#### Box 1. List of co-workers and cooperation partners

- *Study centre:* Robert Koch Institute – Section of Environmental Medicine: Dr. D. Eis (Director), Dr. N. Birkner, Dr. A. Dietel, Dr. D. Helm, L. Jordan, Dr. T. Mühlinghaus.
- *Aachen centre:* RWTH Aachen University, University Hospital, Institute of Hygiene and Environmental Medicine, Prof. Dr. G.A. Wiesmüller, W. Weißbach; in cooperation with Prof. Dr. H.F. Merk (Dermatological Clinic), Dr. K. Podoll (Psychiatric and Psychotherapeutic Clinic).
- *Berlin centre:* Charité-RKI Research Network “Clinical Environmental Medicine”, Environmental medicine outpatient unit – Medical Polyclinic (Campus Virchow): Dr. T. Mühlinghaus, Dr. A. Dietel, Dr. T. Rupp, Prof. Dr. U. Frei; Department of Dermatology, Venerology and Allergology: Dr. I. Traenckner-Probst, Prof. Dr. M. Worm; in cooperation with PD Dr. M. Rose (Department of Psychosomatic Medicine).
- *Bredstedt centre:* Speciality Hospital/Fachkrankenhaus Nordfriesland – Environmental medical department and outpatient unit: Dr. E. Schwarz, Dr. C. Mai, R. Tönnies.
- *Giessen centre:* Justus-Liebig-University, Giessen, Institute of Hygiene and Environmental Medicine: Prof. Dr. T. Eikmann, Prof. Dr. C. Herr, Dr. D. Stinner; in cooperation with Prof. Dr. U. Gieler (Institute for Medical Psychology, Justus-Liebig-University, Giessen and Clinic for Psychosomatics and Psychotherapy, University Hospital Giessen and Marburg).
- *Munich centre:* Ludwig-Maximilians-University, Munich University Hospital, City Campus, Institute and Outpatient Clinic for Occupational and Environmental Medicine: Prof. Dr. D. Nowak, Dr. E. Scharrer, PD Dr. G. Wiesner; in cooperation with Dr. F. Pedrosa Gil (Psychosomatic Outpatient Clinic).
- *Further cooperation partners:* Institute of Experimental and Clinical Pharmacology of the University Erlangen-Nuremberg: Dr. B. Renner.
- University Hospital Göttingen, Department of Clinical Pharmacology: Prof. Dr. J. Brockmöller, C. Meineke.
- *Expertise support and supervision:* Federal Environmental Agency (Berlin), Dr. J. Dürkop, Dr. N. Englert.
- *Scientific advisory board (study phase I):* Prof. Dr. M. Bullinger (Hamburg), Prof. Dr. M. Hüppe (Lübeck), Prof. Dr. Dr. Kappos (Hamburg/Frankfurt), Prof. Dr. V. Mersch-Sundermann (Freiburg), Dr. K.E. Müller (Isny), Dr. Ohnsorge (Würzburg), Dr. Suchenwirth (Hannover), PD Dr. Dr. Dr. F. Tretter (Munich).

allelic variants (polymorphisms), which could hypothetically be involved in chemical susceptibility, i.e. due to genetic variants of metabolic enzymes, transporter proteins, receptors and cytokines. Study results have been published in more detail elsewhere (Brockmüller et al., 2003; Mühlinghaus et al., 2005).

As MCS has been linked to altered odour sensitivity or odour intolerances by some authors (Bell et al., 1996; Nethercott, 1993), a second subproject, “MCS and neurogenic inflammation”, was carried out in collaboration with the Institute of Experimental and Clinical Pharmacology of the University Erlangen-Nuremberg. The ability to identify and to discriminate between odours (olfactory performance), olfactory evoked potentials, and inflammation mediators in the nasal lavage fluid were measured for a subsample of patients with suspected MCS and for healthy volunteers after olfactory stimulation. This project is described in some detail in the research reports (Eis et al., 2003a, 2005a).

In a third subproject detailed follow-up telephone interviews were carried out in 2003 with the patients examined in 2000. Results of this follow-up have already been published elsewhere (Eis et al., 2005a).

Whether a patient – in the given context: an outpatient of an Environmental Medical Unit (“EM outpatient” and “EM units”) – is assigned to the group of the MCS patients or to the group of the non-MCS patients, is highly dependent on the case criteria used. The problems relating to this “diagnostic” assignment have frequently been discussed but so far could not satisfyingly be resolved (e.g. Bolt and Kiesswetter, 2002; Labarge and McCaffrey, 2000; Lacour et al., 2005; Henningsen and Priebe, 2003; Salvaggio and Terr, 1996). On the one hand the (hypothetical) case definitions given in the literature are predominantly based on the personal clinical experiences of their proponents; the criteria used describe a relatively indefinite phenomenon with unclear etiology, unknown pathogenesis and questionable unity (no scientific accepted entity). The theoretical and empirical base of the existing case definitions is unsatisfactory. One problem is the lack of biomarkers and clear-cut parameters of dysfunction. The indicated case criteria are usually only vaguely formulated and are open to multiple interpretations. This problem occurs even when a single physician makes the diagnostic assignments, but is intensified when the assignments (for various patients) are made by several physicians, as it is usually done in larger studies, in multicentric studies or among different studies. Large discrepancies in evaluations can be expected if physicians with different attitudes to the MCS phenomenon make the diagnostic assignments. To address this problem we have chosen a pragmatical way of dealing with the MCS phenomenon in form of a multistep MCS-concept. Different MCS operationalisations are

used in parallel. Apart from the patients’ self-reported MCS (sMCS) and the clinical assignment (cMCS) of the physicians in charge we developed a more strongly operationalised and computer-assisted classification system which resulted in the fMCS categories (f = formalised).

The present contribution shows and discusses the goals, methods, sample-characteristics and results of the German Multicentre Study on MCS. Primarily it is an outpatient-based cross-sectional study with particular emphasis on the comparison of MCS and non-MCS patients (in a broader sense “cases” and internal “controls”). We deal also briefly with aspects of a possible genetic predisposition for MCS and elevated olfactory dysfunctions, to which two of the above-mentioned subprojects were dedicated. A complete list of all co-workers and cooperation partners involved is given in Box 1.

## Study aims and hypotheses

The aims of the German multicentre study on MCS were to describe collected data (e.g. patients’ statements to exposure and complaints, physician’s assessment of possible exposures, diagnoses and judgement), as well as to perform an explorative statistical analysis of possible subgroups, and to test hypotheses that were formulated beforehand with regard to the support of a toxic-somatic concept of MCS. The following hypotheses were evaluated and tested as far as possible under the given conditions:

**H1.** MCS has a circumscribable symptom pattern or complex of symptoms.

**H2.** Statistical associations between (subjectively incriminated) chemicals and self-reported complaints can be detected.

**H3.** MCS can be initiated and triggered by verifiable exposure with environmental chemicals (H3a for initial exposure; H3b for subsequent exposures).

**H4.** MCS is associated with a definable genetic disposition or increased susceptibility to everyday (not elevated) exposures to xenobiotics.

**H5.** “Hyperosmia” (increased olfactory performance) is more frequent in patients with MCS than in controls.

**H6.** The mental disorders found in MCS patients are sequelae/complications of MCS, occurring after the onset of environmentally related symptoms.

These hypotheses concern primarily the phenomenology of MCS (symptom patterns, consistency of the

relations between subjectively incriminated agents and symptoms, environmental medical proof of increased exposures, occurrences of psychological conspicuousness and disorders) and they deal, insofar, with “superficial aspects”. With the study approach available – a cross-sectional study during the routine operation of the outpatient units – the investigation of elaborated psychosocial, psychophysiological or psychosomatic pathogenesis models was neither possible nor intended.

### Further restrictions

The above-mentioned problem of uncertain validity and low reliability of “MCS-diagnoses” was virulent also in the German Multicentre Study on MCS described here. According to the specifications of the contracting authority (the German Federal Environment Agency, FEA) besides university centres an “environmental clinic” with an orientation towards “Clinical Ecology” was involved (Bredstedt). It should be kept in mind that many interesting variables can only be derived using data provided by the patients which refer partially to retrospective situations. For example, former exposures and health disorders can usually be extracted only from patients’ medical histories. Their evaluation in the context of the diagnostic clarification will differ from physician to physician (resp. from centre to centre). Despite all efforts of standardisation we tried to gain a more uniform clinical application of the soft diagnostic criteria for cMCS by prior agreements and instructions as well as for fMCS by a computer-assisted scoring system. Such attempts are however very limited in clinical-based MCS studies, since the individual cases can be very different in environmental-medical and also in clinical-diagnostic regard and for each individual case completely different examination methods may be used, which makes a standardisation of the diagnostic procedures much more difficult.

## Patients, material and methods

### Study design

The German Multicentre Study on MCS was based on a clinical–epidemiological approach in cooperation with six (later five) environmental medicine outpatient clinics/departments/units. Accordingly, it was a “clinical”-based multicentre study, which primarily featured a cross-sectional design. The division of the study population into MCS and non-MCS groups, and the comparison of these can be seen as stratification within the framework of the cross-sectional design or – in a broader sense – as a nested case-control segment, since the data analysis was the same as in a case-control

study. In the given context we prefer the term “case control comparison”.

### Study population

The study population (sample) should be representative of patients, who have been referred to and were examined in environmental medicine outpatient departments in Germany (target population). Five university centres for environmental medicine (Aachen, Berlin, Freiburg,<sup>1</sup> Giessen, Munich) and the environmental medicine unit of a specialist hospital (Bredstedt) have been included. In total, around half of all universities’ environmental medicine centres in Germany participated in the study, enabling a high sampling ratio.

All new patients who were referred to the outpatient units during the investigation period were asked to participate in the study. Since the study aroused extraordinarily large interest in the patients, a participation rate of about 80% could be achieved. However, the number of patients contacting the outpatient units for the first time (either by phone or by mail) differed largely, and the proportion of those appointed for examination varied from unit to unit, depending upon personnel and technical capacities. Additionally, in 2000 the participating units were contacted by fewer patients than expected, so that the recruiting phase had to be extended to further 6 months, in order to achieve the required numbers of participants (due to financing reasons the second recruiting could not be realised before the first half of 2003).

In total, 291 patients were willing to participate and fulfilled the required conditions, i.e. completion of two questionnaires and the medical baseline documentation. Of these patients, 30.2% were recruited in the environmental medicine centre Berlin, 24.7% in Bredstedt, 17.5% in Giessen, 13.7% in Munich, 9.3% in Aachen and 4.5% in Freiburg (for age and gender distribution see Table 2). Patients younger than 18 years were excluded from the study. The youngest participant was 22, the oldest 80 years of age; the mean was 48 yr (S.D. = 12 yr). The complete sample comprised 202 women (69.4%) and 89 men (30.6%).

