Medically unexplained symptoms and somatoform disorders: prevalence, course and comorbidity.

An eleven year general population study in Norway.

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About research method:
“First record what you see and then investigate the functions of the observed form.”

“Let us keep looking, in spite of everything. Let us keep searching. It is indeed the best method for finding, and perhaps, thanks to our efforts, the verdict we will give this patient tomorrow will not be the same as we must give him today.”

Jean-Martin Charcot (1825-1893) (Charcot 1987)

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Background

Among outpatients presenting with physical symptoms, one third have been found to be not fully medically explained (Kroenke 2003). Modern history of Somatoform disorders (SDs) began in the 1960-70's when the Hysteria disease was renamed to Briquet's syndrome, after the work of Purtell et al. in 1951 (Purtell, Robins *et al.* 1951) and Perley and Guze in 1962 (Perley, Guze 1962). With the introduction of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM)-III (American Psychiatric Association 1980) the category of Somatoform disorders (SDs) appeared and Briquet's syndrome renamed into Somatization disorder (SDz). Diagnostic criteria of the SDs category were based the exploration of MUSs, and a 37-item symptom list was devised from the old 59-item hysteria symptom list for examination of SDz (DeSouza, Othmer 1984; Katon, Lin et al. 1991). Although SDz was validated by the five Feighner criteria (Feighner, Robins *et al.* 1972), like other disorders of the DSM-III, the SDs criteria have mainly been descriptive, pragmatic and derived from consensus (First 2005). Since their introduction the SDs have been constantly been subjected to change in classification revisions, of both DSM-IV (American Psychiatric Association 1994) and *International Classification of Diseases, Tenth Revisio*n (ICD)-10 (World Health Organization 1993). Alternative diagnostic constructs and suggestions have increasingly been put forth along the way, and the Multisomatoform disorder (MSD) based on the exploration of current and not lifetime symptoms accepted in the primary care version of DSM (DSM-IV-PC) (American Psychiatric Association 1995). The ongoing debate of what to do with SDs in the future and the need for change (Wise, Birket-Smith 2002) is at the moment quite compelling. All suggestions have been made, from, keeping the SDs category as today, (Hiller, Rief 2005; Hiller 2006), relocating it within the next DSM-V to "Psychological Factors Affecting Medical Conditions" category (Fava, Fabbri et al. 2007), moving it outside to Axis III, General Medical Conditions (Kroenke 2006) and even - radically - abolishing it altogether (Mayou, Kirmayer et al. 2005). With the increasing pressure of mental disorders and diagnoses to be more empirically based, the crucial question is whether there is enough evidence to justify their belonging to the realm of mental disorders or not (Rief, Isaac 2007).

On this background this thesis has sought to contribute to the present SDs discussion, by elucidating the distinction of medically explained (MES) and unexplained symptoms (MUS),

and exploring differences in lifetime and current symptom criteria of SDs, exploring course and stability, overlap and comorbidity with anxiety, depression and musculoskeletal disorders and presenting prevalence based on newer suggested current MUSs criteria for the first time in Norway.

Research questions

The topic of the present thesis is on somatoform disorders (SDs) and their symptoms, i.e. medically unexplained symptoms (MUSs). The thesis endeavours to answer five main research questions.

- How accurate is the recall of lifetime symptom data (both medically unexplained and explained), and what are the predictors for the failure at follow-up to recall symptoms reported previously at baseline, i.e. symptoms "lost"? (Paper I)
- What is the course of medically unexplained pain (MUS-pain) (a disorder at the one-symptom level) over time, and what are the predictors of recent MUS-pain? (Paper II)
- What is the extent of overlap, or comorbidity, with anxiety and depression, what is the stability of SDs, and are there differences between SDs according to "lifetime" and "current" symptom criteria? (Paper III)
- What are the prevalence rates of current SDs in Norway in 2001? (Paper IV)
- Should current SDs be regarded as mental or physical conditions? Are risk factors of severe current SDs different from those of anxiety/depression and musculoskeletal disorders, and are there differences in psychological distress, utilization of health care and medication in the co-morbid subclasses of severe current SDs (Paper IV)?

Material and methods

The material of this thesis is based on two general population samples, of randomly drawn subjects 18 years or older, from two geographical areas in Norway (Lofoten, Northwest coast district and Oslo, Holmlia suburb area). The thesis consists of four papers I-IV. The three first (Paper I-III) are based on respondents interviewed with the Composite International Diagnostic Interview (CIDI) over a time span of 11 years (in 1990 at baseline and 2001 follow-up), and the last (Paper IV) on new respondents CIDI interviewed in 2001.

Paper I deals with the stability of lifetime MUSs and MESs, and the reliability of the MUS/MES distinction, as well as that of symptom recall. In Paper II the course of MUS–pain (representative of SDs at the one symptom level) is described, and factors related to chronicity and predictors of MUS-pain in 2001 explored.

Paper III and IV deal with the disorders of the SDs category. In Paper III, disorder discreteness and overlap are examined, and differences between SDs according to lifetime or current symptom criteria explored. Paper III also examines stability of SDs and comorbidity with anxiety and depression. In Paper IV, prevalence of current SDs in 2001 is presented and psychological distress examined by the Hopkins Symptom Checklist 25-item scale (HSCL-25) in comorbid subclasses of SDs. Whether current SDs should be regarded as mental or physical conditions is discussed in Paper IV on the basis of the differences found in comorbid subclasses of SDs and differences in risk factors of current SDs, versus anxiety/depression and musculoskeletal disorders.

Results

A wide range of individual lifetime symptoms, from 22 to100%, were lost to recall at follow-up. Recall was better when the number of symptoms was grouped (approx. 50% for 1 to 3 symptoms). The large degree of measurement error was mainly due to faulty recall over time. Gender and age emerged as significant ($P<.01$) markers for MUSs-lost, and a decrease in physical morbidity for MESs-lost. Men tended to forget more symptoms than women, and younger respondents with high levels of baseline MUSs to remember slightly better at follow-up. The transition of MUS to MES and visa versa over time was large, casting doubt about the reliability of the medically unexplained and explained distinction at when applied to lifetime symptoms.

A small stable (present at baseline and present at follow-up) group of recent MUS-pain sufferers (8% out of all re-interviewed and 33.6% out of those with recent MUS-pain at baseline) was identified, almost all were women. Female gender was a significant ($P<.05$) marker, giving a twofold risk compared with men of having recent MUS-pain in 2001. Only co-morbid depression in 2001 and not the report of recent MUS-pain in 1990, remained a significant ($P<.05$) predictor, increasing the likelihood of having *recent* MUS-pain at follow-up threefold (Paper II).

Overlap for some disorders, such as PD and SDud was 100%, in both 1990 and 2001. Clear distinctions between individual SDs were very hard to make, except for a slight distinction being revealed between pooled “current SDs” and “lifetime SDs” (i.e. the SDs were pooled according to the MUSs criteria being either current or lifetime). Co-morbidity by OR ranged from 2.9 to 5.1 for depression and from 2.0 to 2.5 for anxiety. Co-morbidity was somewhat more pronounced for current SDs compared to lifetime SDs, and current SDs 4 times more likely to occur among depressed respondents. Diagnostic stability was highest not

for lifetime SDs but for current SDs (retrospective consistency; 42% for current SDs, 33.1% for lifetime SDs). Among individuals with a SD at baseline, 54% to 67% fulfilled the criteria of *any* SD at follow-up.

The overall prevalence rate for pooled severe current SDs was 10%. Prevalence rates were generally twice as high for women. The main risk factor associated with severe current SDs was anxiety. Co-morbidity of severe current SDs with anxiety/depression and/or musculoskeletal disorders was 69%. Psychological distress in the subclass "only severe current SDs" (without any anxiety/depression/musculoskeletal co-morbidity) was significantly higher ($P < .05$) compared to respondents without disorders. Mental healthcare utilization among those with severe current SDs depended on the co-morbidity of anxiety/depression, and not on the SDs diagnosis alone.

Conclusion

Lifetime symptoms are often forgotten over time. Lifetime data elicited in community surveys by diagnostic instruments such as the CIDI should be viewed with caution. Methodological errors weakening the data credibility could lead to false impressions of true change over time. A distinction between medically unexplained and explained physical symptoms is difficult to maintain.

A course of re-currency and remittance of MUS-pain is the rule rather than the exception. Except for a small group (mainly women) prone to chronicity, the prognosis of MUS-pain is relatively good. Clinicians should examine for depression when confronted with MUS-pain patients and be aware of the increased twofold risk for women compared to men to have debilitating pain symptoms over a long time.

The prevalence rate of severe current SDs in 2001 is 10%. Prior depression and physical disease are risk factors for current SDs, whereas only prior anxiety is for lifetime SDs. Present anxiety is a main risk factor associated with severe current SDs. Overlap between different SDs is high (up to 100%). Diagnostic stability of current SDs is not much different to that of lifetime SDs. Current SDs are 4 times more likely to occur among depressed respondents and the comorbidity of severe current SDs with anxiety/depression and/or musculoskeletal disorders is 70%.

Comorbid symptoms of anxiety/depression rather than medically unexplained symptoms per se, should qualify the patient for a psychiatric diagnosis. Disorders of the SDs category should be merged in future revised classifications. Future diagnostic criteria should be based on current rather than lifetime symptoms.

Acknowledgements

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Oslo, March 2007

Kari Ann Leiknes

Preface

The paradoxes of counting are many, we can count people but not individuals, and when numbers fail we usually collect more numbers, but counting the wrong thing gives no progress. For scientists, numbers are an international tool allowing us to speak the same language.

However, this thesis is not only about the counting of symptoms. Motivated by my clinical experience as a psychiatrist in the field of psychosomatic medicine, from endless medical history taking and the counting of diverse medically unexplained symptoms in order to explore for the presence of somatoform disorder(s), this thesis is also about by the learning of the meaning behind such figures. Similar to my psychosomatic patients and their relentless search for reasons behind their symptoms and for better ways of coping, this research work is about arduous scientific probing, penetration and explanation.

The beginning was in 2001, when I was offered a research grant in the Oslo-Lofoten mental health and general population follow-up study. The first year passed participating in the extensive collecting of data, interviewing and relocating "old" respondents from 1990, discovering how laborious the research task of longitudinal epidemiological studies was and how valuable the fundament made in 1990 by previous conscientious research colleagues was. Not only did I make telephone calls, obtain consent, make interview appointments, conduct computer based interviews in the afternoons and evenings, in diverse private homes or working places, but I also participated in the teaching programme and education of lay interviewers. In order to ensure the highest possible response rate, I was also faced with the challenge to travel, conducting several follow-up interviews with respondents who had moved to other parts of Norway. My contribution in the data collecting and punching from paper to statistical data program prompted my understanding of how important it was to ensure high quality raw data. Interrupted by a period of clinical work (2002 to 2003) at the Department of Psychosomatic Medicine, Rikshospitalet, I returned again to my research work in 2004. I am indeed grateful to all Oslo-Lofoten research colleagues for finalizing the collecting of 2001 data under my leave of absence. On returning, the remaining research time was allocated to extensive 1990 and 2001 raw data analyses and to collaborative scientific article. The ultimate aim of my research work being to unravel a little more of the intriguing puzzle of medically unexplained symptoms and their related syndromes. Hopefully, when adding a new building stone of knowledge onto the existing one, the greater understanding in the end will contribute to an increased quality of psychosomatic medicine, to benefit of future patients.

Abbreviations

CIDI	Composite International Diagnostic Interview
CI	Confidence interval
DSM	Diagnostic Statistical Manual of Mental Disorders
ECA	Epidemiologic Catchment Area study
FGID	Functional Gastrointestinal Disorders
FSS	Functional somatic syndromes
HC	Hypochondriasis
HSCL-25	Hopkins Symptom Checklist 25-item scale
ICD	International Classification of Diseases
MES	Medically explained symptom
MSD	Multisomatoform disorder
MUS	Medically unexplained symptom
MUS-pain	Medically unexplained pain symptom
NCS	National Comorbidity Survey
OR	Odds ratio
PD	Pain disorder (chronic) associated with psychological factors (Synonymous to Persistent somatoform pain disorder)
PSD	Physical symptom disorder
SD	Somatoform disorder
SDnos	Somatoform disorder not otherwise specified
SDud	Undifferentiated somatoform disorder
SDz	Somatization disorder
SSI	Somatoform Symptom Index
SSI-3/5	Abridged somatoform disorder by SSI-3/5 (3 symptoms for men/5 for women)
SSI-4/6	Abridged somatoform disorder by SSI-4/6 (4 symptoms for men/6 for women)
WHO	World Health Organisation

List of papers

Papers I-IV

I *Leiknes KA,* Finset A, Moum T, Sandanger I.
Methodological issues concerning lifetime medically unexplained and medically explained symptoms of the Composite International Diagnostic Interview: a prospective 11-year follow-up study. J Psychosom Res 2006;61:169–79.