### Questionnaires and psychometric tests

Due to the restricted conditions of the study and the reduced aims only a very limited set of environmental medical data collection, documentation, and psychometric questionnaires could be applied. For each patient the Medical Baseline Documentation (MBD) was completed by the same physician taking the medical

<sup>1</sup>Centre Freiburg was enlisted only in 2000.

history, performing the physical examination and discussing any patient in a medical case conference with specialists of each Medical Centre. The MBD contained 58 questions, predominantly those about the patient's complaints related and unrelated to exposure (according to the patient's statement), behaviour to avoid exposures, the physician's rating of former and present exposures and their clinical relevance, the physician's rating of causality between environmental chemicals and the reported complaints, as well as the concluding diagnostic judgements, including environmentally caused disease, especially cMCS (clinical MCS). Laboratory results and other clinical findings, which constituted the diagnostic judgements were not available for the statistical evaluation in the study centre (RKI).

The Environmental Medicine Questionnaire (EMQ) was completed by the patient at home. This self-administered questionnaire covered 163 questions about why the patient was referred to the environmental medicine unit, health complaints and their alleged relation to environmental chemicals, current health status, former and current diseases, dental materials, nutrition, active and passive smoking, medication, domestic and ambient conditions (incl. in- and outdoors), work place conditions, previous diagnosis, therapies applied and other topics.

The MCS questionnaire, adopted from Hüppe et al. (2000), was used to record MCS-related environmental agents and symptoms. This self-administered questionnaire is available only in a German version and contains two lists. The first list refers to 42 environmental agents that evoke symptoms (including allergens and control items). The patient is asked about how intense the complaints are triggered by the substances listed when they occur in concentrations too low to cause complaints in other people (answer formats: 0 = no complaints, 1 = very mild complaints, ..., 5 = very strong complaints). The other list refers to symptoms that are evoked by contact with environmental agents. The patient is asked to give the likelihood for that his or her complaints are evoked by environmental agents that occur in concentrations too low to cause complaints in other people on a 5-step scale, ranging from 0 = not at all, 1 = hardly to 4 = very probably.

For the assessment of psychosocial problems, health impairments and coping strategies, the patients also completed the following psychometric questionnaires at home:

- B-L, "Beschwerden-Liste"/Complaint List CL, adopted from von Zerssen (1976).
- SCL-90-R, Symptom Checklist 90 – revised, adopted from Derogatis (1977), German version by Franke (1995).
- SF-36, Short Form 36, German version, adopted from Bullinger and Kirchberger (1998), for the

assessment of perceived health-related quality of life.

- SAQ, Somatosensory Amplification Questionnaire, adopted from Barsky et al. (1990).
- SUB, "Skala für Umweltbesorgnis"/Environmental Worry Scale, adopted from Hodapp et al. (1996).
- WI, Whiteley-Index for Hypochondriasis, adopted from Pilowsky (1967).

For the assessment of mental disorders, according to the definitions and criteria of ICD-10 (10. Revision of the International Classification of Diseases) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association), a modified German version of the Composite International Diagnostic Interview (CIDI) was applied (Wittchen and Pfister, 1997). The CIDI version used in our study comprised modules A for demographic characteristics; C, D, E for somatoform/anxiety/depressive disorders; K for obsessive compulsive disorders; G for psychotic disorders, and the minimal variants of B, I and L for substance abuse disorders (nicotine, alcohol, illicit substances). The section for post-traumatic stress disorders (PTSD) was not used, because the PTSD module facilitates the formal diagnostics of relatively serious clinical-psychiatric disorders, but it is not suitable for subthreshold disorders in the context of environment-related disorders.

Diagnoses achieved with CIDI are in accordance with the definitions and criteria of ICD-10 and DSM-IV. The CIDI-Interview was an inherent part of the study routine and was applied to all patients who gave consent. CIDI and its German version (distributed under the denotation DIA-X, Diagnostic Expert System) have, according to the authors, high inter-rating reliability, satisfactory test-retest reliability, and sufficient validity for the use in epidemiological studies (Wittchen and Pfister, 1997). The CIDI version used in our multicentre study is compatible to that applied in the German National Health Interview and Examination Survey 1998, so that comparisons with the reference data achieved in the Survey are possible (see Computer-assisted psychiatric diagnostic).

### MCS scoring system

As self-assessment of a patient to determine whether he or she suffers from MCS (so called sMCS) was highly subjective, and as the physicians' clinical judgement (so called cMCS, based on Cullen's criteria) varied since there were considerable differences between individual physicians' judgements, and therefore also between the involved centres (cf. Eis et al., 2003a,b), a more formalised MCS classification was realised. To this end the study centre developed a scoring system for the formalised computer-assisted classification (f-MCS)

**Table 1.** Formalised computer-aided scoring system for judgement of MCS status (f1MCS: only highlighted rows; f2MCS: all rows)

Question/item	Answer	Score
<i>Former exposure/initial exposure</i>		
Former exposure of hygienic relevance <sup>a</sup> (MBD)	Yes	+1
Former exposure of toxic relevance (MBD)	Yes	+2
Initial exposure (MBD)	Yes	+1
<i>Current exposure/trigger</i>		
General intolerance (EMQ)	No	-1
	Yes	+1
Environmental factors responsible for complaints (EMQ)	Surely/probably responsible	+1
Current exposure of hygienic relevance <sup>a</sup> (MBD)	Yes	+1
Current exposure of toxic relevance (MBD)	Yes	+2
<i>Number of chemicals suspected</i>		
According to EMQ	0–1 substances	-2
	2 substances	-1
	3 substances	0
	4 substances	+1
	5 substances and more	+2
According to MCS questionnaire	Less than 5 substances	-1
	5 substances and more	+1
<i>Number of complaint domains<sup>c</sup></i>		
According to MBD	No or 1 domain	-1
	2 domains	0
	≥3 domains	+1
According to MCS questionnaire (complaints per suspected substance)	<7 complaints	-1
	≥7 complaints	+1
<i>Avoidance behaviour</i>		
Ranging from 'not at all' = (1) to 'extraordinarily' = (6) (MBD)	(1)–(2)	0
	(3)–(4)	+1
	(5)–(6)	+2
<i>Etiological assessment</i>		
Judgement of causality (MBD)	Improbable	-2
	Possible	-1
	Probable	+1
	Very probable	+2
Environmental exposure causal for reported health complaints (MBD)	No	-2
	Yes	+1
	Extra score if diagnosed as MCS	+1
<i>Negative criteria<sup>d</sup></i>		
Partially mental causation/mental cocausation (EMQ)	Yes	-2

**Table 1.** (continued)

Question/item	Answer	Score
Explanatory diagnosis <sup>b</sup> (MBD)	Yes	-2
Smoking (EMQ)	Current smoking	-2
<i>Chronicity</i>		
Duration of disorder (EMQ)	<6 months → exclusion	
Sum of scores		

<sup>a</sup>Exposure that justifies preventive measures even if toxicological thresholds are not surpassed.

<sup>b</sup>Except diagnosis of "MCS".

<sup>c</sup>In this paper we define 'complaint domains' as complaints referring to the same organ or organ system.

<sup>d</sup>Yielding negative scores when fulfilled; EMQ, environmental medicine questionnaire; MBD, medical baseline documentation.

with two variants (f1MCS and f2MCS). Whilst f1MCS was solely based on information provided by the patient questionnaires, f2MCS additionally used information documented in the MBD by the physician (cf. Table 1). Whereas f1MCS is closer to the self-assessment (sMCS), f2MCS is closer to clinically estimated MCS (cMCS) based on Cullen's case criteria (Cullen, 1987). This approach was an attempt to improved diagnosis reliability in a pragmatic way.

The two computer-assisted MCS classifications were created in a two-step process by expert judgement. In the first step questions were selected from the study questionnaires that corresponded best to the MCS case criteria. The questions selected were related to former initial exposure, current exposures/triggers, number of chemicals suspected to be reasonable for the complaints, number of complaint domains, avoidance behaviour, etiological assessment, chronicity (≥6 months), and negative exclusion criteria (e.g. current smoking, explanatory diagnoses). A score was given, based on the usefulness and value of the criteria/items. MCS promoting features got positive score points, contra-MCS features got negative score points (see Table 1). The case criterion "multiple, chemically unrelated substances" or "diverse environmental factors" was operationalised by scoring them. The different kinds of questions (open vs. closed answer formats) justified the assignment of different score points according to the experts' opinion.

In the second step the threshold (cut-off) values was derived to subdivide the patients into f1MCS and non-f1MCS categories. The threshold values were defined pragmatically in such a way that the resulting proportions of f1MCS and f2MCS lay in between those of sMCS and cMCS. Hence, f1MCS was closer to sMCS whilst f2MCS was closer to cMCS. Rather than recognise the 'true' MCS syndrome (which seemed impossible), the scoring system aims to balance between

the self-assessment of the patient (“I suffer from MCS”/“I don’t suffer from MCS”) and the clinical assessment of the physician (“The patient suffers from MCS”/“The patient does not suffer from MCS”).

The short form of the scoring system, f1MCS, comprised 8 items and one exclusion criterion (Table 1). A sum score was calculated when no more than one item had missing values (i.e. no answer or ‘don’t know’). The resulting sum score had a theoretical range from  $-10$  to  $+7$ ; however, we observed a range from  $-8$  to  $+7$ . Since the positive criteria predominantly constitute ‘MCS’, the threshold value had to be a positive one. Selection of the threshold value was carried out pragmatically: The resulting proportion of f1MCS should be lower than that of sMCS but higher than that of the more stringently subsumed f2MCS. This could be achieved with a threshold of 4 or 5. Since a threshold of 4 led to a higher proportion of f1MCS positives, a fact that facilitates the statistical evaluation, we decided on that value.

The long form, f2MCS, comprised of 17 items and one exclusion criterion (Table 1). Sum score was computed when no more than 2 items had missing values (either no answer or ‘don’t know’). The theoretical range was  $-16$  to  $+20$ , but we observed only values between  $-13$  and  $+19$ . Furthermore, a threshold value had to be defined for the separation of the f2MCS group from the non-f2MCS group. As no Gold Standard was available for the ascertainment of MCS, reliable validation of the scoring system proposed here was not possible. In consideration of this, the threshold value for the f2MCS scoring system was pragmatically chosen in such a way that all participating centres had patients with MCS ( $n > 0$ ) and the total resulting proportion of f2MCS lay between those obtained for cMCS and f1MCS. These preconditions were fulfilled by a threshold value of 4 or 5. Since a threshold of 4 resulted in a higher proportion of f2MCS positives than 5, which again, facilitated statistical evaluation, we chose a threshold value of 4 instead of 5.

For each study participant the score points were added up to a total, and this was done for the f1MCS scheme as well as for the f2MCS scheme. The personal total sum score was then compared with the corresponding cut-off and the patient was classified according to the following rules (details in Eis et al., 2005a, c):

- f1-scheme: f1MCS, if sum score  $\geq 4$ ; non-f1MCS if sum score  $< 4$ .
- f2-scheme: f2MCS if sum score  $\geq 4$ ; non-f2MCS if sum score  $< 4$ .

### MCS-questionnaire and analyses of pollutant/symptom pattern

In order to examine whether MCS patients can be distinguished from non-MCS patients by certain

pollutant patterns and/or certain symptom patterns, and whether certain pollutant combinations do more frequently occur than others, we took two different approaches.