II *Leiknes KA*, Finset A, Moum T, Sandanger I.
Course and predictors of medically unexplained pain symptoms in the general population. J Psychosom Res 2007;62:119-28.

III *Leiknes KA*, Finset A, Moum T, Sandanger I.
Overlap, comorbidity and stability of somatoform disorders, and the use of current versus lifetime criteria. Psychosomatics [in press, accepted 2006].

IV *Leiknes KA*, Finset A, Moum T, Sandanger I.
Current somatoform disorders in Norway: prevalence, risk factors and co-morbidity with anxiety, depression and musculoskeletal diseases. [submitted].

The papers will be referred to by their Roman numerals.

1. Introduction and background

This thesis is about physical complaints that cannot be fully explained by a known general medical condition, the direct effects of a substance or a medication. The terms applied in this thesis for such complaints and their related disorders will be medically unexplained symptoms (MUSs) and somatoform disorders (SDs). In order to understand the context and controversy in which MUSs and the category of SDs find themselves today, and to provide a background for the discussion of contemporary classification issues, a brief historical overview is needed, followed by a clarification of terms and a short depiction of where this field in medicine stands today.

1.1 Historical background

The roots of SDs and MUSs as we know them today, can be traced all the way back to ancient Greek and Egyptian medicine (Merskey, Merskey 1993; Trimble 2004) up to the downfall of Hysteria (Micale 1993) in the twentieth century.

1.1.1 Ancient Greek medicine

In the time of ancient Greek medicine, Hippocrates (460-370 BC) and Plato (428-347 BC), Hysteria was described as a condition afflicting women and the symptoms attributed to the uterus (Micale 1990; Merskey, Merskey 1993). Hence the disease name from Greek *hystera*, the womb. Similarly Hypochondria was depicted as a disease afflicting mostly men and the symptoms attributed to the upper abdomen (Berrios 2001), again taking on the name from Greek *hypochondrium*, meaning the abdominal region underlying the rib cage. Mobility of abdominal organs was then believed to be the source of disordered emotions, and hysterical symptoms were explained by a wandering womb (Allison, Roberts 1994). The causal mechanisms of Hysteria were poetically and lavishly attributed to the arid (non menstrual) and angry womb, behaving like “an animal within an animal” and migrating around the body cavity exerting pressure on other organs, such as the liver and lungs (Merskey, Merskey 1993). Although understood differently today, the medical names of diverse hysterical symptoms described from this time, for example feelings of suffocation or breathlessness (*dyspnoe*), loss of voice (*aphonia*) and lump feeling in throat (*globus hystericus*), pain during intercourse (*dyspareunia*) have lived on.

1.1.2 Sixteenth to nineteenth century

With increasing anatomical knowledge from dissection of the human body in the 16th century by the great masters of anatomy such as Andreas Vesalius (1514-1564) (Vesalius 1968) and Leonardo da Vinci (1452-1519) (Cianchi 1998), ancient Greek theory of mobile body organs was gradually forsaken. Continuing this, a model of mental illness arose in the 17th century concentrated on the nervous system from the influential works of Thomas Willis (1621-75) and Thomas Sydenham (1624-89) (Trimble 2004). Even though a clear etiological shift was made, moving the anatomical placement of mental disorders from the body to the mind/brain, the Scottish physician Sir Robert Whytt's (1714-66) still believed that hysteria affected females and hypochondria males (Berrios 2001; Trimble 2004). Alongside his discovery of the reflex, Whytt introduced the term "nervous" and divided patients with mental illnesses into three groups: the nervous, the hysterics and the hypochondriacs (Berrios 2001; Trimble 2004). A broad etiological theory of all diseases being diseases of the nervous system, was further launched by William Cullen (1712-1766) and with nervous disorders being transformed to neurosis, Hypochondria was re-conceptualized into a form of insanity (Berrios 2001).

1.1.3 Nineteenth to twentieth century

A landmark of extensive influence in the mid 19th century, which can be traced up to the somatoform diagnoses of today (see, 1.5 Classification of somatoform disorders) was the work of the French doctor *Pierre Briquet* (1796-1881) (Briquet 1859). Based on personal examination of about 450 patients Briquet described extensively the symptoms and treatment of Hysteria in 1859, as a condition of multiple physical symptoms with "pseudo-neurological" character having no clear medical (physical) evidence for the cause (Briquet 1859; Trimble 2004). In contrast to earlier beliefs, hysterical symptoms were now clearly described to occur among men.

In the late nineteenth century, often referred to as the "age of hysteria" the renowned French neurologist *Jean-Martin Charcot* (1825-1893), claimed that there was a female preponderance of Hysteria (ratio 1:20), and declared the cause to be neuropathological in males and psycho-pathological in females (Micale 1990). Similar to Briquet, Charcot believed Hysteria to be neurological and genetic in origin, and although bodily in symptomatology, seated in the mind or head. In his differential diagnostic struggle between epilepsy and hysteria, Charcot continued to uphold a strong association between hysterical symptoms and the reproductive organs for both genders (Charcot 1987; Micale 1990). As quoted from one of

Charcot's famous Tuesday case demonstrations at the Salpêtrière Hospital in Paris on Hysteria (Charcot 1987):

«….*c'est toujours la chose genitale, toujours*….»

(…it has always to do with the genitalia, always….)

Directly influenced by his own medical theory, disease explanation and causation, Charcot, utilized hypnotic treatment techniques and developed technical genital compression devices, such as the "ovary corset" for his female patients, whereby physical external point pressure could be induced on particular body zones in the pelvic area, in order to start and stop hysterical fits (Micale 1990; Hermundstad 1999).

Due to the experience of hypnotic abreaction techniques failing to relieve patients of their hysterical symptoms, *Sigmund Freud* (1856-1939), a former pupil of Charcot, turned to systematic analyses of the patient's free associations (Gabbard 2004). Thus, in this strife to understand the symptoms of hysteria and the unconscious factors or etiological mechanism behind the symptoms, *psychoanalytical theory* was developed. A clear turning point in the history of medicine was hereby created, and emotions regarded as no longer seated in the body but in the brain. Although some of Freud's original ideas have required revision, his theory has resulted in the evolution of modern psychiatry and neurosciences (Gabbard 2004), laying the foundation for the need to examine brain function, the mapping of conscious and unconscious memory and the emotional brain (LeDoux 1996).

Fifteen years after his death, the diagnosis of Hysteria established by Charcot through rigorous clinical observation was officially denounced by his successor Joseph Bakinski (1857-1932) and colleagues of the Parisian neurological society (Micale 1993). A new concept and the re-ordering of symptoms with unknown disease pathology into groups of symptoms called "hysterical syndromes" were suggested as a replacement. A main reason behind this development was the discovery of the Spirochaetes bacterium, Treponema pallidum, in 1905 by the German bacteriologist Fritz Schaudinn (1871-1906) (Waugh 2005), giving Charcot's followers the ability to differentiate neurosyphilis from other psychiatric and neurological diseases (Micale 1993). Since many of Charcot's male hysteria cases came from the working class population, the likelihood of misclassified neurosyphilis was quite high. By the beginning of the twentieth century the Hysteria category had vanished completely from psychiatric nosologies (Micale 1993; Allison, Roberts 1994). Even so, the need for Hysteria's reappearance has recently been advocated (Akagi, House 2002).

1.1.4 Briquet's syndrome

When Hysteria was renamed to Briquet's syndrome in the 1960-70's, the modern history of the SDs began. The background for the renaming was the research work of Purtell et al. in 1951 (Purtell, Robins *et al.* 1951) and that of Perley and Guze in 1962 (Perley, Guze 1962). The reason for the renaming was to reduce controversy and avoid the pejorative implications associated with Hysteria (Guze, Woodruff, Jr. *et al.* 1972). Following the same principles as that described by Pierre Briquet in 1859, and taking on his name, Briquet's syndrome was defined (Guze, Woodruff, Jr. *et al.* 1972) as:

"A polysymptomatic disorder beginning early in life, characterized by recurrent or chronic ill health, presenting with dramatic, vague or complicated medical history. Characteristic features of the clinical history are many and varied pains, anxiety symptoms, gastrointestinal disturbances, urinary symptoms, menstrual difficulties, sexual and marital maladjustment, nervousness, mood disturbances and conversion symptoms. Frequent visits to physicians, excessive hospitalization and excessive surgery."

Diagnostic criteria were derived from this definition and checklist criteria based on 59 symptoms distributed in 10 groups were presented in 1972 by Feighner et al. (Feighner, Robins *et al.* 1972). (See Appendix 1 for the symptom checklist criteria and grouping.) The diagnostic validation by the Feighner criteria (see also Table 1) which made Briquet's syndrome eligible as a psychiatric disorder was based on 50 patients diagnosed with Hysteria in an observational study from 1951 (Purtell, Robins *et al.* 1951) and a follow-up study in 1962, including a family study, consisting of 39 patients (Perley, Guze 1962; Guze 1967). In the follow-up sample, only 2 out of the 39 were men, and both men in addition had other diagnoses at follow-up. Similarly, Hysteria was diagnosed among 14% of the female relatives in the same female dominated sample.

1.2 Somatization and somatoform

Under the strong influence of psychoanalytical theory, the term "somtization" was introduced in the beginning of the 20th century. The neologism "somatization" referring to the German word "Organsprache" first appeared in the writings of the Viennese psychoanalyst *Wilhelm Stekel* (1868-1940) and was first established by Stekel's English translator *JS van Teslaar* in 1925 (Marin, Carron 2002). The original meaning of "Organsprache" was "physical symptoms expressing physical conflict" - in content quite different from the psychoanalytically influenced somatization definition: "conversion of emotional states into

physical symptoms". The concepts of early psychoanalytical theory posited that physical symptoms could be manifested in the body, as a reaction to unconscious conflicts of the mind. This bodily conversion concept, referring to the patient's symbolic expression of mental distress as somatic symptoms, was further strengthened in the 1970s and 1980s by Kleinman (Kleinman 1977) and Lipowski (Lipowski 1987) and by Ford's work with the introduction of the "somatizing" and SDs (Ford 1986). A definition of somatization which is still accepted today was proposed by Lipowski (Lipowski 1988), namely "a tendency to experience and communicate psychological distress in the form of somatic symptoms." Although this process-orientated definition is still accepted today, it is not easy to operationalize, hence a second definition was put forth. Crucial to this definition was the absence of an underlying medical condition and the presence of psychological factors that were either causing or contributing to the symptom (Kroenke, Rosmalen 2006), thus establishing somatization and SDs according to the number of clinically significant medically unexplained symptoms (MUSs) (Kirmayer, Robbins 1991).

1.3 Symptoms

The word symptom, derived from Latin symptōma, and Greek sumptōma, sumptōmata meaning "anything that has befallen one" is defined in the American Heritage dictionary as "a characteristic *sign* or indication of the existence of something else"(2000). Traditionally a symptom has been interpreted as "any sensation or change in bodily function experienced by the patient and associated with a particular disease". Disease in this sense has in both the doctor's and patient's mind been connected with a physical disorder and a "medically explainable" anatomical or biological mechanism.

Clear tissue pathology or biological correlates of symptoms have not always been so easy to find. In the struggle of putting aside the term hysteria and with the intent of studying somatization free from its legacy (Wool, Barsky 1994) by applying neutral terminology, the terms medically explained symptoms (MESs) and medically unexplained symptoms (MUSs) were introduced by Melville (1987) (Melville 1987). The identification of MUSs has in practice been done by exclusion, i.e. that which is left when the doctor cannot find any objective data or conventionally defined medical/physical disease to explain the patient's complaints (Wessely, Nimnuan *et al.* 1999). The expressions "subjective health complaints" (Ihlebaek, Eriksen *et al.* 2002) and "functional somatic symptoms" (Wessely, Nimnuan *et al.* 1999) have also been used synonymously to MUSs.