The first approach was based on data from the standardised MCS questionnaire (MCS-Q, adopted from Hüppe et al., 2000) with a 42-item list about agents that evoke symptoms, including “MCS agents”, allergens and control items (6-step rating scales), as well as a 48-item list about environmentally related symptoms (5-step rating). Firstly, a principle component analysis was performed methodically considering all symptom items. Subsequently, for each principle component a multiple linear regression with the stepwise inclusion method was calculated, where the components obtained served as criterion variables, which should be predicted using the 42 pollutant items. Possible confounders f1MCS category, age and gender were included in the analysis.

The second approach was based on the free-text answers of the patients (in the EMQ) about their main complaints (related by them to the environment) and the suspected agents (pollutants, chemicals). The noxious agents reported by the patients were concentrated into seven categories (indoor pollutants, outdoor pollutants, dental materials, products of daily life, biogenic pollutants, physical influences, biocides) by an environmental physician in the study centre. Each agent could be only assigned to one of these categories. The main complaints reported by the patients were classified in the study centre by a clinically experienced physician. Seven symptom categories could be differentiated, based on the affected organ systems. A main symptom could be assigned to one (and only one) of the mentioned symptom classes. To keep the number of possible combinations of toxicant categories by symptom categories manageable (and, thus, analysable given the small sample size), a further reduction to five categories of agents (by combining the categories “dental materials” and “products of daily life”) as well as to four symptom categories (head, musculoskeletal system, cardiovascular system, skin and mucosa, including intestinal tract) was necessary when conducting this evaluation step. By making this classification, information inevitably was lost, but this approach enabled the possibility of an evaluation in a cross-patient manner. To what extent, however, the high aggregation level is still justifiable, must be critically analysed (see Discussion).

### Olfactorial tests and gene analysis

In a partial project to olfactory functions the smelling test “Sniffin’ Sticks” with its three sections (smelling threshold, discrimination and identification) was

performed in a subsample of 45 consecutive outpatients from Berlin centre; the test results can be compared with population reference values (Kobal et al., 2000). Further examinations comprise olfactory evoked potentials and the analysis of inflammation mediators (prostaglandin E2 and substance P) in the nasal lavage fluid after provocation with 2-propranolol.

In a further partial project “MCS and susceptibility”, 26 variants of 17 candidate genes for susceptibility (xenobiotic metabolising enzymes, receptors relevant for toxicology, carrier proteins and mediators of inflammation) were examined. The genotyping was carried out by DNA sequencing (Sanger’s chain termination method using fluorescence labelled dideoxynucleotides) as well as by fragment analysis (with or without restriction enzyme splitting) using real-time Taqman<sup>®</sup> PCR.

### Statistical analyses

Frequencies were compared with the Chi-square test; for expected frequencies below 5, the Haldane-Dawson test was used. To judge differences between observed and expected frequencies, the standardised residues were considered: when the standardised residue is greater or equal to 2 and the expected frequency is greater or equal to 5, the observed frequency is statistically significantly different from the expected frequency.

Ordinal data were compared with the Mann-Whitney U test; for differences between means the effect size was also calculated as Cohen’s *d* where a value of 0.2 is considered a small effect, 0.5 a medium, and 0.8 a large effect size (Cohen, 1988).

Hierarchical clusteranalysis aimed to detect groups of patients which show maximum similarity to each other and where these groups show simultaneously maximum differences.

To identify possible subgroups of patients with distinctive and distinguishing symptom patterns we summarised the free text answers concerning complaints under seven categories and tried to identify characteristic symptom patterns or “syndromes”. In order to reveal patterns of symptoms and patterns of alleged exposures, as well as relationships between them, principal component analyses and regression analyses (method = stepwise, *pin* = 0.05, *pout* = 0.10) were performed.

Statistical significance was accepted at the level of  $\alpha = 5\%$  ( $p \leq 0.05$ ). All calculations were done with SPSS<sup>®</sup> for Windows 12.0.

### Ethical approval

The Ethics Commission of Charité university hospital approved study phases I and II as well as the subprojects

without additional requirements. No monetary incentives were paid to the participants.

## Results

### Demographic features and frequencies of different MCS categories

Age and gender distribution of the study population are given in Table 2. Like in many other studies on environmental patients, the proportion of females is about 70%. Mean age was 48.2 yr (median: 40 yr) and statistically significant differences could not be observed between centres, neither in respect to age nor to gender proportions. As for the different MCS categories (sMCS, f1MCS, f2MCS, and cMCS) no statistically significant differences were observed, too.

Approximately 40% of the environmental medicine outpatients reported suffering from MCS (sMCS), but the proportions differed considerably from centre to centre. Even more pronounced differences were observed for cMCS. Here the proportions varied between 0% (Berlin, Giessen) and over 80% (Bredstedt), despite the specification of uniform case criteria. The application of the developed scoring system (fMCS construct) led, in comparison to the clinical estimate, to a remarkable reduction of the centre differences (see Table 3).

The decreasing order of the MCS proportions (sMCS > f1MCS > f2MCS > cMCS), which we intended to obtain with the development of our scoring system, was only observable for the centres Berlin and Giessen, while in Bredstedt and Munich the high sMCS and cMCS proportions had strong influence onto the outcome of the fMCS scoring, so that in these centres the expected order was not evident. Aachen is not considered here, due to small case numbers.

Furthermore it should be noted that the percentage figures in Table 3 are valid percents; i.e. the percentage

**Table 2.** Gender proportion and age of the patients

Centre	<i>N</i>	Gender <sup>a</sup>		Age <sup>b</sup>		
		Males (%)	Females (%)	Mean	S.D.	Median
Aachen	27	29.6	70.4	44.4	12.0	44.0
Berlin	88	29.5	70.5	50.2	12.0	51.0
Bredstedt	72	27.8	72.2	48.4	11.7	48.0
Freiburg	13	30.8	69.2	47.2	11.8	46.0
Giessen	51	41.2	58.8	46.9	11.6	48.0
Munich	40	25.0	75.0	48.0	11.2	49.5
Total	291	30.6	69.4	48.2	11.8	49.0

<sup>a</sup>Chi-square test,  $p = 0.61$ .

<sup>b</sup>Kruskal–Wallis test,  $p = 0.19$ .

**Table 3.** Proportions of sMCS, f1MCS, f2MCS and cMCS

MCS category	Total ( <i>N</i> = 278) <sup>a</sup>		Aachen ( <i>N</i> <sub>1</sub> = 27)		Berlin ( <i>N</i> <sub>2</sub> = 88)		Bredstedt ( <i>N</i> <sub>3</sub> = 72)		Giessen ( <i>N</i> <sub>4</sub> = 51)		Munich ( <i>N</i> <sub>5</sub> = 40)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
sMCS	109	40.1	9	33.3	28	31.8	35	50.0	11	21.6	26	72.2
f1MCS	76	28.9	3	11.5	21	25.3	30	42.9	6	13.0	16	42.1
f2MCS	83	33.9	3	13.6	12	15.0	48	72.7	4	10.3	16	42.1
cMCS	76	27.9	2	7.7	0	0	56	81.2	0	0	18	47.4

Percentage figures are always valid percents, i.e. disregarding missing values. sMCS = self-reported MCS. f1MCS = formalised computer-aided scoring system, short form (sum score  $\geq 4$ ). f2MCS = formalised computer-aided scoring system, long form (sum score  $\geq 4$ ). cMCS = clinically estimated MCS, concluding medical assessment (on the basis of Cullen's case criteria).

<sup>a</sup>Without Freiburg, because it participated only in the year 2000 with 13 patients.

base (100%) for the calculation are the patients without missing values. The number of patients with missing values increased from sMCS, over f1MCS and f2MCS, to cMCS.

### Symptom groups

Like in many other studies on Idiopathic Environmental Intolerance (IEI) or MCS more than two-thirds of the patients were experiencing rather unspecific and general symptoms, followed by complaints of the musculoskeletal system or other complaint domains.<sup>2</sup> But as shown in Table 4, no essential differences between MCS and non-MCS patients with respect to the symptom groups could be found, since only one of seven symptom groups showed a significant difference, general symptoms on level f1 and, respectively, GI tract-related symptoms on level f2. This is an inconsistent result. In addition, when we consider the problem of "multiple testing" and apply appropriate corrections, then there are no significant differences at all. Thus, hypothesis H1 (MCS comes together with a circumscribable symptom pattern or complex of symptoms) was not supported.

### Associations between pollutants groups and symptom groups

Furthermore, we wanted to clarify whether statistical associations between subjectively incriminated pollutants and symptom groups could be detected (hypothesis H2). EM outpatients provided information about their complaints and the alleged pollutants when they answered the MCS questionnaire, adopted from Hüppe et al. (2000). This questionnaire comprised of a list of 48 different complaints (five-point ratings) and a list of 42

<sup>2</sup>In this paper, we define 'complaint domains' as complaints referring to the same organ or organ system.

**Table 4.** Frequencies of symptom groups, given for the total sample, MCS and non-MCS patients

Symptom group	Frequency (%)			<i>p</i>
	Total sMCS	Non-sMCS		
1. Respiratory system	28.1	24.6	30.4	0.28
2. Musculoskeletal system	38.6	42.1	36.3	0.32
3. Cardiovascular system	11.6	14.9	9.4	0.15
4. Gastrointestinal tract	29.5	36.8	24.6	0.03
5. Skin or mucosa	24.9	21.9	26.9	0.34
6. Head/sensory system	36.1	38.6	34.5	0.48
7. General symptoms	69.1	72.8	66.7	0.27
	Total f1MCS		Non-f1MCS	<i>p</i>
1. Respiratory system	27.9	26.9	28.3	0.82
2. Musculoskeletal system	38.4	37.2	38.9	0.79
3. Cardiovascular system	11.6	12.8	11.1	0.69
4. Gastrointestinal tract	30.4	41.0	26.3	0.02
5. Skin or mucosa	25.7	24.4	26.3	0.75
6. Head/sensory system	34.8	39.7	32.8	0.28
7. General symptoms	70.3	82.1	65.7	<0.01
	Total f2MCS		Non-f2MCS	<i>p</i>
1. Respiratory system	27.1	26.2	27.6	0.81
2. Musculoskeletal system	38.4	35.7	39.7	0.54
3. Cardiovascular system	10.9	11.9	10.3	0.71
4. Gastrointestinal tract	30.6	44.0	24.1	0.001
5. Skin or mucosa	26.4	23.8	27.6	0.52
6. Head/sensory system	33.3	34.5	32.8	0.78
7. General symptoms	70.2	78.6	66.1	0.04
	Total cMCS		Non-cMCS	<i>p</i>
1. Respiratory system	29.5	28.8	29.8	0.87
2. Musculoskeletal system	37.9	35.0	39.0	0.53
3. Cardiovascular system	11.9	13.8	11.2	0.55
4. Gastrointestinal tract	29.5	37.5	26.3	0.06
5. Skin or mucosa	25.3	23.8	25.9	0.71
6. Head/sensory system	35.1	33.8	35.6	0.77
7. General symptoms	69.5	73.8	67.8	0.33

*p* = result of Pearson's Chi-square test.

pollutants (six-point ratings). A principal component analysis (PCA) of the complaints data yielded nine components, which explained 65.8% of the variance for the total sample. Six of them, comprising the highest amounts of variance explained, could be interpreted and described as follows: F1, psychic ill-being (11.5% of the variance explained); F2, gastrointestinal complaints (10.4%); F3, neurological malperformance or dysfunction (10.0%); F4, irritation of the upper respiratory tracts' mucosa (7.5%); F5, disturbed perception (7.3%); F6, breathing complaints (6.7%).