Symptoms are the reasons why a person goes to the doctor and most of a physician's professional life is spent dealing with symptoms (Komaroff 2001). More than one half of all outpatient encounters is reported to be due to symptoms, and out of these one half are pain complaints (Kroenke, Rosmalen 2006). Among outpatients presenting with physical symptoms, one fourth (20 to 25%) have been found chronic or recurrent and one third (33%) to be MUSs (Kroenke 2003). However, the dichotomous concept of physical symptoms being either explained by disease pathology *or* unexplained by mental illness or psychopathology, does not seem to fit so well any longer into modern medicine (Bradfield 2006). Symptoms-based research is a growing field of scientific inquiry (Kroenke 2001), and knowledge concerning specific symptoms is increasing, for example with respect to chronic dizziness in neurology (Staab 2006), chronic pelvic pain, and dyspareunia in gynaecology (Dennerstein 2005; Haugstad, Haugstad *et al.* 2006). Although diagnoses at the single one-symptom level have been warned against (Dennerstein 2005), for the patient, no matter what the cause or disease process, one or more very bothersome physical or mental symptoms are not only the sign(s) and the "something, indicating something else" but also the disease itself (Hahn 1999).

The controversies over MUSs and "syndromes of MUSs", be they mono– or poly symptomatic conditions, have increased over the past years, and issues concerning how to conceptualize, classify, validate, and name these conditions in the future have been undergoing vigorous debate (Wessely, Nimnuan et al. 1999; Wise, Birket-Smith 2002; Wessely, White 2004; Hiller, Rief 2005; Mayou, Kirmayer et al. 2005; Fink, Rosendal et al. 2005; Rosendal, Fink et al. 2005; Binik 2005; Bradfield 2006; Kroenke 2006; Sykes 2006; Sharpe, Mayou et al. 2006; Starcevic 2006; Rief, Henningsen et al. 2006; Creed 2006b; Fink, Toft et al. 2007). Not only do symptoms still continue to puzzle, but also to constantly split the medical field in a "mind or body" approach (White, Moorey 1997; Komaroff 2001). In spite of an integrated biopsychosocial approach having won acceptance (Engel 1997), the controversy between "organic" or "functional" disease-states still seems to linger at the bedside.

1.4 Terms and definitions

Terms relevant to this thesis, definitions and nomenclature related to SDs and their symptoms are further clarified below.

1.4.1 Medically explained and unexplained symptoms

In view of the fact that the Somatoform Section of the Composite International Diagnostic Interview (CIDI), used in the studies of this thesis, is based on the probing and exploration of clinically significant physical symptoms, categorizing them as either MES or MUS, with the intent of these terms being neutral, the terms MES and MUS corresponding to the definitions by Melville (Melville 1987) will be used in this thesis:

i) MES(s) – symptom(s) which *can* be attributed to a valid disease or known pathological mechanism.

ii) MUS(s) – symptom(s) which *cannot* be attributed to any known valid disease or pathological mechanism.

1.4.2 Somatization

For the purpose of research, three forms of somatization have been identified by Kirmayer and Robbins (Kirmayer, Robbins 1991), namely i) high levels of MUSs, ii) levels of somatic preoccupation or illness worry beyond what is expected for demonstrable disease and iii) predominantly or exclusively somatic presentation of psychiatric disorder, most commonly depression and anxiety. In this thesis somatization will be used according to definition i) above, i.e. as high levels of MUSs.

1.4.3 Psychiatric epidemiology

Psychiatric epidemiology can be defined as the study of mental illness in populations. The essence of all epidemiology is about what to measure and how to measure it. A good psychiatric epidemiological study depends not only on the selection of a representative and suitable population sample, but on a valid, reliable and usable case definition, and case establishment as well as the identification of relevant risk factors.

1.4.4 Disease, illness, disorder, syndrome, functional, organic, comorbidity

According to the Merriam-Websters Online Dictionary (2005) the above terms can be defined as:

Disease: a condition of the living animal or plant body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms
Illness: an unhealthy condition of body or mind - synonymous to *malaise*: a generalized feeling of discomfort, or lack of well-being that can be associated with a disease state.
Disorder: an abnormal physical or mental condition (noun)
Syndrome: a group of signs and symptoms that occur together and characterize a particular abnormality or condition ***or*** a set of concurrent things (as emotions or actions) that usually form an identifiable pattern
Functional: affecting physiological or psychological functions but not organic structure
Organic: relating to, or arising in a bodily organ – o*rgan*: a differentiated structure (as a heart, kidney) consisting of cells and tissues and performing some specific function
Comorbidity: refers to the co-occurrence of disorders within persons, i.e. two or more distinct concurrent disorders, occurring in the same person at the same time.

In the 19th century the terminology: "nervous and mental *diseases*" was customary, based on the assumption that organic origins would soon be found (Taylor 1983). However, since this has not uniformly been the case, the terms mental *illness* or *disorder* are found more appropriate expressions in today's medicine. The term *disorder* is applied to those conditions where function is altered without identifiable morphological change, often implying an unknown or psychological cause. In other words *disorder* implies a dysfunction, resulting in the individual being at risk for experiencing harm – in the form of *distress* or *disability* (Wakefield, Spitzer 2002). Distress refers to the consciously perceived painful effects of the condition and disability to the extent that the condition interferes with social expectations, work or activities.

The term *illness* is broader than disease and disorder since it also includes the patient's experience, in addition to the physician's biomedical disease concept (Longstreth 2005). On the other hand since the patient presents with his/her illness by bringing to the doctor their own idiosyncratic expressions, illness can only be a partial representation of any particular disease or disorder (Trimble 2004). The term *syndrome* implies a more complex bio-psycho-social disease concept, in that it applies a set or group of symptoms (symptoms of either bodily/organic and/or psycho-social/emotional character) which collectively define or characterize a disease or disorder. In the field of psychiatry syndromes are in effect the clinical representations of illness (Trimble 2004). The term *functional*, has implied meaning no demonstrable organic basis (for example, "functional somatic symptoms") (2001) or been used as an synonym for a mental disorder (Trimble 2004). When asked about diverse

diagnostic labels, including the terms “functional”, “medically unexplained”, “psychosomatic” and “hysterical”, patients have preferred the term “functional” (Stone, Wojcik *et al.* 2002). Today, *functional* is recommended used in contemporary medicine to indicate an altered function in the nervous system and not as a synonym for psychogenic or a mental disorder (Trimble 1982). For example in Functional Gastrointestinal Disorders (FGID) (Jones, Crowell *et al.* 2007), functional implies a complex malfunctioning or disturbance of the gut in, myogenic, neural and hormonal control mechanisms also involving psychosocial factors and emotional functioning. The term *organic*, implying a biological origin and basis, has often been used as the antonym of functional. The term organic mental disorder is still used in ICD-10, and applied to such disorders as delirium and dementia. However, organic is not applied in DSM-IV, due to the incorrect implication that other mental disorders have a non-biological basis. The term *comorbidity* referring to the possibility of different diseases occurring simultaneously in the same person will be used synonymously to co-occurrence and concurrent (Krueger 2002).

In this thesis the terms mental disease, illness, disorder and syndrome will be used synonymously (Taylor 1983). The terms functional and organic will be used when relevant in the background literature, discussion and/or to future suggested diagnostic changes.

1.4.5 Psychiatric taxonomy, diagnostic validity, reliability and utility

Psychiatric taxonomy refers not only to the classification of mental illness and disorders but also to the *principles* underlying the classification. The term “taxon” meaning “class, category or type” with plural “taxa” is increasingly used in the ongoing DSM-V diagnostic debate (Joiner, Jr., Schmidt 2002). Given a new taxon, the improvement of the taxonomy has been suggested judged by whether it is i) more comprehensive, ii) easier to use, iii) deals better with the issues of “clinical significance”, iv) has a higher reliability, and v) has a higher validity (Kendell 2002).

Validity in science has generally been accepted to mean “the nature of reality” (Kendell, Jablenski 2003). Formal criteria for establishing the validity of a mental disorder were first described by Robins and Guze (Robins, Guze 1970) and later known as the *Feighner criteria* (Feighner, Robins *et al.* 1972) when introduced together with DSM-III. The five-step process given in Table 1, has dominated to date as the gold standard for establishing validity of a mental disorder or diagnostic class (Beauchaine, Beach 2006). An adaptation of the Feighner criteria into antecedent, concurrent and predictive validators were later presented by Kendler (Kendler 1980) and additional external validators, including modern genetics and

neurosciences by Andreasen (Andreasen 1995), see Table 1. Validation by course of the disease, preceding that of disease onset has also been emphasized (Panzetta 1974), as well as making validation progress by understanding the relationship between the concepts of dysfunction, disability and distress (Wakefield, Spitzer 2002).

Table 1. Diagnostic construct validity and Feighner criteria

The Five Feighner Phases:	**Diagnostic validity - establishing a clinical syndrome by:**
1. Clinical description	Cluster of symptoms and etiologic precursors
2. Laboratory studies	Reliable physiological, biological and/or psychological markers
3. Delimitation from other disorders	Readily definable exclusionary criteria
4. Follow-up study	Predictable course
5. Family Study	Increased rates of the same disorder among first-degree relatives
Type of validators:	
1. Antecedent	Familial aggregation, premorbid personality, demographic, precipitating factors
2. Concurrent	Tests, including psychological tests
3. Predictive	Diagnostic consistency over time, rates of relapse and recovery, response to treatment
4. Additional external	Molecular genetics and biology, neurochemistry, neuroanatomy, neurophysiology, cognitive neurosciences

Validity of a diagnosis refers to the adequacy with which it reflects the clinical reality and medical knowledge about the condition. Validity is often described from several aspects, for example a mental disorder can be accredited as valid by:

i) Face validity – the extent of obviousness, how easy the disorder is recognized clinically

ii) Content validity – the extent to which all component elements of the disorder (as conceived) are measured

iii) Consensual validity – the extent to which experts agree on how real the disorder is

iv) Criterion (or concurrent) validity – the extent to which the disorder coincides with the "gold standard criterion", i.e. a standard believed to be true

v) Predictive validity – the extent to which the disorder has a typical outcome, course, prognoses, complications or treatment response.

vi) Construct validity – the extent to which the disorder can be verified by an underlying construct or causal mechanism/etiology (or genetics)

In summary, diagnostic validity has been defined by Beauchaine and Beach (Beauchaine, Beach 2006) as the extent to which a symptom criterion set identifies a non-

arbitrary class of individuals who suffer from a single condition that confers increased risk of morbidity, mortality and/or psychological distress.

Reliability of an instrument or test can be defined as the capacity to give the same result. Diagnostic reliability in this thesis will be explored by i) prospective consistency: the extent to which the diagnoses at baseline are the same at follow-up and ii) retrospective consistency: the extent to which the diagnoses at follow-up were the same at baseline.

Since the study of mental disorders generally struggle with issues of low validity, diagnostic utility (or usefulness) defined as the essence of what the diagnosis conveys regarding course, outcome, and aetiology (Kendell, Jablenski 2003) also is vital. In addition to utility, diagnostic discreteness or the finding of a "point/zone of rarity" which discriminates or separates the disorder from other neighbouring disorders also is a tool in the work to attain a more valid taxonomy (Kendell 2002). Although schizophrenia has been demonstrated to have such a zone of rarity or discontinuity, discriminating it from other psychiatric syndromes, this has not been so easy to demonstrate for other psychiatric syndromes (Kendell 2002).

1.5 Classification of somatoform disorders

The category of SDs appeared for the first time in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM)-III (American Psychiatric Association 1980). The first disorder in the whole SDs category was Somatization disorder (SDz), the renamed multi- or polysomptomatic equivalent to Briquet's syndrome (DeSouza, Othmer 1984). A reason for the re-naming and re-classification was to separate Briquet's syndrome from conversion, Pain disorder (PD) and Hypochondriasis (HC) (DeSouza, Othmer 1984). Simultaneously, the grouping of symptoms in SDz were re-organized into seven domains (sickly; conversion or pseudoneurological; gastrointestinal; female reproductive; psychosexual; pain; cardiopulmonary) and the 59-item symptom list of Briquet's syndrome reduced to 37 by committee consensus (DeSouza, Othmer 1984; Katon, Lin et al. 1991). Physical symptoms related to major depression were eliminated, and the number of MUSs required for SDz, reduced compared to Briquet's syndrome and set at fourteen for women and twelve for men.