Multiple linear regression analyses with stepwise inclusion were performed using each one of these principal components as criterion variable and the 42 pollutants as predictor variables plus the three potential confounder variables f1MCS, age and gender; i.e. we aimed to predict a given principal component (F1–F6) in dependence of environmental variables. The resulting models explained between 19.0% (F3) and 32.9% (F4) of the variance. Most pollutants, such as smell of gasoline, interior of new cars, nail varnish, perfume, deodorant, fresh print products, solvents and/or glue, biocides, carpeting and tobacco smoke did not contribute significantly to the variance explained and are, therefore, not listed in Table 5. Significant contributions to the explained amount of variance (i.e.  $> 1\%$ ,  $p \leq 0.05$ ) were observed only with exhaust emissions, plasticisers and fragrance of fresh strawberries for F1 (“psychic ill-being”), alcohol and mineral water for F2 (“gastrointestinal complaints”), fresh paintwork and animal hair for F3 (“neuropsychological complaints”), house dust (-mites), new furniture and unknown substances for F4 (“irritation of the upper respiratory tracts' mucosa”), cleansers, mould fungi, fragrance of vanilla pod and pollens for F5 (“disturbed perception”), mountain air and smell of tar (10.4%) for F6 (“breathing complaints”). Of the predictors age, gender and MCS, which were regarded as potential confounders, only age contributed to the explained variance (4.1% in the model for F2, and 3.2% in the model for F3); for the results displayed in Table 5 the potential predictor f1MCS was used. The standardised regression coefficients  $\beta$  and the zero-order correlation coefficients are not included in the table. Altogether the analysis provided rather heterogeneous, sometimes contradictory and inconclusively interpretable results.

When we repeated the PCA for the subgroup of f1MCS positive patients, we achieved 13 principal components, which accounted for 75.7% of the total variance. Five out of the six first components could be well interpreted and were largely in agreement with the components of the PCA for the complete sample. The sixth component, however, which explained the majority of the variance, namely 75%, was only poorly interpretable. It corresponded with the above stated F2 (gastrointestinal complaints), but included additionally

the item joint/muscle pain, which loaded highest to this component. In analyses with small sample sizes and many predictors the actual multiple associations will be overestimated, thus making the application of a shrinkage formula for correction necessary. We used Carter's shrinkage formula (Carter, 1979) and after its application the maximal R<sup>2</sup> declined from 75% to 48%. The other extreme was principle component F5 that could not be explained sufficiently by any combination of predictors. The remaining four components attained explained variances between 25.0% and 41.9%. As no plausible interrelations could be achieved for the MCS patients and f1MCS was not a predictor in the first regression model (Table 5) hypothesis H2 was not supported by our results.

In addition to the above data analysis which based on the MCS questionnaire we used the free-text answers of the Environmental Medical Questionnaire (EMQ) to test whether certain symptom combinations (strictly speaking: combinations of symptom categories/groups/classes) are statistically associated with certain pollutant combinations (strictly speaking: combinations of pollutant categories/groups/classes) for the EM outpatients.

To achieve a manageable number of combinations we restricted our analysis to four complaint patterns and five groups of alleged pollutants. With a number of four symptom groups  $2^4 = 16$  combinations are possible and all of them were observed. The eight most frequent combinations accounted for approx. 72% of the whole sample. In contrast, with five groups of pollutants  $2^5 = 32$  combinations are possible from which only 26 were realised. The nine most frequent combinations of pollutant groups accounted for approx. 81%.

A cross-table analysis with the eight “symptom combinations” by the nine above-mentioned “pollutant combinations” was carried out and the Haldane-Dawson test for global check of independency of both variables was performed. Test results showed that both variables were independent of each other ( $u = -1.06$ ,  $p = 0.85$ ). In respect to the attributes considered here no global association between symptom groups and pollutant groups was determinable. Furthermore we tested for each cell of the cross-table whether the standardised residuals (differences between expected frequency and observed frequency) were equal to or greater than the (absolute) value of 2. A standardised residual greater than +2 (or smaller than -2) and an expected frequency equal to or greater than 5 indicates an association between the corresponding column and row. None of the cells fulfilled both conditions.

Hence no statistically obvious associations between symptom and pollutant group combinations could be demonstrated for the EM outpatients (total sample). Because of the small sample size this analysis could not be conducted for the MCS patients.

**Table 5.** Regression analysis models for the principal complaint components (F1–F6) explained by exposure agents (predictors) for relevant proportions of explained variance ( $>1\%$ ,  $p \leq 0.05$ ); not significant values are represented by empty cells

Predictor variables (exposure agents)	Criterion variables (principle components of complaints)											
	F1		F2		F3		F4		F5		F6	
	Var	<i>p</i>	Var	<i>p</i>	Var	<i>p</i>	Var	<i>P</i>	Var	<i>p</i>	Var	<i>p</i>
Exhaust emissions	8.1%	0.038										
Plasticisers	8.4%	0.022										
Fragrance of fresh strawberries	4.3%	0.023										
Alcohol			14.8%	<0.001								
Mineral water			6.1%	0.006								
Fresh paintwork					13.9%	<0.001						
Animal hair					1.9%	0.024						
House dust/house mites							9.1%	0.012				
Pollen							8.7%	0.003	2.6%	0.02		
New furniture							8.2%	0.010				
Unknown substances							7.1%	0.018				
Mountain air											14.3%	<0.001
Cleansers									10.2%	0.001		
Fragrance of vanilla pod									3.9%	0.026		
Mould fungi									4.8%	0.029		
Smell of tar											10.4%	0.002
Age			4.1%	0.017	3.2%	0.016						

Abbreviations: Var = amount of variance explained; *p* = *p* value (result of *F* test).

### Environmental medical assessment

For about 10% of the EM outpatients the centres' physicians found sufficient hints for a relevant initial exposure to pollutants, whereas Bredstedt with approx. 20% and Munich with approx. 28% were significantly outstanding. Our analysis showed no significant differences between f1MCS and non-f1MCS with both having approx. 14% initial exposure, whereas for f2MCS and non-f2MCS it was 24% and 6%, respectively, and for cMCS and non-cMCS 28% and 4%, respectively (each with  $p < 0.01$ ). Those patients who were, according to physicians' assessment, initially exposed came largely from Bredstedt (i.e. 10 of 17 patients with f2MCS, 12 of 21 patients with cMCS). Consequently, hypothesis H3a, which postulated that the onset of MCS is linked with an initial exposure could not be confirmed for sMCS and f1MCS. The hypothesis could not be properly tested for f2MCS and cMCS in this study.

The number of patients with exposures of "hygienic relevance" was higher than the number of patients with exposure of "toxic relevance" (both according to physicians' assessment; Table 6).<sup>3</sup> As both exposure

groups were for the majority of the cases in the past, they could only be evaluated through the exposure history. Moreover, considerable differences were observed between centres with highest numbers for Bredstedt. If the exposure assessment was differentiated for the MCS categories the result depicted in Fig. 1 was obtained. With the exception of the sMCS group, in most cases, exposure was more often assumed for patients of the MCS category than for patients of the corresponding non-MCS category. These differences increased continuously from f1MCS to cMCS for all exposures (current or former, hygienic or toxic).

Thus, hypothesis H3b cannot be confirmed regarding sMCS vs. non-sMCS (internal comparison group). For the remaining MCS constructs, in particular for f2MCS and cMCS, a testing of hypothesis H3b in the context of the study was not possible in an adequate manner, since due to the definition of the case criteria a person with supposed exposure had a greater chance to be assigned to one of the MCS categories (circular reasoning).

(footnote continued)

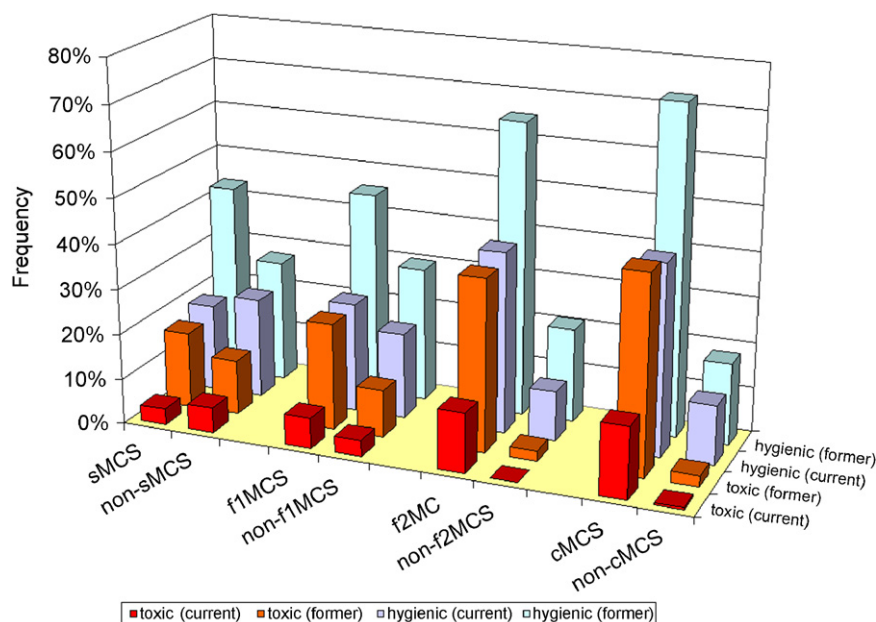
constituents of commodities and dental materials (but no drugs, no classical allergens, no mould fungi). (B) Toxicological/clinical relevance: Increased exposure to xenobiotics, which could be made responsible, with sufficient evidence, for pathological findings and/or symptoms of the patient (expert's estimate – regional case conference). If (B) is affirmed, (A) has to be answered in the negative! "Current exposure" means that the exposure still existed at the time of investigation; "former exposure" means that there was an exposure episode at an earlier time (currently no longer existent) which is not synonymous with "initial exposure".

<sup>3</sup>In this study the following rules applied and must be considered by the judging environmental physicians in the centres involved (according to the MBD = Medical Baseline Documentation): (A) Hygienic relevance: Increased exposure to xenobiotics without clinical relevance (no adverse effects demonstrable/plausible); here are primarily chemicals meant in the sense of environmental chemicals/pollutants, e.g. indoor pollutants, chemical contaminants of tap water, but also

**Table 6.** Number of patients with former or current exposure

Exposure	Total		Aachen		Berlin		Bredstedt		Giessen		Munich	
	<i>n/N</i>	%yes	<i>n/N</i>	%yes	<i>n/N</i>	%yes	<i>n/N</i>	%yes	<i>n/N</i>	%yes	<i>n/N</i>	%yes
Former exposure of												
Hygienic relevance	93/268	35	<i>1/27</i>	4	<i>18/87</i>	21	<i>56/66</i>	85	<i>5/48</i>	10	<i>13/40</i>	33
Toxicol. relevance	40/273	15	<i>1/26</i>	4	<i>2/87</i>	2	<i>35/72</i>	49	<i>0/48</i>	0	<i>2/40</i>	5
Current exposure of												
Hygienic relevance	58/267	22	<i>1/27</i>	4	<i>16/87</i>	18	<i>38/66</i>	58	<i>1/47</i>	2	<i>2/40</i>	5
Toxicol. relevance	13/267	5	<i>0/25</i>	0	<i>0/87</i>	0	<i>13/68</i>	19	<i>0/47</i>	0	<i>0/40</i>	0

Chi-square test:  $p < 0.001$  for all four criteria. Italicised numbers differed explicitly from the expectancy value; standardised residual was beyond the interval of  $[-2, +2]$ . For the categories hygienic/toxicological there are two cases possible: either former exposure or current exposure (in each case only one category possible).



**Fig. 1.** Physician's assessment of current and former exposure, of hygienic or toxic relevance: physician's assessment of current and former exposure, of hygienic or toxic relevance.

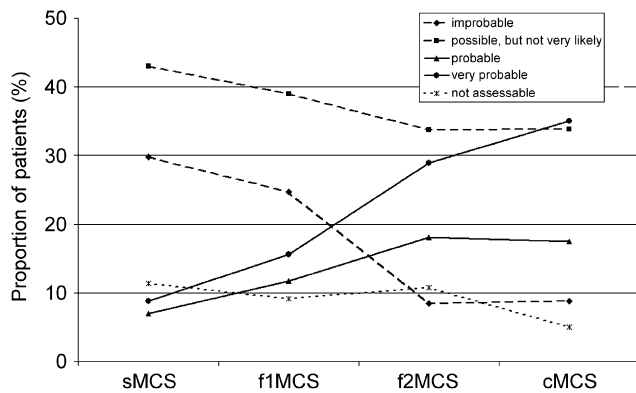
However, multiple logistic regression analyses showed that the differences regarding the medical exposure assessment as presented in Fig. 1 were due to a clearly pronounced centre's effect (Bredstedt vs. all others) rather than to the underlying MCS definition.

With respect to the physician's assessment of causality between exposure and complaints of the patients or between exposure and diagnoses we found a similar picture. The categories 'very probable' and 'probable' increased from sMCS to cMCS whereas the categories 'improbable' and 'possible, but not very likely' decreased (Fig. 2; please note, that the lines drawn to connect the categorical attribute values are only for better readability). And again, multiple logistic regression indicated that besides the centres' factor (Bredstedt vs. non-Bredstedt), which determined the assessment of causality, the f2MCS factor (positive vs. negative)

contributed, as expected, to the amount of variance explained. Once more, the category cMCS is strongly affected by the factor 'centre' whereas the MCS definition factor is of weaker influence.

### Analysis of susceptibility

The extent to which MCS patients had increased somatic susceptibility to xenobiotics was analysed by the use of possible susceptibility markers (hypothesis H4). Altogether 26 allelic variants of 17 different candidate genes have been selected for this analysis. Blood samples of 205 EM outpatients were molecular-genetically evaluated. We found no significantly different frequencies between any of the MCS groups and the corresponding non-MCS groups for any of the alleles



**Fig. 2.** Physician's assessment of causality between exposure and complaints or diagnoses.

investigated here. Environmental patients did not differ from the general population in respect to these alleles' frequencies. Diagnostic relevant differences would have been detectable with sufficient test power of 80% and sufficient statistical significance ( $\alpha = 0.05$ ). For more details see Brockmüller et al. (2003), Eis et al. (2005a) and Mühlinghaus et al. (2005).

### Olfactory findings

Is "hyperosmia" (increased olfactory performance), as was postulated in hypothesis H5, a symptom more frequently observed for patients with MCS and is it even a risk factor for MCS? About 93% of the sMCS patients (f1MCS: 97%, f2MCS: 93%, cMCS: 94%) self-reported hyperosmia, but so did nearly two-thirds of the other environmental patients. Forty-five consecutively recruited patients from Berlin EM-unit were subjected to the "Sniffin' Sticks" smelling test. MCS positive patients did not show consistently better olfactory performance than MCS negative patients. This was true for the sMCS, f1MCS and f2MCS categories. MCS positives were only significantly different from the MCS negatives for the identification of odours, as on average, they could identify one odour more (14 of 16 vs. 13 of 16) whereas, the non-MCS patients could identify one odour fewer than the reference group (13 of 16 instead 14 of 16).

Furthermore, we tried to test a hypothesis repeatedly raised in the MCS debate – namely the neurogenic inflammation hypothesis – by a case-control study with 19 cases and an equal number of age and gender matched healthy volunteers. The analysis of inflammation mediators in the nasal lavage after provocation with 2-propranolol yielded no significant differences between cases and controls. The only difference ascertained was the higher values for prostaglandin E2 (but not for substance P), which was observed independently for the provocation and for the side of the nose provoked.

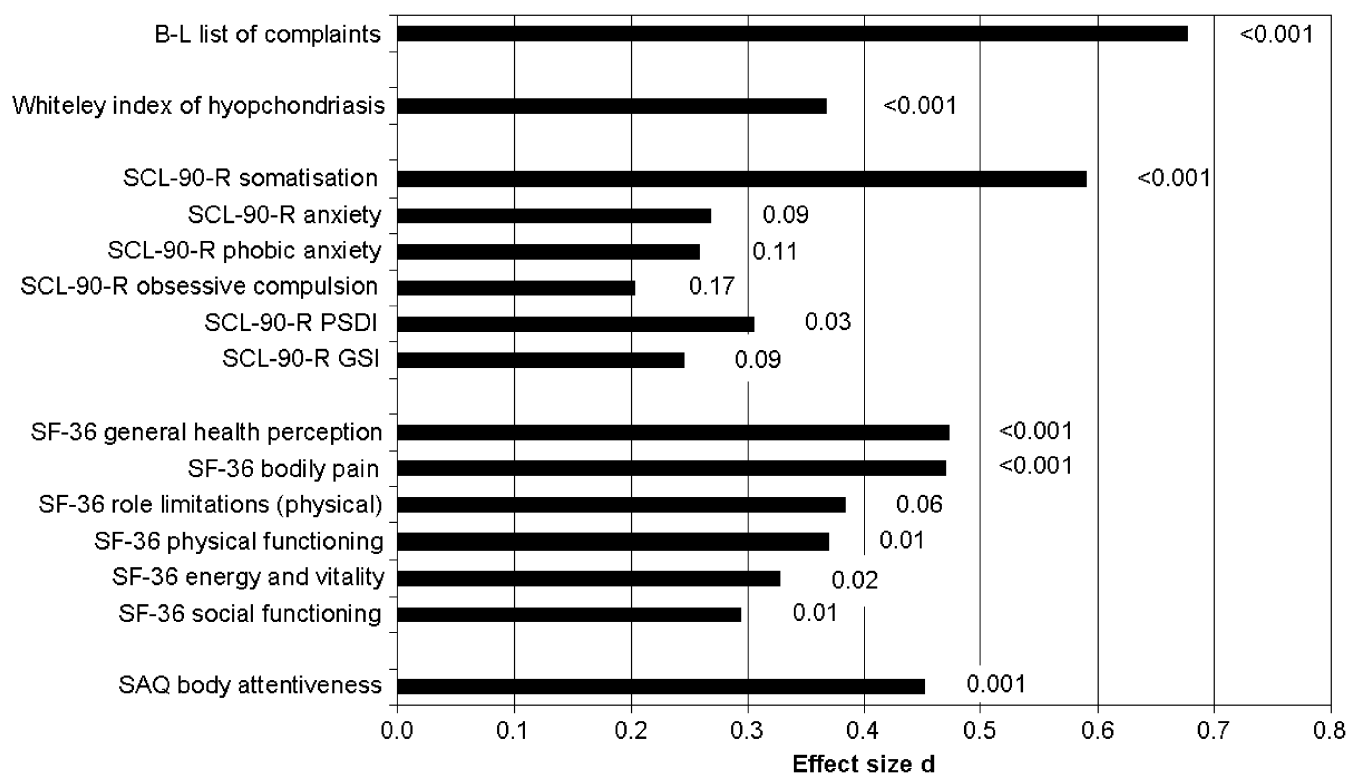
Besides the possible changes in the degradation kinetics of prostaglandin E2 in the stored samples, ENT-specific causes must also be considered. For example, inflammatory paranasal diseases were diagnosed for some patients in the case group. Substantial hints on neurogenic inflammation events could not be found. Already in phase I of the study, olfactory evoked potentials yielded results which were borderline conspicuous for the case group. Due to the small sample size, it was not possible to decipher whether this was a systematic difference or random chance. If the former is true, either disturbed habituation or changed cognitive processing are possible (cf. Eis et al., 2003b).

### Psychometric findings

As already demonstrated in previous reports of our study, environmental patients show more often psychometrical peculiarities and mental disorders than the general population or patients with defined physical diseases (Eis et al., 2003a, b). Patients with self-reported MCS generally score higher than other environmental patients, but these differences are not very serious in most cases. Similar results were obtained in respect to the formalised MCS categories (f1MCS, f2MCS).

When the effect sizes for all of the scales, subscales, and item scores for the psychometric tests (B-L, SCL-90-R, WI, SF-36) were calculated, the sMCS, f1MCS and f2MCS patients generally show a stronger impairment than the corresponding non-MCS groups (the cMCS grouping was not considered here because of the serious centres' effect). This is exemplarily shown in Fig. 3 for f1MCS; for differences between means the effect size is calculated as Cohen's *d* where a value of 0.2 is considered a small effect, 0.5 a medium, and 0.8 a large effect size. f1MCS positive patients (i) had higher symptom scores (especially high on 'somatisation scales') compared to f1MCS negative patients, (ii) tended to attribute their complaints to environmental factors, (iii) suffered comparatively strong from their disorder, and (iv) they reacted, according to their own subjective assessment, to minor exposures with health impairments. The MCS questionnaire result met expectations since the instrument used assigned those persons who supplied many data about complaints or environmental factors to the MCS category when a threshold (or cut-off) was exceeded. Age and gender seemed to have no influence, since the statistics (median, mean and standard deviation) of the respective distributions are virtually identical or do not differ significantly with respect to the comparison discussed here (f1MCS vs. non f1MCS).