Due to the very stringent criteria of SDz in DSM-III, Undifferentiated Somatoform Disorder (SDud) with the criteria of at least one MUS was added to the of DSM-III, *Revised Edition* (DSM-III-R) (American Psychiatric Association 1987) in 1987. In each revision of DSM number of diagnoses has grown substantially (Follette, Houts 1996). In the mid 1990's, Body dysmorphic disorder and Somatoform disorder not otherwise specified (SDnos), appeared in the DSM, *Fourth Edition* (DSM-IV) (American Psychiatric Association 1994), as substitutes of the previous DSM-III, Atypical somatoform disorder. In contrast to number of disorders steadily having increased by each diagnostic revision, the number of MUSs required for SDz has decreased. The MUS requirement was by the DSM-IV reduced to six symptoms and to eight by the *International classification of diseases, Tenth Revision* (ICD)-10 (World Health Organization 1993) (see Table 2). SDnos described by the DSM-IV, *Text Revision* (DSM-IV-TR) (American Psychiatric Association 2000) included the criteria of MUSs of less than 6 months duration. Criteria of SDs in DSM-IV-TR and SDs including Dissociative [conversion] disorders in ICD-10 are given in Table 2, revealing also the differences between the two classification systems. A criterion introduced by the DSM-IV was that of "clinical significance"(Regier, Narrow 2002), i.e. the SDs and their symptoms should cause marked distress or significant interference with social, occupational or other areas of functioning.

Table 2. Somatoform and dissociative (conversion) disorders in DSM-IV and ICD-10

DSM-IV Somatoform disorders (SDs)		**ICD-10 Somatoform disorders (SDs)**	F45
Somatization disorder (SDz): - a history of many MUSs before age 30 - resulting in treatment sought or psychosocial impairment - a total of 8 or more MUSs in groups I-IV, at least 4 pain, 2 gastrointestinal, 1 sexual, 1 pseudoneurological (33-item MUS list) I Pain (10) II Gastrointestinal (5) III Sexual (5) IV Pseudoneurological (13)	300.81	Somatization disorder (SDz): - at least 2 year history of MUSs - resulting in repeated (3 or more) primary care or specialist consultations - a total of 6 or more MUSs, from at least 2 separate organ groups I-IV (14-item MUS list) I Gastrointestinal (6) II Cardiovascular (2) III Genitourinary (3) IV Skin and pain (3)	F45.0
Undifferentiated somatoform disorder (SDud)	300.81	Undifferentiated somatoform disorder (SDud)	F45.1
Hypochondriasis (HC)	300.7	Hypochondriacal disorders (HC)	F45.2
Pain disorder associated with psychological factors (PD) - acute - chronic	307.80	Persistent somatoform pain disorder (PD) - (chronic)	F45.4
Pain disorder associated with both psychological factors and a general medical condition - acute - chronic	307.89		
Pain disorder associated with a general medical condition -		Other somatoform disorders	F45.8
Somatoform disorder not otherwise specified (SDnos) -	300.82	Somatoform disorder, unspecified (SDnos)	F45.9
-		Somatoform autonomic dysfunction	F45.3
Body dysmorphic disorder	300.7	Hypochondriacal – dysmorphophobia	F45.2
Conversion disorder	300.11	**Dissociative [conversion] disorders**	F44
		- dissociative amnesia	F44.0
		- dissociative fugue	F44.1
		- dissociative stupor	F44.2
		- trance and possession disorders	F44.3
- with motor symptom or deficit		- dissociative motor disorders	F44.4
- with seizures or convulsions		- dissociative convulsions	F44.5
- with sensory symptom or deficit		- dissociative anaesthesia and sensory loss	F44.6
- with mixed presentation		- mixed dissociative disorders	F44.7
		- other dissociative disorders	F44.8
		- dissociative disorder, unspecified	F44.9
(- Chronic fatigue)		(Neurasteni	F48.1)

1.6 Sub-threshold somatoform disorders and alternatives

The problem of the SDs category of disorders being either too narrow or too broad in criteria, has further been manifested by several alternative diagnostic constructs of SDs with even less numbers of MUSs put forth along the way (Trimble 2004). For example, the Abridged Somatoform Disorder (SSI-4/6) (Escobar, Burnam *et al.* 1987) based on the fifteen item symptom list Somatoform Symptom Index (SSI) (Escobar, Rubio-Stipec *et al.* 1989; Escobar,

Waitzkin *et al.* 1998)used four MUSs for men and six for women, hereafter referred to as SSI-4/6. This DSM-III-R based SSI-4/6 construct has since been recommended modified to a SSI-3/5 (three MUS for men and five for women) equivalent for DSM-IV (Rief, Heuser *et al.* 1996).

Due to the critique that symptom lists are not being empirically derived and fail to take into account other factors such as illness behaviour, a diagnostic concept named "Polysymptomatic somatoform disorder" was launched (Rief, Hiller 1999). Multi-axial SDs classification approaches and other criteria in addition to number of MUSs, such as degree of psychosocial impairment, attribution of symptoms, ongoing physical disease, associated anxiety and depression, have also been proposed (Wessely, Nimnuan *et al.* 1999).

In order to facilitate criteria based diagnoses of mental disorders in primary care the PRIME-MD (Pfizer Inc, New York, NY) instrument was developed (Spitzer, Williams *et al.* 1994). The assessment of eight commonly occurring mental disorders in primary care were based on a self-administered Patient Health Questionnaire (PHQ), out of which a 15-item somatic symptom subscale (the PHQ-15) (Kroenke, Spitzer *et al.* 2002) was derived for the screening of somatoform disorder. The PHQ-15 (see Appendix 2) screens for 15 physical symptoms occurring during the last month on a severity scale from 0- not bothered, 2-bothered a little to 3-bothered a lot, making no distinction between explained or unexplained (Kroenke, Spitzer *et al.* 2002). Since the somatization disorder was far too complicated for use in primary care, the Multisomatoform disorder (MSD) (Kroenke, Spitzer *et al.* 1997) was introduced (see Table 3). In contrast to earlier diagnoses of SDs being based on *lifetime* symptomatology the MSD was based on three *current* (within the last one month) MUSs combined with at least one lifetime MUS (with duration at least 2 years). The MSD has since been recognized by the primary care version of DSM-IV (DSM-IV-PC) (American Psychiatric Association 1995) and the criteria of the disorder based on the exploration of fifteen symptoms (14 symptoms for men and 15 symptoms for women) by the PHQ-15 (see Appendix 2).

Recently the MSD has been recommended modified into a Physical symptom disorder (PSD) (Kroenke 2006) and the symptom criteria again reduced to a disorder at the one symptom level (see Table 3). In accordance with an earlier controversial proposal to do away with the SDs category altogether (Mayou, Kirmayer *et al.* 2005), the PSD has been suggested moved to Axes III (the axes in DSM for coding relevant General medical conditions) of future DSM-V (see Table 3).

Other collective terms such as “Common distress disorders” (Henningsen, Zimmermann et al. 2003) and “Psychosomatic distress syndromes” (Starcevic 2006) for all somatization-spectrum conditions have also been suggested. Recently a “Bodily distress disorder” (Fink, Toft *et al.* 2007) has been promoted, based on factor analyses of multiple symptoms falling into three categories; cardiopulmonary, gastrointestinal and musculoskeletal tension or pain. Furthermore, it has been suggested that the already existing section, “Psychological Factors affecting Medical Conditions” in DSM-IV be designated as a new section in future DSM-V to include the 7 disorders: hypochondriasis, disease phobia, persistent somatization, conversion symptoms, illness denial, demoralization and irritable mood (Fava, Fabbri *et al.* 2007).

Table 3. Diagnostic criteria of multisomatoform and physical symptom disorder

Multisomatoform Disorder (MSD)
A. Three or more somatoform symptoms [a] ***currently present*** (i.e. ***within the past month***)
B. A somatoform symptom meets with criterion 1 or 2: 1. After appropriate investigation, the symptom cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g. a drug abuse or a medication) 2. When there is a related general medical condition, the physical complaint or resulting social or occupational impairment is in excess of what would be expected from the history, physical examination, or laboratory findings.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. Although specific symptoms may come and go, the person has had one or more somatoform symptoms, for more days than not, for at least 2 years.
E. Criteria for somatization disorder are not met nor are the symptoms part of the diagnostic criteria for a mental disorder that is currently present (e.g., fatigue or insomnia in a patient with a depressive disorder or chest pain and dizziness that only occur during a panic attack in a patient with a panic disorder).
F. The symptoms are not intentionally produced or feigned (as in factitious disorder or malingering).
Physical Symptom Disorder (PSD)
1. Key diagnostic criteria for PSD:
a. One or more physical symptoms [b] ***currently present*** and causing ***impairment*** in social, occupational, or other important areas of functioning.
b. Symptoms are ***not fully explainable*** by another medical or psychiatric disorder, with the exception of syndromes manifested solely by symptoms (e.g. irritable bowel syndrome, fibromyalgia, tension headache, chronic fatigue syndrome, temporomandibular disorder, interstitial cystitis, etc.)
c. Duration of ***at least 6 months***
2. Additional specifiers:
a. Severity of somatic symptom burden can be graded as mild, moderate or severe according to PHQ-15 [a] total 0-30, scores of (5-9) mild, (10-14) moderate or greater (15-30) severe.
b. Type of symptoms or symptom syndromes can be specified (e.g., lumbago, dizziness, irritable bowel)
3. Resides on Axes III
4. Replaces several somatoform disorders: somatization disorder, undifferentiated somatoform disorder and pain disorder.

[a] Primary care evaluation of mental disorders and use of PHQ-15 item symptoms list (Kroenke, Spitzer *et al.* 1997; Kroenke, Spitzer *et al.* 2002)

[b] Physical symptoms according to the PHQ-15 symptom list (Kroenke, Spitzer *et al.* 2002)

1.7 Characteristics of somatoform disorders

Considering all the classification dilemmas and the continuous change of SDs since their very beginning, what do we know about SDs today and how can we identify and measure the phenomena of SDs as accurately as possible? How are SDs classified today? What do we know about prevalence rate, course over time, diagnostic stability, risk factors and co-morbidity of SDs, and what do we not know?

1.7.1 Diagnostic features

The common criterion for all SDs as classified today in both DSM-IV (American Psychiatric Association 2000) and ICD-10 (World Health Organization 1993) is the screening of MUSs. The diagnostic characteristics are, however, quite different in both content and criteria in the two systems Table 2. The differences are manifested clearly in the SDz entity; for example pseudoneurological symptoms are included in DSM-IV but in ICD-10 this symptomatology is kept in the Dissociative (conversion) disorder (F44) category. A common feature of SDs in both DSM-IV and ICD-10 is that criteria range from detailed numbers and combination of MUS from different organ/body parts in SDz, down to very lax criteria with only one clinically significant symptom being required, in for example SDud or chronic Pain Disorder (Persistent somatoform pain disorder) (PD). Other shared conceptions are those of long lasting or lifetime perpetuating symptoms combined with adverse healthcare seeking behaviour.

1.7.2 Symptom screening and symptom lists

Even though it has been convincingly argued that the pure counting of clinically significant MUSs using checklists is descriptively insufficient (Fink 1996; Burton 2003) in the diagnosing of the MUS-syndromes (Sharpe 2002), this has remained the core criteria of SDs for decades. Many symptoms used in the symptom lists of today have remained almost unchanged since their introduction in the diagnosing of Hysteria (Feighner, Robins *et al.* 1972) (see Appendix 1 for diagnostic criteria of Hysteria, and the overview of MUS screening by symptom-lists given in Table 4.)