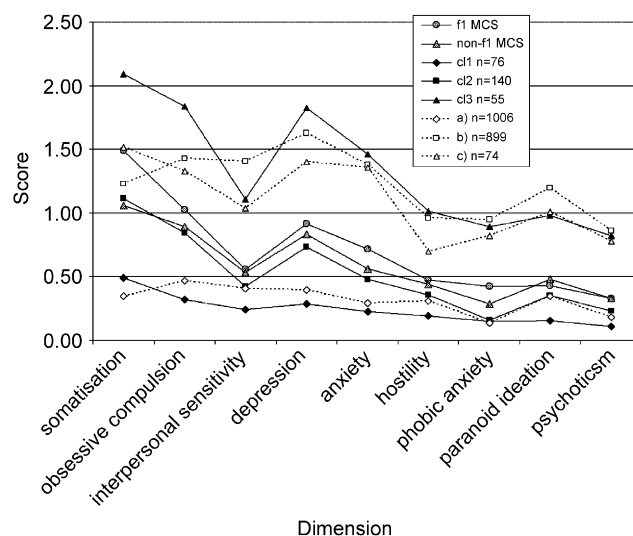
SCL-90-R data have been used to perform a cluster analysis resulting in the separation of groups with differing mental stress (Fig. 4). At first the cluster



**Fig. 3.** Scales of the psychometric tests with at least a weak effect size ( $d \geq 0.2$ ) showing stronger impairment of the f1MCS positive patients compared to f1MCS negative patients ( $p$ -values inserted).

analysis was performed with data from all environmental outpatient clinic patients, i.e. to all patients with health problems relating to the environment. We assumed that this group of patients is very heterogeneous (composed of different subgroups) in regard of their psychometric profiles. The cluster analysis accomplished resulted in three well-defined clusters. The largest group (cl2;  $n = 140$ ) was characterised by partially higher scores in the dimensions somatisation, obsessive compulsion, depression and anxiety in comparison to the general population. The second largest group (cl1;  $n = 76$ ) had a mean SCL-90-R profile that did not differ essentially from that of the general population. The third group (cl3;  $n = 55$ ) was a pooled cluster. It consisted of subgroups with different profiles whose scores were however altogether clearly higher than those of the general population. For comparison purposes, besides the profile of the norm sample (a), SCL-90-R profiles of patients of a clinic for psychosomatic medicine (b) as well as of patients with somatoform disorders (c) have been included in Fig. 4. The comparison samples were similar to that of the environmental patients in regard of age and gender distributions.

In Fig. 4 we have inserted the SCL-90 profiles for f1MCS and non-f1MCS. Only the somatisation dimension shows a clear difference (the same is true for sMCS vs. non-sMCS). In contrast, the profiles of the



**Fig. 4.** Score values for SCL-90-R dimensions of the clusters found and of reference groups: (a) norm sample (Franke, 1992), (b) psychosomatic patients (Rief et al., 1991) and (c) patients with somatoform disorders (Faltermaier-Temizel and Zaudig, 2002).

f2-groups, more strongly aligned to the clinical estimate (noxigene MCS concept), do not differ in respect to the dimension “somatisation”.

The cluster partition was supported by results obtained with other psychometric tests. B-L, SAQ and

**Table 7.** Distribution of MCS and non-MCS in the SCL 90-R clusters (cl = cluster, see Fig. 4)

	sMCS (%)	Non-sMCS (%)	f1MCS (%)	Non-f1MCS (%)	f2MCS (%)	Non-f2MCS (%)
cl1	33.3	66.7	25.0	75.0	38.1	61.9
cl2	41.0	59.0	29.1	70.9	30.4	69.6
cl3	43.4	56.6	33.3	66.7	32.7	67.3
Total	39.3	60.7	28.9	71.1	38.9	67.1

Chi-square test: none was statistically significant.

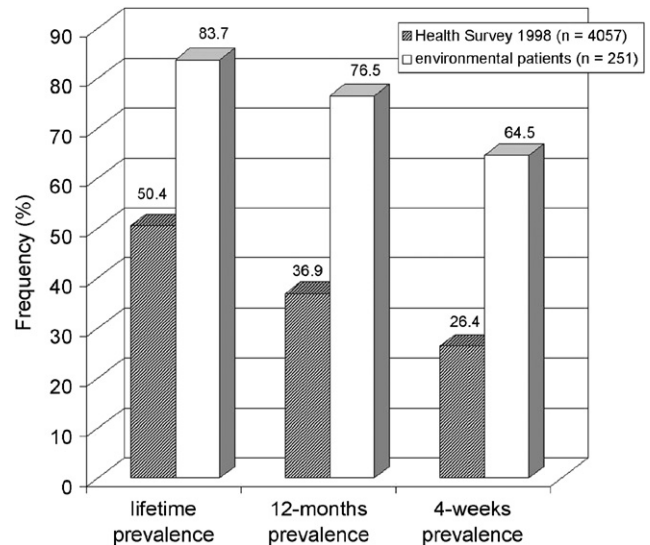
WI also yielded scores, which increased from cl1 over cl2 to cl3, and SF-36 yielded decreasing scores. For example, more than 70% of patients in cl3 are considered hypochondriac according to the results of WI. Particularly impressive were the outcomes of CIDI, which confirmed this trend. Somatoform disorders (including undifferentiated somatoform disorders) have been found for about 50% of the cl1 patients, whereas the same diagnosis resulted for almost 90% of the patients in cl3.

Within each of the patient clusters (cl1–cl3) the proportions of MCS positives were evenly distributed for all MCS categories (sMCS, f1MCS, f2MCS and cMCS; Pearson's Chi-square test:  $p > 0.25$ ). The centres participating in this study were also balanced in the three cluster groups ( $p = 0.48$ ; Pearson's Chi-square test). In Table 7 the proportions of MCS patients and non-MCS patients are given (excepting the cMCS because of low number of cases) for the three clusters. As expected, cluster cl3 had relatively high sMCS and f1MCS proportions (and, accordingly, low non-sMCS and non-f1MCS proportions), whilst the reverse is true for f2MCS. It should be considered here that psychic disorders can function as exclusion diagnoses when a noxigene MCS concept is applied, so that the low f2MCS proportions are quite understandable (see Discussion).

### Computer-assisted psychiatric diagnostic (CIDI)

251 of 291 environmental patients (86%) agreed to take part in CIDI. During the lifetime, 84% of the patients fulfilled criteria for at least one psychic disorder compared to approx. 50% of the general population of Germany (German National Health Interview and Examination Survey). For the 12 months prevalence and the 4 weeks prevalence similar results were obtained (Fig. 5). No significantly different diagnosis frequencies were found for the different centres.

The most frequent single diagnosis was the 'undifferentiated somatoform disorder' (F45.1) or 'subthreshold somatoform disorder' (SSI 4/6) with a lifetime prevalence of 52% followed by the 'persistent somatoform pain disorder' (18%) and the 'severe depressive episode without psychotic syndrome' (14%). With a lifetime

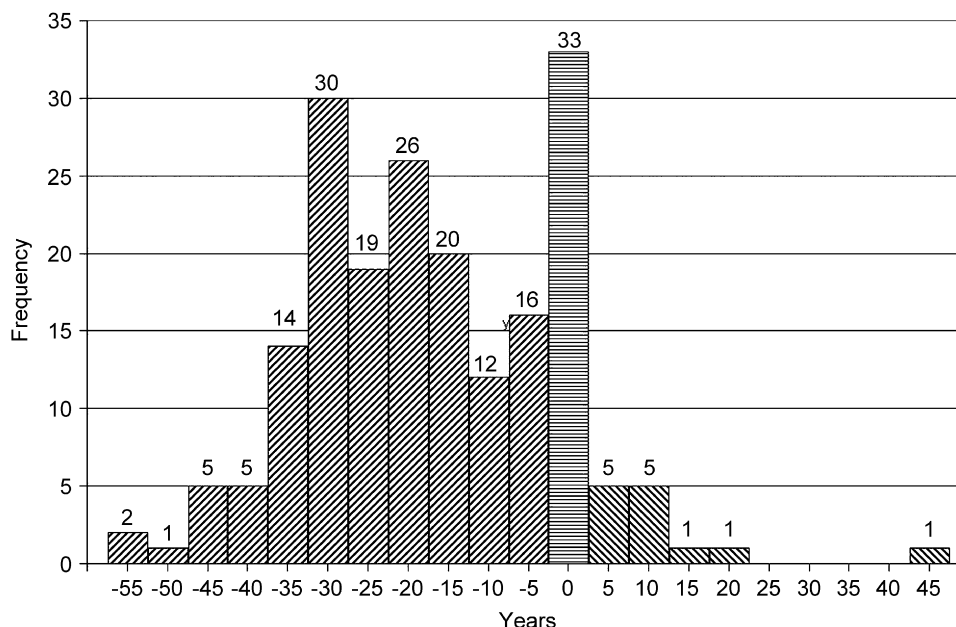


**Fig. 5.** Frequency of patients with at least one CIDI diagnosis, comparison between Health Survey 1998 (German National Health Interview and Examination Survey) and environmental patients.

prevalence of 72% somatoform disorders were the most frequent diagnosis group. They were found for MCS positive patients significantly more often than for MCS negative patients. For more details see Dietel et al. (2006) and Eis et al. (2005b).

According to hypothesis H6 we raised the question whether the mental disorders observed were a consequence of the environmentally associated complaints reported by the environmental patients or if the mental problems preceded the environmentally related complaints. Therefore we compared the time of onset for all patients with mental disorders (according to CIDI) with the patients' statements on the duration of the environmentally related complaints (according to EMQ).

On average the onset of the longest persisting mental disorder dated back 25 years, whereas the environmentally related complaints had persisted since approx. 8 years. For about 80% of the patients the mental disorder persisted longer than the environmental disorder, and for 18% of the patients the environmentally related disorder started earlier than the mental disorder or both had the same onset. Between centres only



**Fig. 6.** Temporal difference between the onset of the environmentally related disorders and the mental disorders; negative numbers (abscissa): onset of the mental disorder prior to that of the environmentally related disorder.

marginal differences were observed. On average, 17 years lay between the beginning of the mental problems and the beginning of the environmentally related disorder. Thus, the mental disorders were preceding the environmentally attributed disorders far in advance (Fig. 6). For the sMCS and f1MCS group the mean temporal difference is also 17 years, for the f2MCS group 15 years.

## Discussion

### Different MCS constructs

Whenever the analysis was focussed on the different MCS categories there were problems of validity and reliability, relating to the uncertain case criteria. The sMCS category based on the self-assessment of the patient and that, in turn, depended on the public debate about “MCS” and the information available to the patient. EM outpatients who have never heard of “MCS” cannot explicitly classify themselves as suffering from “MCS”. Moreover, the self-assessment of the patients give of course no evidence about their actual diagnostic status. Hence, the sMCS category is of little use alone for this reason. As there exists no diagnostic gold standard for the physician’s diagnosis of cMCS, one has to deal with other constructs that enable an approach to the yet uncertain phenomenon of “MCS”. Here the criteria of Cullen can be useful. The diagnostic validity of these criteria is however vague. Moreover, the

question is to be answered of how significant differences in the cMCS proportions between the centres involved in the multicentre study could arise, despite uniformly given definitions for MCS. There was no statistical evidence for more severe cases in the specialized hospital. Rather, patients who received the label “cMCS” in Bredstedt were assigned to the non-cMCS group by the university centres (results of a joint case conference, Berlin 2003, hitherto unpublished data). The crucial points were the different medical judgement of the exposure and symptom statements provided by the patients as well as serious differences of the differential-diagnostic and etiologic evaluation of symptoms for the same patients given by different physicians. This suggests that the centre differences were mainly caused by differences in judgement. In contrast, no evidence of a significant selection bias could be found (consecutive patients form the sample).

Due to the poor reliability of the cMCS diagnosis we undertook a formalised classification of the EM outpatients by means of a computer-assisted MCS scoring system. In this way a significant reduction of the centres’ differences could be achieved. This is particularly true for the f1MCS category. Good agreement was observed for the diagnoses of the university centres in respect to f1MCS as well as to f2MCS while the clinical-ecologically oriented hospital still yielded more deviating f2MCS proportions.

Despite notable improvements which could be achieved for the examination of hypotheses of the MCS phenomenon it is necessary to remark that no completely satisfying stringency could be achieved when

testing the hypotheses. In this respect, the study was hampered by the moderate sample size, the general framework of the outpatient units, the routine operation of which must be kept running, and the clinical multicentre design with differing assessments of the physicians described above. In the following sections some points are discussed in more detail.

### Symptom patterns

Diseases are characterised by defined patterns of symptoms, signs and laboratory findings. Even complexes of symptoms are characterised by a discrete pattern of clinically specifiable symptoms. Also, for MCS a characteristic symptom complex should become apparent, irrespective of a certain intra- or inter-individual variance. We can only consider MCS as a symptomatological entity if this is fulfilled. The question whether subgroups with defined and delimitable symptom patterns can be detected amongst the environmental patients and, if so, whether these subgroups correspond with the different MCS categories (sMCS, f1MCS, f2MCS, cMCS) was not easily to be answered, for the following reasons. Firstly, the spectrum of health complaints is enormously multiform, even when only the 'main presenting complaints' are considered. We should, however, remain cautious since the data have been considerably condensed into highly aggregated categories (see Table 4). Secondly, the necessary categorisation is linked to a loss of information, and the degree of loss depends on the number of categories and the reliability of the categories' system. And, thirdly, when the sample size decreases the number of categories must be reduced (in other words, the categories' broadness must be increased) to obtain statistically sufficient numbers of patients per table cell. Also, in this study aggregation of successive complaints was necessary due to the small sample size. The analyses of symptom patterns was not successful. It cannot be ruled out, that clues to certain symptom patterns would be found when a larger sample size is used. However, a complex of symptoms being characteristic for MCS would have been recognisable even with such a small sample size. Furthermore, the different MCS groups did not differ substantially from the corresponding non-MCS groups in respect to their complaints' spectrum. More clearly pronounced differences would have been expected if the MCS phenomenon were a symptomatologically delimitable disorder.

The search for characteristic symptom constellations (syndromes), this is to say, the statistical analysis of complaints among one another, can still be done in a different way, for example, with an analysis of the latent structures of the environmentally related complaints on the basis of latent class models. This approach, sufficient

sample size and careful recording of symptoms assumed, may clarify whether a configurational pattern can be found for the complaints' structure or whether ordered latent classes and, therefore, ordinally scaled categories of a qualitative personality variable exist (in methodical respect cf. Rost, 2004).

### Associations between pollutants and complaints

Statistical analysis of complaints-pollutants categories, which, due to the multitude of possible combinations, were reduced to 4 categories of complaints and 5 categories of pollutants, provided no statistically significant inter-relationships between the symptom and pollutant categories. Thus, a typical pollutant-complaint pattern was not detectable under the given conditions. In addition the analysis of standardised questions to pollutants and complaints (MCS-Questionnaire) with PCA and multiple logistic regression gave no suggestions to systematic inter-relationships between categories of pollutants and complaints, neither for all environmental patients nor for the MCS groups compared with the non-MCS groups. The data analysis provided no clear support for associations between complaints and pollutants. These results raise uncertainty for the evidence of hypothesis H2 even though unequivocal conclusions cannot be drawn due to the methodical limitations of this study.

Both the standardised and free text questions about pollutants and complaints have reciprocal advantages and disadvantages. The specification of default answers in "closed questions" may influence the responses (apart from the investigator's influence inevitably inherent in the answers) whereas the "open questions" may not influence the answers. However, due to the large spectrum of resulting answers, aggregation or categorisation is always a necessity which is in turn also investigator influenced. Comparative analyses of standardised and free text answers about complaints and pollutants is urgently needed for clinical environmental medicine from a methodical point of view.

### Is MCS induced or triggered by demonstrably elevated pollutant burdens?

Most definitions of MCS include a criterion according to which this condition is acquired, whereupon the existence of an initial exposure is not seen as an essential precondition. But a case criterion being facultative is conceivably inadequate for a case determination. Only about 10% of the environmental patients had an initial exposure approved by the physicians, which additionally reduces the importance of this criterion. Those assessments predominantly rely on medical history data provided by the patients. In most cases, measurements

were not available, since almost all scenarios of exposure occurred in the past. Verification or falsification of hypothesis H3a on the basis of objective data was thus not possible. However, for those MCS conceptions for which initial exposure played a certain role (f2MCS, cMCS), the MCS group will have an increased proportion of initial exposure than the corresponding non-MCS group.

Unlike past exposures, factors currently triggering complaints are more likely to be recorded and to quantitatively measure the actual exposure. But even in these cases we may be confronted with methodical constraints. For example, the alleged exposures frequently are temporary 'olfactory impacts' (off-site from the patient's home), which cannot be recorded analytically or they are no longer recordable at the time of the investigation (because of, e.g., removal of the sources, house moving) or they cannot be distinguished from the background level. Theoretically, elevated long-term exposure without typical triggering traits may play a role. Colleagues from Bredstedt centre hypothesised that the short-time influence of pollutants could be masked as a result of a chronic course of the disorder. Taken together, there is considerable unclarity in the assessment and judgement of current exposures, which can strongly influence the environmental-medical evaluation. The extent to which opinions differed with respect to the assessment and judgement of exposures was revealed during a joint case conference which was held with all participating centres.

The hypothesis that MCS is initiated or triggered by suspicious or demonstrably elevated exposures is difficult to verify since the question is not independent of the MCS case criteria, which determined the case group. In other words, patients whom the physicians stated elevated exposure in MBD had a greater chance to be assigned to the MCS group, in which, an 'elevated exposure' (biased by the case definition) will be found again. This problem cannot be easily solved methodically. At best, a parallel design could be used to ensure if the physician's assessment of exposure is based on a demonstrable exposure. This is not feasible with the data of the present study. Subsequently, it was found that elevated values have been recorded for MCS patients by the physicians, especially for the rarely detectable 'former exposures', and the degree of the attestation increased in the order f1MCS, f2MCS, cMCS. This in turn indicates an influence by the investigator, which especially correlated with the centre's effect, and was particularly pronounced for the cMCS category. In conclusion, there is insufficient evidence to prove that MCS is induced by a possibly elevated pollutant burden. However, if we assume temporarily elevated, hardly detectable exposures, this will raise the principle question whether those exposures would yield 'somatic reactions' immediately or, instead,

by central nervously mediated effects via sensory perceptions, which are subject of cognitive and emotional impacts at the same time.

### **Can indices be found for a genetically conditioned susceptibility of MCS patients?**

Conventional MCS case definitions assume that the complaints are provoked by very low pollutant exposures (which induce no complaints in other persons). For these individuals a particular susceptibility to environmental pollutants is supposed, which can partially have a genetical basis. Gene variants, associated with certain enzyme polymorphisms related to xenobiotics' metabolism, can form a risk factor for MCS, and those polymorphisms can be used as susceptibility markers for the diagnosis of MCS (for a critical review see [RKI, 2004](#)). Within the framework of the German Multicentre Study no significant accumulation of such gene variants with diagnostic relevance was detectable for environmental patients or MCS patients (sMCS, f1MCS, f2MCS, cMCS) ([Brockmüller et al., 2003](#); [Eis et al., 2005a](#); [Mühlinghaus et al., 2005](#)).

### **Is 'hyperosmia' a risk factor for MCS?**

Self-reporting MCS patients react to a multitude of chemical factors, which includes, not least, odours and scented matters. According to [Davidoff and Keyl \(1996\)](#) 85% of the MCS patients (in our study, 95%) complain about chemical odour intolerances. They may exhibit either increased or qualitatively altered perception of odours. This contrasts with the results of olfactory tests from the MCS multicentre study, which used 'sniffin' sticks'. Environmental patients in general and MCS patients in particular, did not exhibit significantly enhanced olfactory performance when compared to a normal sample. The marginally better performance in odour identification, which was observed for MCS patients compared to non-MCS patients, could be due to the increase in sensory attentiveness. Other studies also found no evidence for enhanced olfactory sensitivity or higher-than-average smelling performance in 'MCS patients' ([Caccappolo et al., 2000](#); [Dalton and Hummel, 2000](#); [Doty et al., 1988](#); [Hummel, 1996](#)). An elaborated discussion of our results concerning olfactory sensitivity can be found in the project's final report ([Eis et al., 2005a](#)).

### **Psycho-diagnostic aspects: are the mental disorders observed a consequence of MCS?**

Beside the MCS multicentre study presented here, other studies have shown that environmental patients and, in particular, patients with 'EI/IEI/MCS' suffer

frequently from mental disorders. The announced prevalences ranging between about 40% and above 90% (Black, 1993; Bornschein et al., 2002; Fiedler et al., 1996; Hausteiner et al., 2006; Huss et al., 2004a; Simon et al., 1993; Tarlo et al., 2002; Terr, 1989), depending from study designs, sample sizes and psychodiagnostic methods. Most studies from the 1980s and 1990s were based on very small sample sizes of below 100 or even 50 subjects with environment-related health complaints (Black, 2000). In our study this proportion was approx. 76% for all environmental patients (for MCS positives approx. 80%), compared with 37% for an age and gender matched sample of the general population, both determined with CIDI (12-month prevalence).

It is remarkable that the differences between the MCS groups regarded in the study and the corresponding non-MCS groups were not particularly pronounced. A similar observation is reported by Hausteiner et al. (2006). For example, the proportion of somatoform disorders (12-months prevalence) in the MCS groups amounted to 72–74% compared with approximately 60% in the non-MCS groups. It should be noted that CIDI also includes subthreshold somatoform disorders (via “Somatic Symptom Index”, SSI 4/6, according to Escobar et al., 1987), which might explain the relatively high prevalence, but not however the small difference of prevalences between MCS and non-MCS groups (in all MCS constructs used here). Likewise, the psychometric findings (SAQ, SCL-90-R, WI, etc.) showed no profound differences between MCS and non-MCS groups. Medium effect sizes were observed for the MCS groups only for the complaints (BL/by Zerssen) and for the SCL-90-R dimension “somatisation”. Significantly, the conspicuousnesses decrease from the sMCS group to f1MCS and f2MCS. The key reason for this lies probably in the exclusion diagnosis criteria for MCS. For patients with unambiguously mental disorders the chance of being assigned to the f2MCS group is reduced; this is even more true for the cMCS group (noxious MCS concept). Significantly, in two out of the six environmental centres not a single case of cMCS was confirmed whilst, in contrast, about 80% of the EM outpatients of the clinical-ecologically oriented centre Bredstedt were classified as cMCS (despite the same MCS case criteria). Important in this respect are centre-specific diagnostic assessments, such as the implicit attitudes of investigating clinicians, as no evidence was found for a significant selection bias, as severe cases were not found more frequently at the specialised hospital Bredstedt (see different MCS constructs).