Table 4. Symptom-lists used for establishing diagnoses of somatoform disorders

	WHO-CIDI version 1.2	DSM-IV	ICD-10	PHQ-15	Hysteria (Briquet's syndrome)
Number of symptoms	43	33	14	15	59
Time frame	Lifetime and pooled current [a]	Lifetime	Lifetime	Last month	Lifetime
i) Pain [a]:					
1. abdominal pain	X	X	X	X	X
2. back pain	X	X		X	X
3. joint pain	X	X	X &4	X &4	X
4. leg/arm (extremity) pain	X	X			X
5. chest pain	X	X	X	X	X
6. headache	X	X		X	X
7. painful menstruation (*dysmenorrhoea*)*	X	X		X	X
8. urination pain (*dysuria*)	X	X	X &33		X
9. genital (rectum) pain	X	X	X		X
10. other place pain	X				X
ii) Gastrointestinal and pseudo-neurological [a]:					
11. vomiting (other than pregnancy)	X	X	X		X
12. continuous vomiting during pregnancy*	X	X			X
13. nausea	X	X	X	X &15+16	X
14. diarrhoea	X	X	X	X &45	X
15. excessive gas (bloating)	X	X	X		X
16. food intolerance	X	X			X
17. blindness	X	X			X
18. blurred vision	X				X
19. deafness	X	X			X
20. trouble walking (balance)	X	X			X
21. numb feeling in arm/leg (*anesthesia*)	X	X	X & 35		X
22. paralysis	X	X			X
23. lost voice (*aphonia*)	X	X			X
24. seizures (convulsions)	X	X			X
25. fainting spells	X			X	X
26. unconscious	X	X			X
27. amnesia	X	X			X
iii) Sexual and other symptoms [a]:					
28. double vision	X	X			
29. short breath	X				
30. weakness (*fatigue*)	X			X	X
31. blotchiness or discoloration of the skin	X		X		
32. bad taste in mouth	X		X		
33. urinate too often	X				
34. unable to urinate (urinary retention)	X	X			X
35. numbness (*paresthesia*)	X				X
36. lump in throat	X	X			X
37. irregular menstruation*	X	X			X
38. excessive menstrual bleeding*	X	X			X
39. sexual problems, impotence (frigidity)	X	X			X
40. sexual indifference	X	X			X
41. pain during sexual intercourse (*dyspareunia*)	X	X		X	X
42. sex not enjoyable	X				
43. often felt sickly	X				X
44. hallucinations		X			X
45. constipation					X
46. dizziness				X	X
47. feeling your heart pound or race (palpitations)				X	X
48. shortness of breath			X	X	X
49. sleeping trouble				X	
50. unusual copious or vaginal discharge*			X		

[a] Recency of MUS(s) [occurring during last month, last six months, over six months ago and within last year or over one year ago] explored pooled into 3 categories: i) pain, ii) gastrointestinal and pseudo-neurological, iii) sexual and other symptoms

* women only

1.7.3 Prevalence

Nearly one third of all symptom complaints in the general population have been found to be either psychiatric or inexplicable (Kroenke, Price 1993). Since physical symptoms are so frequent in the general population and in their less severe manifestation almost a naturally occurring phenomena (Ihlebaek, Eriksen *et al.* 2002), one can question whether screening and diagnosing multitudes of diverse symptoms without any clear cut physical detectable cause, is at all meaningful (Kroenke, Harris 2001).

Contrary to symptoms being prevalent in the general population, the initial report of prevalence rate of SDz according to DSM-III criteria from the large Epidemiologic Catchment Area (ECA) study (1991) was very low, 0.1% to 0.38% (Swartz, Blazer *et al.* 1986; 1991). Prevalence rates of SDz by DSM-III/DSM-III-R from other studies have been very low from 0.1% to 1% (Canino, Bird et al. 1987; Bland, Orn et al. 1988; Wells, Bushnell et al. 1989; Kirmayer, Robbins 1991; Wittchen, Essau et al. 1992; Faravelli, Salvatori et al. 1997). Subsequently the disorder was completely dropped in the National Comorbidity Survey (NCS) in both 1994 (DSM-III-R) and 2005 (DSM-IV) (Kessler, McGonagle *et al.* 1994; Kessler, Chiu *et al.* 2005). Then very low prevalence rates of SDz resulted also in many researchers abandoning the DSM-III criteria, in favor of more practical definitions with lower symptom threshold. Consequently, prevalence rates according to the abridged SSI-4/6 construct were reported ranging from 4.4% to 20% (Escobar, Burnam et al. 1987; Escobar, Rubio-Stipec et al. 1989; Kirmayer, Robbins 1991). Although the symptom threshold for SDz in DSM-IV are more lenient, prevalence rates are still not high, ranging from 1% to 1.4% (Simon, Gureje 1999; Lynch, McGrady et al. 1999) and by ICD-10 up to 10.1% (Toft, Fink et al. 2005). PD has been reported as the most frequent SD (Wittchen, Essau *et al.* 1993), and overall prevalence rates for the whole group of SDs reported ranging from 12.6% to 16.1% (Lieb, Pfister *et al.* 2000; De Waal, Arnold *et al.* 2004). Prevalence reports of SDud have also varied greatly, from 13% to 79% (Faravelli, Salvatori *et al.* 1997; Lynch, McGrady *et al.* 1999; De Waal, Arnold *et al.* 2004).

In Norway, studies utilizing the CIDI (Robins, Wing *et al.* 1988), have assessed the overall twelve-month prevalence rates of SDs for the adult population (over 18 years) by DSM-III-R to be 2.1% to 2.2% in the period 1994 to1997 (Kringlen, Torgersen *et al.* 2001; Kringlen, Torgersen *et al.* 2006), while the overall two-week prevalence rate by ICD-10

research criteria from the first cross-sectional data of the Oslo-Lofoten study in 1990 was 5.9% (Somatoform disorder not otherwise specified (SDnos), was not included) (Sandanger, Nygard *et al.* 1999). A recent 27-European country survey with Norway included (Wittchen, Jacobi 2005) based on the CIDI estimated the 12-month prevalence rate of the whole SDs category across all 27 countries to be 18.7%, by either DSM-III-R/DSM-IV or ICD-9/ICD-10.

Prevalence rates for alternative constructs of SDs based on *current* symptom criteria, such as MSD have been estimated to range from 8% to 24% (Kroenke, Spitzer *et al.* 1997; Lynch, McGrady *et al.* 1999). A large German population survey (2,552 persons) assessing current SDs (with severe impairment at the one symptom level) recently reported a 22% prevalence rate (Hiller, Rief *et al.* 2006). For the newly suggested PSD construct (Kroenke 2006) prevalence rates and validation against DSM criteria are lacking.

Due to the multiplicity of definitions and diverging research methodologies, past prevalence rates of SDs have been criticized for being incomparable (Creed, Barsky 2004) and the need for longitudinal population based surveys concerned with SDs has been underlined, as well as the need for improved diagnostic accuracy (Creed 2006a).

1.7.4 Course and stability

Sixty-one percent of lifetime MUSs detected at baseline have been found to be forgotten at follow-up after only 12-months (Simon, Gureje 1999). The consequences of such a large instability of lifetime MUSs recall, and thereby an inaccurate counting of lifetime MUSs, would be very unstable and imprecise prevalence estimates of SDs derived from structured interviews.

The percent re-diagnoses of SDs by CIDI and in the whole DSM-IV group, has been found at 3½ year follow-up to be 48% (Lieb, Zimmermann *et al.* 2002). Stability of DSM-III disorders in other studies has been rated higher, with about two thirds of patients meeting the same diagnostic criteria after 4-5 years (Kent, Tomasson *et al.* 1995; Barsky, Fama *et al.* 1998). For SDz according to DSM-IV, a very low percent of re-diagnosis (28%) was found at one year follow-up (Simon, Gureje 1999).

Although some information does exist concerning course over time as described above, our knowledge is still limited due to the general sparseness of follow-up studies, especially long-term, 10 year or more, follow-up studies. Since criteria of the newer suggested PSD (Kroenke 2006) have a symptom threshold of “at least one” and the recommended 15-item physical symptom list used to examine for MUS includes pain symptoms, examining the course over time at the one symptom level (such as course of MUS-pain) is highly relevant.

1.7.5 Overlap and comorbidity

Multiple unexplained symptoms have been reported 50% comorbid with depression and 11% of depressed patients have been found to deny having psychological symptoms of depression (Simon, VonKorff *et al.* 1999).

Overlap between existing individual functional syndromes (such as chronic fatigue, fibromyalgia, irritable bowel syndrome, multiple chemical sensitivity, tension headache, interstitial cystitis, post-concussion syndrome) has been considered so substantial that similarities outweigh the differences between them (Wessely, Nimnuan et al. 1999; Aaron, Buchwald 2001).

Generally a very high (79%) comorbidity of lifetime mental disorders has been reported (Krueger 2002). In patients presenting with physical symptoms comorbid depression, anxiety and SDs are common (for depression 50%-69% and anxiety 40%-50%) (Kroenke, Rosmalen 2006). The total symptom count and not the specific type of symptom has also been identified as a strong predictor of anxiety and depression (Kroenke, Rosmalen 2006). For SDs, co-morbidity with anxiety/depressive disorders has been reported 3 times more likely than expected by chance (De Waal, Arnold *et al.* 2004), and the prevalence of comorbid depression has been reported to range from 55% to 86% and anxiety disorders from 31% to 43% (Brown, Golding *et al.* 1990; Rief, Hiller *et al.* 1995). The most frequent comorbid SD has been said to be PD occurring alongside depression and anxiety disorders, in which case PD precedes depression/anxiety (Wittchen, Essau *et al.* 1993). Personality disorders according to DSM-III-R, has also been reported in 61% of patients with SDz (Rost, Akins *et al.* 1992) with avoidant, paranoid, self-defeating and obsessive-compulsive (but not histrionic) personality disorder, being the most common.

Although the literature points out that overlap between individual functional syndromes is extensive, data from follow-up studies concerning the amount of overlap and discreteness of individual disorders within the SDs category are missing. Even though there are numerous reports, as referred to above, confirming the high comorbidity with depression and anxiety, these reports are again nearly exclusively related to SDs according to lifetime MUS criteria. Thus co-morbidity with both depression/anxiety and functional disorders such as fibromyalgia and chronic fatigue are still needed to explore diagnostic distinctness.

1.7.6 Predictors and risk factors

Psychological distress has been found associated with MUSs (Kirmayer, Groleau *et al.* 2004) and patients reporting poor health or many (5 or more) physical symptoms to be more likely

to have an underlying mental disorder (Jackson, Houston *et al.* 2001). The likelihood of having a psychiatric disorder has also been shown to increase dramatically with increasing numbers of physical symptoms (Kroenke, Spitzer *et al.* 1994). In patients attending neurology, cardiology and gastroenterology clinics, the number of physical symptoms has also been found to predict outcome more accurately than health anxiety (Jackson, Fiddler *et al.* 2006). Patients presenting with multiple symptom complaints have often been perceived by physicians as "difficult" (Lipsitt 1997; Steinmetz, Tabenkin 2001). Patients characterized as "difficult" have also been found to have a high degree of unmet health care expectations (Jackson, Kroenke 2001; Bell, Kravitz et al. 2002) and to often satisfy the criteria for MSD (Hahn, Kroenke *et al.* 1996).

Predictors of having a stable or chronic course of SDs over a 3 ½ year period, have previously been described as female gender, prior substance use, and anxiety disorder (Lieb, Zimmermann *et al.* 2002). Other risk factors associated with SDs, such as childhood experience of illness in parents (Hotopf 2002) and prior stressful life events (Craig, Drake *et al.* 1994; Aggarwal, McBeth *et al.* 2006), lower educational level and lower household income (Hiller, Rief *et al.* 2006) have also been identified.

Although diverse risk factors associated with SDs have previously been identified, and the female gender preponderance of suffering from MUSs revealed, empirical evidence related to the identification of patients at risk for having a chronic course is still insufficient.

In spite of diagnostic criteria being revised in 2000 by the DSM-IV-TR (American Psychiatric Association 2000), SDs as an entity are still afflicted by many difficulties; conceptual and nosological problems, issues of diagnostic reliability and utility, insufficient empirical evidence behind the SDs of today and future SDs diagnostic recommendations, lack of knowledge in diagnostic overlap, co-morbidity and stability, as well as course and prognosis, including risk factors and aetiology (Kent, Tomasson et al. 1995; Rief, Hiller et al. 1995; Barsky, Fama et al. 1998; Simon, Gureje 1999; Lieb, Zimmermann et al. 2002; Creed, Barsky 2004).

1.8 Classification dilemmas

Controversies over the existing classification of SDs are extensive and many questions have been raised:

- should the category of SDs be abolished altogether in the next fifth edition, DSM-V (Mayou, Kirmayer *et al.* 2005) or should it be retained (Hiller, Rief 2005; Hiller 2006; Rief, Isaac 2007)?