Due to studies, which had resulted in high prevalences of psychic disorders for EI/IEI/MCS patients, the impression had developed in the past that this observation was characteristic for the “MCS syndrome”. With this interpretation it was certainly overlooked that in the studies concerned only IEI/MCS patients were

examined (and/or persons, who were regarded as such), but no other environmentally medical patients. Thus it escaped that high prevalences for psychic disorders also arise in the non-MCS subgroups of environmental medicine patient-samples. In addition it is to be assumed that some studies had operated with a relatively widespread IEI/MCS term by what persons with (subjectively) environmentally related health complaints or “environmental illness” (in a broader sense) were regarded as “IEI/MCS” patients. Amongst these were inevitably also persons, who would have been classified in the non-MCS group in our study. Finally it must also be considered that mental disorders are possibly regarded as exclusion diagnoses – depending on MCS definition/understanding. The situation is obscure in this regard, since not all studies had reported which inclusion and exclusion criteria have been applied in respect to mental disorders. But even if the used MCS definition includes a specification for this, it is not clear how this specification was implemented in the context of a study. Anyhow, for the diagnostics of mental disorders and their differential-diagnostic weighting in the context of MCS a considerable latitude of judgement exists.

Thus, much speaks for the fact that in many studies (see above) with “MCS” patients the high prevalence observed for mental disorders is also to state for other environmental medicine patients (with non-MCS status). Additionally, we could show in our study that there is a subgroup among the environmental medicine outpatients (about 20% of the EM outpatients) with psychometric profiles, which resemble those of clinical psychosomatic/psychiatric populations, particularly with somatisation disorders. The hypothesis that the EM syndromes are variants of somatoform disorders (e.g. see Bailer et al., 2005; Bornschein et al., 2006; Göthe et al., 1995; Hausteiner et al., 2003; Henningsen, 2002; Kraus et al., 1995; Wiesmüller et al., 2003) cannot be dismissed, but this must also be considered for the non-MCS group among the environmental medicine outpatients.

At this feature it should be pointed out to a further problem. By means of CIDI subthreshold somatoform disorders (via “Somatic Symptom Index”, SSI 4/6, according to Escobar et al., 1987) are included, which contributes crucially to the relative high prevalence of the so-called “somatoform disorders” in environmental medicine outpatients (depending on the time-frame considered: 65–72%). For the general population the lifetime prevalence is approx. 20%, after adjustment for gender and age (Dietel et al., 2006). It is to be assumed that according to stricter clinical diagnostic criteria the proportion of seriously psychiatrically disordered persons would be clearly lower among the EM outpatients. Another argument therefore is that approx. 30% of the environmental medicine patients exhibit rather common psychometric profiles and about 50% have only mild to

medium features without clinical-psychiatric relevance. At this the dimensions (not diagnoses!) somatisation, hypochondriasis, depression, obsessive compulsion, and anxiety seem to play a certain role as well as a more pronounced body attentiveness and health perception.

Moreover, Staudenmayer (1996) assumed that stressful life events such as a history of traumatisation and post-traumatic stress disorders (PTSD) can be pathogenetically important for some IEI/MCS patients. A Canadian research group reported a link between IEI and panic responses (Poonai et al., 2000; Tarlo et al., 2002). IEI subjects scored significantly higher than controls on self-reported measures of anxiety, agoraphobic symptoms, stress and depression (Poonai et al., 2001), but somatization questionnaires were not used and high scoring for agoraphobic symptoms is not surprising, because IEI patients avoid places with “environmental pollutants”. The Canadian scientists conclude that IEI subjects may represent a group whose impairment is intermediate between a clinical psychiatric population and a nonclinical population.

Whether the mental disorders are a sequel of MCS or, in contrary, precede them, such that MCS can be seen as expression of a mental or psychosomatic disorder (cf. Henningsen, 2002), is still a matter of debate. Such questions can only be reliably clarified with prospective studies. In contrast, retrospective identification of the onset of the disorder is subject to failures in memory, but it should account for both mental and environmentally related complaints. Such errors are less problematic the longer the time distance between the onset of the mental complaints and the onset of the environmentally related complaints (or vice versa). As was shown in the present study, for about 80% of the environmental patients the mental problems precede the complaints reported in the environmental medicine examination by many years (on average 17 years). The same is true for sMCS and fMCS patients. Although this is only a rough estimation, due to the different instruments used (CIDI and EMQ) and due to the inevitable recall bias, the observed difference is nevertheless so considerable that it cannot be ignored despite the extant data uncertainty. This is, however, at the most an additional indication but no strict evidence for a psychomedical theory of MCS (see Staudenmayer et al., 2003a, b).

The results clearly do not support the hypothesis that mental disorders are merely a concomitant phenomenon or even sequel of the ‘environmental disease’. A study conducted at the speciality hospital in Bredstedt (Bauer et al., 2003) showed that approx. 30% of patients with MCS had had a preceding psychiatric or psychosomatic disorder. According to the opinion of the Bredstedt working group a predisposition of such kind is a ‘vulnerability factor’ for MCS if additionally pollutant burden occurs.

## Conclusions

Despite a uniformly given case definition and appropriate diagnostic instructions the medical assessment concerning cMCS (yes/no/unclear) turned out to be not very reliable since it was significantly influenced by the pathogenetic, nosological and diagnostic views of the examiners and by the “diagnostic culture” of the environmental unit. When we regard only the university centres and restrict our view thus to the diagnostic paradigm of evidence-based environmental medicine, then only relatively small but nevertheless existing centre differences are observable which are due, as far as we know, to the medical indeterminateness of the MCS phenomenon. By implementation of a formal fMCS category a further and, in view of the university centres, satisfactory reduction of the centres differences could be achieved.

With the study approach chosen (primarily a cross-sectional design, based on EM outpatients, secondarily with internal MCS/non-MCS comparison) and in regard of the pragmatic MCS categorisation as well as the not particularly large sample size, only representative for EM outpatients, the underlying questions of the study, respectively, hypotheses H1–H6 (see Study aims and hypotheses) could investigate only to some extent. We will not dwell on the category “clinical MCS” (cMCS) which was diagnosed not at all in the centres of Berlin and Giessen but amounted to more than 80% of the EM outpatients in Bredstedt (cf. instead f1MCS and f2MCS).

The results of the German Multicentre Study on MCS do not support the six hypotheses which have been formulated in regard to an assumed toxicogenic-somatic concept of MCS. We found

- no evidence for a circumscribable symptom pattern or a complex of symptoms in reference to sMCS, f1MCS or f2MCS vs. non-MCS groups (H1);
- no consistent and statistical significant associations between (subjectively incriminated) chemicals and self-reported complaints in the EM outpatients sample or in the fMCS subgroups (H2);
- no statistical evidence, that sMCS and f1MCS can be caused by verifiable “initial exposure” (H3a), whereas the hypothesis could not be properly tested for f2MCS and cMCS, because “initial exposure” serves as a definition criterion for these MCS categories;
- no statistical evidence for increased subsequent trigger exposures in the group of sMCS patients (H3b in respect of sMCS); for the remaining MCS constructs, in particular for f2MCS and cMCS, a testing of hypothesis H3b was not possible in an adequate manner (element of case definition), but multiple logistic regression analyses showed that the differences in regard to the physicians exposure

assessment were due to a clearly pronounced centre's effect (Bredstedt vs. all others) rather than to the underlying MCS definition;

- no significantly different frequencies between any of the MCS groups and the corresponding non-MCS groups or the general population comparison groups for any of the 26 investigated gene variants, which partly deal as markers of susceptibility (H4);
- no significantly better olfactory performance for sMCS, f1MCS or f2MCS patients (Sniffin' Sticks test) in comparison with the corresponding non-MCS groups (MCS patients had only a slightly better identification of odours than non-MCS patients or a external reference group);
- a high proportion of persons with "mental disorders" (approximately 70%) amongst the EM outpatients, where sMCS and f1MCS patients were significantly more likely to be affected than the corresponding non-MCS groups, whilst such differences could not be meaningfully examined for the f2MCS and cMCS categories due to their definition (excluding diagnostics); in general, mental disorders of EM outpatients and also in the subgroups sMCS and f1MCS existed much longer – in the mean 17 years – than the environmental-related complaints, so that H6 ("the mental disorders found in MCS patients are sequels of MCS and occur thus after the onset of environmentally related symptoms") is not supported by the results of our study.

As a qualification, we would like to stress that the results achieved apply only to the MCS constructs used here due to the methodological limitations of the study. It cannot be ruled out that there are persons with a particular chemical sensitivity among the EM outpatients or in populations not seen in EM units, who have, thus, an intolerance to environmental substances hitherto medically (toxicological/immunological) unspecified.

It has to be noted that EM outpatients are a very heterogeneous group according to the results of psychodiagnostic measures (BL, SCL-90-R, SAQ, WI) and CIDI diagnosis. Nevertheless, a fourth to a third of these patients have been psychodiagnostic inconspicuously. The others showed moderately increased psychometric scores (about 50% of EM outpatients) or severely elevated scores as they are found for psychosomatic patients (about 20% of EM outpatients). Predominant were somatisation, depressive mood, anxiety and hypochondriacal tendencies or, in addition, the corresponding disorders. Altogether, we found rather moderate mental/psychosomatic disorders and subthreshold disorders (e.g. like undifferentiated somatoform disorder or the Somatic Symptom Index according to Escobar), whereas the more severe mental disorders, as known from clinical psychiatric population, occurred seldom in EM outpatients.

In our opinion the conventional psychodiagnostic categories (including conventional somatisation disorders) provide no sufficient classification basis for MCS and comparable environmental attributed disorders. To what extent IEI/MCS or related "environmental syndromes" are variants of somatoform disorders, as this and other studies suggest, should be examined in further sophisticated investigations. In our view, a deeper understanding can be achieved only in the scope of complex socio-psycho-somatic models with consideration of components, such as perceptual, cognitive and emotional aspects, persuasive influences (environmental doctors, support groups, mass media), opinions, focus of attention, processes of conditioning, focus on autonomic sensations, self-attentiveness and alexithymia, processes of attributions and externalization as well as the evaluation of neurobehavioral features using CNS-functional diagnostic methods.

According to all available data, environmental-psychosomatic research approaches should be given priority in future studies. Allergologic-immunologic focal points seem to be also necessary for the explanation of somatic susceptibility correlates. Above all, clinical-experimental studies on the basis of double-blind, placebo-controlled and randomised exposure studies are urgently needed. However they will rise, in addition to ethnical problems, an array of examination problems which are by no means trivial, and result from diverse blinding problems and from the necessity of complex exposure scenarios in the low-dose domain (Bornschein et al., 2004; Devriese et al., 2004; Eis et al., 2003a; Haumann et al., 2003; Österberg et al., 2003; for review of older literature see Staudenmayer, 2001). Nevertheless there is no alternative to such studies from a methodical point of view. Experimental and non-experimental examinations in research on IEI/MCS must meaningfully complement one another.

On balance the result of the investigations do not support the assumption of a toxicogenic-somatic basis for the MCS phenomenon. In contrast, numerous indicators for the relevance of behavioural accentuations, psychic alterations or psychosomatic impairments were found in the group of EM-outpatients with subjective "environmental illness". Given the methodological limitations of the study these results should be considered as mere indications. However, their importance increases when considered in conjunction with the multitude of other relevant studies with similar results and with many experts' opinions.

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