- should SDs be renamed and moved to Axis III in DSM-V (Kroenke 2006; Sykes 2006) or moved within the next DSM-V to the "Psychological factors affecting medical condition" category (Fava, Fabbri *et al.* 2007)?
- should a new category of SDs encompass disorders like Chronic fatigue, Fibromyalgia, Irritable bowel syndrome or the Functional gastrointestinal disorders (FGID) (Jones, Crowell *et al.* 2007), redefined into a category of Functional somatic syndromes (FSS) (Henningsen, Zipfel *et al.* 2007) and merged as "interface disorders" belonging to both the realm of mental and physical disorders (Strassnig, Stowell *et al.* 2006)?
- should gynaecological symptoms, such as dyspareunia be part of a future SDs pain category or not (Binik 2005; Spitzer 2005; First 2005)?
- which symptoms should be examined and how many counted (Kroenke 2006), and should number of symptoms be the same for women and men?
- should the dichotomizing of bodily symptoms into "medical" and "psychiatric" types be completely done away with (Sharpe, Mayou *et al.* 2006)?
- should disorders of the SDs category be lumped together or differentiated (Kroenke 2006; Henningsen, Lowe 2006) and do the assumed distinctive characteristics of SDs actually distinguish them from other disorders or not (Kendell, Jablenski 2003)?
- should utilization of health care be regarded as a symptom to screen for SDs (Smith, Gardiner et al. 2001; Smith, Gardiner 2006) or excluded as being in effect an outcome measure?

Work has already begun on the DSM-V, with its publication anticipated in 2011(2006) and the revision of SDs has been pointed out as highly needed (Wise, Birket-Smith 2002). Recommendations to resist political pressures for a change of terms, and to change terminology only if this has a clear clinical advantage have also been emphasized (Starcevic 2006). Fundamental issues are the rethinking of traditional taxonomy of SDs and how to decipher whether the taxa are valid psychopathological syndromes or not, and if so, whether they are best represented by a descriptive or etiological approach, and by a categorical or graded/dimensional approach (Joiner, Jr., Schmidt 2002). The importance of utility (First 2004), as well as reliability and psychosocial impairment criteria (Mayou, Kirmayer *et al.* 2005) should also be remembered when defining case thresholds.

2. The thesis

On this background the present thesis is about SDs and their symptoms (MUSs), elucidating the problems concerned with lifetime symptomatology and the MUS/MES distinction, exploring the course, stability, overlap and comorbidity of SDs with anxiety/depression and musculoskeletal disorders, examining risk factors and predictors, with a focus on presenting prevalence of SDs according to *current* symptom criteria for the first time in Norway. In effect, a main aim has been to contribute to the ongoing debate of the future of SDs by attaining more knowledge and shedding light on conceptual issues, diagnostic validity and reliability, thus providing more empirical evidence for future recommendations.

2.1 Aims of the thesis

The main object of this thesis was to explore discrepancies of the existing criteria of SDs, for example of that between MUS and MES, *lifetime* and *current* by examining course over time, overlap, stability, co-morbidity and risk factors of SDs. A main aim was to present for the first time in Norway, occurrence of SDs according to recently suggested current criteria. A central object was to provide more empirical evidence to the debate of future suggested changes to SDs and whether SDs should be considered mental disorders or not.

Problems that this thesis tries to answer are:

Paper I:

- How stable are *lifetime* symptoms over time and is the differentiation of symptoms into the MES/MUS categories reliable?
- What are the factors influencing the tendency to lose symptoms to recall?

Paper II:

- What is the course of MUS-pain (representing SDs at the one symptom level) over time?
- What are the characteristics of chronic or persistent MUS-pain sufferers who report *recent* (within the last 6 months) MUS-pain in 1990 and 2001?
- What are the predictors of recent MUS-pain in 2001?

Paper III:

- What is the extent of overlap between SDs, and can boundaries or disorder discreteness "zones of rarity" be identified?
- What is the stability of SDs over time?
- To what extent are SDs comorbid with anxiety and depression?
- Are there differences in predictors between *current* SDs versus *lifetime* SDs criteria?

Paper IV:

- What are the prevalence rates of *current* SDs in 2001?
- What is the co-morbidity of current SDs with anxiety/depression and musculoskeletal disorders?
- Do co-morbid sub-groups of *current* SDs differ in psychological distress?
- What are the arguments for still regarding SDs as mental disorders?

3. Material and methods

3.1 Materials

Two general population samples from The Oslo-Lofoten study, all 18 years of age or older are studied in this thesis (Paper I, II, III and IV).

Table 5. Characteristics of Papers I-IV

Paper	Subjects	Selection	Year	N	Response rate	Women	Geographical Area	Design	Mean age
I, II, III	General population - CIDI somatoform section interviewed **1990-2001 Follow-up**	Pre-selection by HSCL-25	1990 & 2001	421	70% out of 605 at baseline	57.5%	44.2% (Oslo)	Prospective	42.9 (baseline) 53.9 (follow-up)
IV	General population - CIDI somatoform section interviewed **2001 Sample**	Excluded - subjects from 1990 interviewed again in 2001 (N=421)	2001	1247	61% out of all 2049 actually contacted	50.8%	44.4% (Oslo)	Cross-sectional	46.8

3.2 Methods

3.2.1 Design of the studies

3.2.1.1 Longitudinal prospective design

A longitudinal prospective design was utilized in Paper I, II and III, following up respondents who had been interviewed with the Somatoform section of the Composite International Interview (CIDI) in 1990. Respondents interviewed at baseline in 1990 were contacted again and interviewed for the second time in 2001. Respondents from 1990 who had been lost to follow-up due to death or other reasons were also identified.

3.2.1.2 Cross-sectional design

A cross-sectional design was utilized in Paper IV. New randomly selected respondents, added on to the old 1990 cohort, interviewed with the CIDI somatoform section for the first time were selected. All respondents from 1990 who had been interviewed again in 2001 (N=421) were excluded, reasons for the elimination are given in 3.2.2.3.

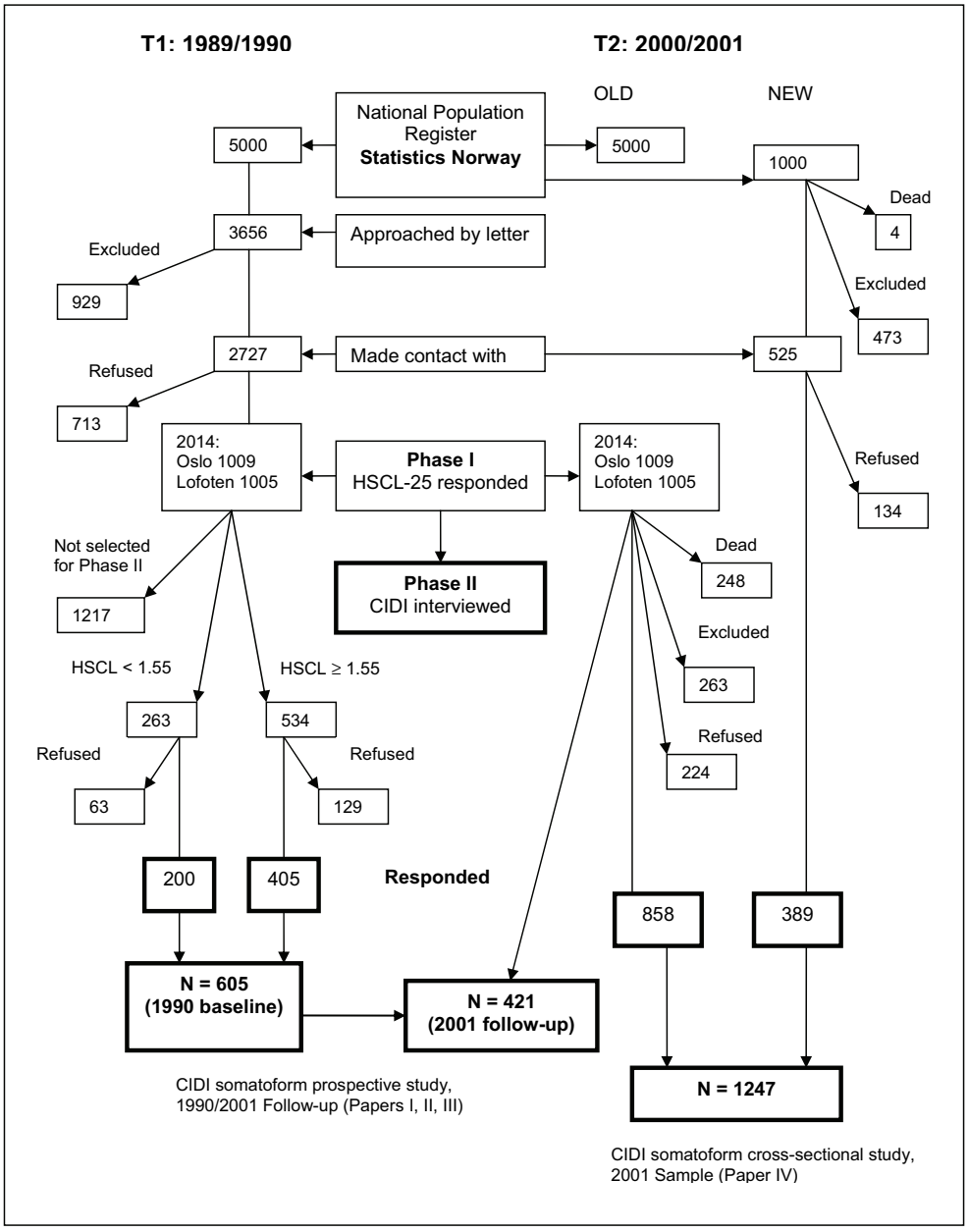

Figure 1. The Oslo–Lofoten study, CIDI somatoform section interviewed, 1990 and 2001

3.2.2 Method design

The studies of this thesis encompass both a retrospective and prospective methodology, since questions about the past "have you ever had" and present "here and now" were asked in both 1990 and 2001. Respondents in all the studies were recruited from two geographical areas, 1) Lofoten - representing a typical traditional ethnic Norwegian rural west coast population and 2) Holmlia suburb, Oslo – representing a more modern Norwegian city diverse population of both ethnic Norwegian and immigrant origin.

3.2.2.1 Inclusion criteria, 1990/2001 Follow-up

Paper I, II and III:

An initial general population random sample of 5,000 individuals, 18 years of age or older (2,600 from Holmlia and 2,400 from Lofoten), was drawn from the National Population Registry administered by Statistics Norway in 1989 (see Figure 1). Since the goal was to obtain a high number of persons, approx. 2000 included, information letters were sent to a random selection of 3,656 (2,055 in Oslo, 1,601 in Lofoten) out of the initial 5,000 draw. Altogether, 929 persons out of 3,656 were excluded since they had moved, could not be located or were dead. The final number of 2,727 persons left were approached with the Hopkins Symptoms Checklist 25-item self-rating scale (HSCL-25), out of which 713 refused and 2,014 (1,009 in Oslo and 1,005 in Lofoten) consented to participate, i.e. 74% of the eligible 2,727 population sample. All respondents (N=405) in 1989 with HSCL-25 scores <1.55 as well as a random selection (N=200) of those with HSCL-25 scores ≥1.55 were interviewed with the CIDI somatoform section and included (N=605) in 1989/1990 (hereafter "baseline" or 1990 (Papers I-III)). Altogether 184 out of 605 (30%) respondents were lost to follow-up in 2000/2001 (hereafter "follow-up" or 2001 (Papers I-III)), leaving a total of 421 respondents interviewed at both time points (114 or 62% of whom were women).

3.2.2.2 Lost to 1990/2001 Follow-up

Table 6. Respondents lost to follow-up

Paper	Subjects lost to follow-up (N=184)	N	Women	Mean HSCL-25	Mean age in years (at baseline)
I, II, III	- dead	73	47.9%	1.69	68.9
	- refused	49	71.4%	1.73	35.4
	- not found again	36	69.4%	1.70	34.1
	- dement or too sick to be interviewed	26	73.0%	1.77	67.5

Information in 2001 concerning respondent's place of residence (moved or emmigrated) or date of death was retrieved from the records of the National Population Register, stored by Statistics Norway. Death attrition was strongly related to old age. Mean age in years when lost to death was 71 for women and 67 for men (Paper I). The gender distribution and HSCL-25 scores were not significantly different between those interviewed again and those lost to follow-up. However, when applying the Bonferroni post hoc test, significant differences between those lost to follow-up and those interviewed again in 2001 were found in numbers of lifetime MUS and MES at baseline (Paper I). For number of lifetime MUS at baseline, a significant difference (P <.05) was found between those lost due to death and those lost to follow-up for reasons other than death, but not for those interviewed again. For number of MES, the difference was significant (P <.001) between those who had died and those interviewed again and also significant (P <.05) between lost to follow-up other than death.

3.2.2.3 Inclusion criteria, 2001 Sample

Paper IV:

In 2001 a new random draw of 1,000 individuals, 18 years of age or older, from the National Population Register by Statistics Norway, was added to the "old" original 1990 cohort (see Figure 1). Reasons for the drawing of a new sample were to strengthen the cohort for later follow-ups and to increase the number of younger individuals and immigrants. Five hundred persons born between 1972 and 1982 were randomly drawn in Oslo and 400 in Lofoten, in addition a random draw of 100 persons born as close to 1972 as possible in Lofoten. Altogether 94 persons were excluded because they had moved, emigrated, were too sick to participate, had died or had been included previously in 1990 (see Table 7). In spite of many attempts, contact was not established with 193 persons, leaving a sample of 713 eligible respondents. Due to limited resources and time restraints 188 were not contacted. Out of the remaining 525 persons contacted, 134 refused and 2 were excluded due to missing data on CIDI somatoform section, leaving 389 included. Response rate in the "new" 389 sample was 55% (389/713) of the potentially eligible or 74% (389/525) of those actually contacted.

From the original cohort of 2014 individuals in 1990, 511 respondents were excluded and 224 refused to participate, see Table 7. Due to the pre-selection by HSCL-25 score in 1990 for CIDI interview, all follow-up respondents from 1990 who were re-interviewed with the CIDI somatoform section in 2001 (N=421) were excluded. Respondents missing data in

the CIDI somatoform section 2001 interview (N=21) were also excluded. Response rate in the "old" 858 sample was 49% (858/1766) of the potentially eligible and 56% (858/1524) of those actually contacted. The 858 respondents from the "old" cohort (interviewed with the CIDI somatoform section for the first time in 2001) were included alongside the 391 respondents from the "new" sample. This left a final total of 1,247 included, with overall response rate 50% (1247/2479) of potentially eligible, and 61% (1247/2049) of actually contacted.

Table 7. Subjects excluded in the 2001 Sample

Paper	Reasons for exclusion in 2001	Old 2001 cohort (N=2014) N	New 2001 cohort (N=1000) N
IV	- dead	248	4
	- dement or too sick to be interviewed	31	3
	- too severely ill to participate	37	3
	- emigrated	36	3
	- not recovered from the Census Register	19	-
	- impossible to find	119	193
	- not contacted due to time limit	-	188
	- included previously in 1990	-	5
	- did not speak Norwegian	-	8
	- moved from study regions	-	68
	- interviewed in 1990, interviewed again in 2001 (1990/2001 Follow-up)	421	-
	- not interviewed with CIDI somatoform section in 2001	21	2
	Refused	224	134
	Total	1156	611

Age and gender distribution of the 2001 Sample compared to that of the Norwegian general population of 2001 (Sandanger, Nygard *et al.* 2006) are given in Table 8.

Table 8. The Norwegian population and 2001 Sample, gender and age distribution

	The Norwegian Population 2001:				The 2001 Sample:			
	Women		Men		Women		Men	
Age	N	%	N	%	N	%	N	%
18-34	511997	29	527497	31	134	21	134	22
35-49	480501	27	499452	29	276	44	237	39
50-65	409312	23	416044	24	146	23	157	25
66+	378171	21	267652	16	77	12	86	14
Total	1779981	100	1710645	100	633	100	614	100

3.2.3 Samples and studies

3.2.3.1 1990/2001 Follow-up

Paper I, II and III:

Participating respondents (2,014; 74% of the eligible 2,727 source population) in 1989 comprised a sample that was representative with respect to age (18–39 years 49%, 40–59 years 28%, 60 years and above 23%) and gender (women 53%, men 47%) of the source population. The HSCL-25 questionnaire was used as a screen for mental health and chosen for its ongoing (present and last week) symptom load assessment and as a measure of psychological distress (Derogatis, Lipman *et al.* 1974; Rickels, Garcia *et al.* 1976; Winokur, Winokur *et al.* 1984). In 1990 all respondents with HSCL-25 cut off point <1.55 in addition to a random sample of those with HSCL-25 score ≥1.55 were selected for CIDI interview. All interviewers (both professional and lay interviewers) underwent CIDI interview training conducted by the study's leading psychiatrist.

Reasons for the choice of a longitudinal prospective design were to be able to assess the same respondents over an eleven year interval, making it possible to evaluate the stability of reported lifetime MUS and MES (Paper I), course of MUS-pain and factors associated with chronicity (Paper II) and overlap, co-morbidity and stability of disorders (Paper III).

3.2.3.2 2001 Sample

Paper IV:

In 2001, all randomly selected respondents from the National Population Register by Statistics Norway who had responded to the HSCL-25 questionnaire (N=2014) were selected for CIDI interview (see Figure 1). All those who had responded to the CIDI somatoform section were included, no sub-sampling was undertaken. Even after all follow-up respondents from 1990 interviewed again in 2001 (N=421) were excluded, the number of respondents who had been included in the 2001 sample was still high (N=1247).

Reasons for the choice of the cross-sectional prevalence design were to examine prevalence of SDs according to new *current* symptom criteria as accurately as possible, by the updated somatoform section of the WHO-CIDI version 1.2 used in 2001. In addition the supplementary interview schedule and self-questionnaire developed by the Oslo-Lofoten study (see 3.2.4.1) had been revised in 2001, making it possible to identify risk factors and the use of health care more extensively, as well as examining comorbidity with musculoskeletal disorders (including Fibromyalgia and Chronic Fatigue, see Appendix 7).

3.2.4 Instruments and variables

3.2.4.1 Instruments

The Composite International Diagnostic Interview (CIDI):
Respondents in the Oslo-Lofoten study in 1990 were interviewed with the CIDI version 1.0 (Robins, Wing *et al.* 1988) and in 2001 with the computerized M-CIDI 1.1 (updated electronic version of WHO-CIDI version 1.2) (Wittchen, Lachner *et al.* 1998) in 2001. According to ICD-10 research criteria the diagnostic focus in 1990 was on the following disorders: panic disorder, generalized anxiety disorder, phobic disorder, major depression and dysthymia, and SDs (including dissociative disorders)) (Sandanger, Nygard *et al.* 1999).

The CIDI version 1.0 somatoform algorithms in 1990 consisted of SDz (F.45.0) and PD (F45.4) (see Table 2). In 2001 the updated CIDI version 1.2 somatoform algorithms also included SDud (F45.1), HC (F45.2) and SDnos (F45.9) (see Table 2). All computerized somatoform diagnostic computations using the WHO-CIDI algorithms in 2001 were based on DSM-IV criteria, with just a simple conversion to the corresponding ICD-10 numbers.

Due to the somatoform diagnostic assessment by the CIDI algorithms not being completely identical in 1990 and 2001, and therefore not comparable between the two time points – all SDs referred to in this thesis (Paper III and IV) had to be computed directly from the MUSs raw data in the somatoform section according to DSM-IV based criteria algorithms for both 1990 and 2001. The DSM-IV based criteria and algorithms were applied to the MUSs

raw data are given in Paper III and IV. In 1990 the CIDI 1.0 Somatoform section examined 41 symptoms (Appendix 3) and in 2001 the WHO-CIDI 1.2, 43 symptoms (Appendix 4). Since the question "Have you been sickly for the majority of your life?" (see item 43 in Appendix 3 and 4) was not considered as a specific symptom per se, it was excluded from the data analyses in all Papers I-IV.

The main reasons for the choice of the CIDI in the Oslo-Lofoten study had to do with its feasibility in population studies (Robins, Wing *et al.* 1988) and its previous application in many countries (Wittchen, Robins et al. 1991; Rubio-Stipec, Canino et al. 1993). Diagnoses by the CIDI had also been reported to show a high reliability (Wittchen 1994; Wittchen, Lachner *et al.* 1998) and the Cohen's κ measurement of agreement (inter-rater reliability) for the somatoform section to be good (0.68) (Wittchen 1994). The CIDI somatoform section flow chart had also been reported to adequately screen for somatic symptoms in many countries (Rubio-Stipec, Canino *et al.* 1993).

The Oslo-Lofoten Interview Schedule:

In 1990, the interview schedule consisted of altogether 182 items. In addition to demographic variables the items were wide-ranging covering many diverse topics, for example education; income; the experience of alcohol problems/mental illness among parents; utilization of health services, including mental health care; use of narcotics and medication, including sedatives and tranquillizers; experience of significant and traumatic life events; religious beliefs; social support; physical diseases, including cancer; smoking habits; coffee drinking and eating habits; housing, leisure time activities and hobbies; health care contact, including mental health care, and admission to hospital; satisfaction with the health care provided.

In 2001 the interview schedule had been updated and improved, and altogether it consisted of 131 items. Several items, for example those pertaining to nutrition and housing, were not found sufficiently relevant to be continued in 2001. Since the 1990 schedule was extremely long and time consuming, items were either compressed or reduced, and updated also as for relevance. For example, the exploration of physical diseases which consisted of a 22-item physical disorder list in 1989 was reduced to a 17-item disorder list in 2001, yet adding such disorders as Chronic Fatigue and Fibromyalgia. Even though most items were, for research purposes, kept identical at both time points, several items contained more detail in 2001, either by additional questions relating to the time frame involved or to the degree of severity (mild, moderate, or severe). For example, stressful life events examined by the 52-

item Stress Life Event list, was improved in 2001 with the addition of severity for each event added (i.e. affected by the event; a little, somewhat, or very much).

The Oslo-Lofoten Self-questionnaire:

In 1990, the self-questionnaire consisted altogether of 52 items. The items comprised self assessed health; satisfaction with life; general well-being; working ability; global opinions on the health services (including mental health care) provided; alcohol use and drinking habits; opinions on housing, neighbourhood and working conditions; experience of social support and social environment; and in addition included the HSCL-25 questionnaire.

In 2001 the self-questionnaire consisted altogether of 59 items and was primarily a follow-up and an update of the 1990 questionnaire. Nearly all items were either identical (for example the HSCL-25) or improved with more detail (for example related to the time frame). A few questions from 1990 were found either not applicable in 2001 or too elaborate to be continued, for example items related to detailed health concerns/opinions applying to the local environment.

3.2.4.2 Variables

An overview of dependent variables are given in Table 9, and independent variables in Table 10. The choice of independent variables to be explored in the regression analyses of Papers I-IV were either based on theoretical considerations, earlier literature reports of significant associations or a significant bivariate correlation (Pearson's r, $P<.05$) with the dependent variable being examined in the present study.

Table 9. Dependent variables included in Papers I-IV

	Paper I	Paper II	Paper III	Paper IV
Number of MUS-lost to recall	X			
Number of MES-lost to recall	X			
Recent MUS-pain in 2001		X		
“Lifetime” SDs in 2001			X	
“Current” SDs in 2001			X	
Severe current SDs				X
Anxiety disorders				X
Depressive disorders				X
Musculoskeletal disorders				X
Health care utilization (last 12 months):				
- Mental health care				X
- Admission to hospital				X
- Consultation with general practitioner/hospital physician				X
Use of medication:				
- Analgesics (daily or weekly)				X
- Benzodiazepines (daily or weekly)				X
- Antidepressants (last 12 months)				X

Table 10. Independent variables included in Papers I-IV

	Paper I	Paper II	Paper III	Paper IV
Gender	X	X	X	X
Age	X	X	X	X
Education	X	X		
Residential area, Oslo / Lofoten		X		X
Experience of alcohol problems/mental illness among parents		X		X
Living alone		X		
HSCL-25 score	X			
HSCL-25 anxiety sub-score				X
HSCL-25 depression sub-score				X
Stressful life events, 52-item scale		X		X
Working ability score				X
Satisfaction with life score				X
Self assessed health score				X
MUSs	X			X
MESs	X			X
Recent MUS-pain		X		
Physical disorders, 15-item list	X	X	X	
Physical disorders, 13-item list				X
Musculoskeletal disorders, 4-item list				X
Depression		X	X	
Anxiety		X	X	
Lifetime SDs			X	
Current SDs			X	
Use of analgesics (daily or weekly)				X
Use of antidepressants (last 12 months)				X

3.2.4.3 Description of variables

For research purposes variables examined in the 1990/2001 Follow-up (Paper I, II and III) had to be directly comparable, at both time points. Variables explored from the comprehensive Oslo-Lofoten Interview Schedule or the Self-Questionnaire were chosen according to this requirement in Paper I, II and III and if necessary adapted accordingly, as described below. In Paper IV all variables from the improved Oslo-Lofoten Interview Schedule 2001 or Self-Questionnaire 2001, were chosen in order to give more detailed information, for example the use of antidepressants during the last year (asked in 2001 but not in 1990).

Sociodemographic variables:

In all regression analyses (Papers I-IV) age and education in years was divided into 10-year groups (decades). Results in Papers I-III were also presented according to the following age groups: <35 years, 35 to 55 years, >55 years (Paper I), 18 to 28 years, 29 to 44 years, 45 to 60 years, >61 years (Paper II) and <50 years, >50 years (Paper III).

In Paper IV prevalence rates of current SDs was stratified by gender and age, into age groups: 18 to 34 years, 35 to 49 years, 50 to 65 years, >65 years. Residential living area was in all papers treated according to the dichotomy Oslo/Lofoten according to the address by the National Population Register. Other dichotomous socio-demographic variables were experience of alcohol problems/mental illness among parents, and living alone.

Somatoform, anxiety and depression disorders:

All disorders in all papers were dichotomous, yes/no. All SDs of Paper III and IV were computed from the MUSs raw data according to disorders described in the SDs category of DSM-IV-R (American Psychiatric Association 2000) including the MSD of DSM-IV-PC (American Psychiatric Association 1995) and MSD criteria described by Kroenke et al. (Kroenke, Spitzer et al. 1997). The diagnostic criteria (number of MUS, duration and onset) in the computation of SDs from the MUS raw data for Paper III are given in the Table 1 of Paper III. In Paper IV the diagnostic criteria for MSD and SDnos, and the groups “current SD” and “severe current SDs” with impairment added, are given in Appendix B of Paper IV.

Due to differences in the physical symptom lists of the somatoform section of CIDI version 1.0 (Appendix 3) and WHO-CIDI version 1.2 (Appendix 4), only 38 physical symptoms, identical at both time points in 1990 and 2001, were utilized in the data analyses pertaining to Paper I, II and III. In Paper IV the feeling item 43 “often felt sickly” was omitted

and the remaining symptoms (42-items) used diagnostic computation according to the criteria of DSM-IV-R.

Anxiety and depressive disorders examined were those computed by the CIDI program's computerized algorithms according to ICD-10. Depressive disorders were dichotomized into yes/no, and yes consisted of those recorded from F31.3 to F34.1, present during the last 12 months. Likewise, anxiety disorders were dichotomized (yes/no) by ICD-10, and yes consisted of those recorded from F40.0 to F41.8, present during the last 12 months.

The Hopkins Symptoms Checklist 25-item self-rating scale (HSCL-25):

The HSCL-25 score (Appendix 5) was treated as a continuous variable in all analyses. In Paper I, the HSCL-25 was chosen as a measure of current psychological distress (Derogatis, Lipman *et al.* 1974; Rickels, Garcia *et al.* 1976; Winokur, Winokur *et al.* 1984), not least since it has been recognized as a sensitive case-finder of anxiety and depression (Sandanger, Moum *et al.* 1999; Frojdh, Hakansson *et al.* 2004). The HSCL-25 score was not chosen as an independent variable in the regression analyses of Paper II and III since the ICD-10 disorder categories anxiety and depression (see paragraph above) were chosen here instead. In Paper IV the HSCL-25 anxiety and depression subscales (given in Appendix 5) were chosen as independent variables rather than the total HSCL-25 score, since information specific to each of the dimensions was the focus of interest.

Physical disorders:

Since physical disorders in the Oslo-Lofoten Interview Schedule of 1990 and 2001 were categorized slightly differently at the two time points (see 3.2.3.3 Instruments), the disorders were pooled into a 15-item Physical disorder list (see Appendix 6) in order to be directly comparable for the analyses in Paper I, II and III.

In Paper IV, the physical disorders examined were divided into two groups, i) a 4-item musculoskeletal disorder list and ii) a 13-item physical disorder list (see Appendix 7). Only disorders recorded as having a moderate to severe impact were analyzed. The number of disorders was employed as continuous variables in the logistic regression analyses of Paper IV. The musculoskeletal disorders were also dichotomized into yes/no, in order to examine co-morbidity and to identify sub-groups of severe current SDs (Paper IV).

Stressful Life Events Scale:

Stressful life events were examined according to the 52-item Stressful Life Event Scale (see Appendix 8) by the Oslo-Lofoten Interview Schedule in 1990 and 2001. The 52-items scale was developed for the Oslo-Loften study, based on a reduced version of Paykel and Mangen's 63-item schedule "Interview for Recent Life Events" (Paykel, Mangen 1980; Paykel 1983). The life events included events of both an acute and a more enduring chronic strain nature (Avison, Turner 1988) and encompassed nine areas: work, education, finance, health, bereavement, migration, courtship, legal, family and social relationships. Only events experienced during the last year were included (both in Paper II and IV) and in 2001, only events having a moderate to severe impact. In 1990 (Paper II), all events were included, since severity of impact was not measured at this time point.

Self assessed health score:

Assessment of global health by the Oslo-Lofoten self-questionnaire 2001 was measured by requesting the respondent to assess, his/her global health at present on a scale from (1) very bad to (4) very good (Paper IV).

Satisfaction with life score:

Satisfaction with life by the Oslo-Lofoten self-questionnaire 2001 was measured by requesting the respondent to assess, his/her general life satisfaction at present on a Cantril ladder scale from (1) worst life situation to (10) best life situation (Paper IV).

Working ability score:

Working ability by the Oslo-Lofoten self-questionnaire 2001 was measured by requesting the respondent to assess, his/her working ability at present on a scale from (1) very reduced to (6) not reduced at all (Paper IV).

Health care utilization and use of medication:

Health care utilization, both mental health care and general health services, by the Oslo-Lofoten self-questionnaire 2001 was measured by having been to inpatient or outpatient treatment and/or consultation during the last 12 months. Use of medication, such as analgesics was reported as daily or weekly, and the use of antidepressants during the last year (Paper IV).

3.3 Ethics

The Oslo–Lofoten study, 1990 and 2001, was approved by the Norwegian Data Inspectorate and the Norwegian Social Science Data Services. The study was conducted in accordance with the guidelines of the Helsinki II declaration. Informed consent was obtained from all participants at both time points.

3.4 Statistical analysis

Paired-samples *t*-tests were used to examine mean changes from baseline to follow-up for continuous variables, for example numbers of symptoms (Paper I), numbers of physical diseases and stressful life events (Paper II). Degree of statistical association between pairs of variables was examined by the Pearson's r (Phi for dichotomous variables) product moment correlation coefficient and Spearman's rho (ρ) non-parametric test of correlation (Paper I). Associations between pairs of nominal variables were measured by Kendall's tau-b (Paper I), Chi-square (χ^2) and Cohen's kappa (κ) (Paper II, III), and by the tetrachoric correlation coefficient (r*) (Paper III). The reason for the choice of r* in Paper III was that κ is influenced by trait prevalence (distribution or base-rates) while r* allows for the assumption that (liability for) the underlying trait is continuous and normally distributed.

In Paper IV reliability of the HSCL-25 scores based on internal consistency was estimated by Cronbach's alpha. The Cohen's *d* was also used to calculate effect sizes on total HSCL-25 score and HSCL-25 anxiety and depression sub-scores, between the "severe current SDs only" subclass and other subclasses (Table 4 of Paper IV).

The Bonferroni post-hoc test was applied to compare those interviewed again in 2001 and those lost to follow-up. Multiple linear regression analyses were conducted in Paper I and IV and logistic regression analyses in Paper II, III and IV. Reasons for the choice of independent predictor variables were either i) significant bivariate correlation by Pearson's r ($P<.05$) with the dependent variable ii) a clinical relevance pertaining to factors often associated with the dependent variable or iii) factors previously described in the literature as being associated with the dependent variable . Two-way statistical interactions between all pairs of independent variables entered in the regression analyses were tested separately, one pair at a time. Logistic regression analyses were also used to test gender and age group prevalence rate differences in Paper III, with the diagnosis or diagnostic group as the dependent variable, and age and gender as independent variables.

Stability of diagnoses (Paper III) was measured by prospective and retrospective consistency, i.e. prospective consistency: the percent of respondents with diagnoses in 1990 having the same diagnoses again in 2001, and retrospective consistency: the percent of respondents with diagnoses in 2001 having had the same diagnoses in 1990. The likelihood of having the same diagnoses again in 2001 was also estimated by calculating the Odds Ratio (OR).

Six month prevalence rates (%) and 95% confidence intervals (CI) of current SDs (individual diagnoses and groups), according to gender and age, were computed by one-way analyses of variance (Paper IV).

In all Papers I-IV the level of significance (*P*-value) was set at $P < .05$ and the statistical significance reported as either $P < .05$, $P < .01$, $P < .001$, or non-significant (NS). Statistical data analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) versions 12.0 and 14.0 for Windows.

4. Summary of papers and results

4.1 Paper I

Leiknes KA, Finset A, Moum T, Sandanger I.
Methodological issues concerning lifetime medically unexplained and medically explained symptoms of the Composite International Diagnostic Interview: a prospective 11-year follow-up study. J Psychosom Res 2006;61:169–79

This paper presents results from the Oslo-Lofoten study at baseline (1990) and at follow-up (2001). The sample comprised 605 respondents interviewed with the CIDI somatoform section at baseline and 421 (242 (57.5%) women and 179 (42.5%) men), interviewed again in 2001. The response rate was 69.6% (421/605) and among those lost to follow-up, 73 (39.7%) were lost due to death.

The aims of this paper were

- to elucidate methodological problems arising when examining lifetime symptom data by exploring the accuracy of recall of MUSs and MESs, for those interviewed by the CIDI, somatoform section in 1990 and 2001.
- to find predictors of "symptoms lost", i.e. symptoms that had been reported at baseline but were not recalled at follow-up

A wide range of individual lifetime symptoms, from 22 to100%, were lost to recall at follow-up. This indicated a large degree of measurement error, mainly due to faulty recall over time. The recall of lifetime symptoms when grouped into broader categories of number of symptoms was somewhat better than for individual symptoms (approx. 50% recall for 1 to 3 symptoms). Gender and age emerged as significant (P<.01) markers for MUSs-lost, and a decrease in physical morbidity for MESs-lost. Men tended to forget more symptoms than women. Younger respondents with high levels of baseline MUSs tended to remember slightly better at follow-up. The large degree of recall variability and transition of MUS to MES and visa versa over time, cast doubt on the credibility of the medically unexplained and explained distinction. Lifetime symptom data elicited in community surveys by diagnostic instruments such as the CIDI should be viewed with caution.

Methodological errors weakening the data credibility could lead to false impressions of true change over time. The distinction between medically unexplained and medically explained physical symptoms seems difficult to maintain.

4.2 Paper II

Leiknes KA, Finset A, Moum T, Sandanger I.
Course and predictors of medically unexplained pain symptoms in the general population. J Psychosom Res 2007;62:119-28.

This paper presents results from the Oslo-Lofoten study at baseline (1990) and at follow-up (2001) pertaining to clinically significant and *recent* medically unexplained pain symptoms (MUS-pain). Recent symptoms are defined as those present within the last six months preceding the CIDI interview at baseline and at follow-up. The sample comprised 605 respondents interviewed with the CIDI somatoform section at baseline and 421 (242 (57.5%) women and 179 (42.5%) men), interviewed again in 2001.

The aims of this paper were

- to explore the course of MUS-pain (a SDs disorder at the one-symptom level) over time and to identify "persistent" or chronic cases (i.e. recent MUS-pain in both 1990 and 2001)
- to find predictors of recent MUS-pain in 2001, related to sociodemographic background, level of and/or change in physical morbidity, depression and anxiety, and number of stressful life events experienced within the last year

A small "stable" group of recent MUS-pain sufferers (8% out of all reinterviewed and 33.6% out of those with recent MUS-pain at baseline) was evident. Almost all were women. Female gender was a significant ($P<.05$) predictor, giving a twofold risk compared with men of having recent MUS-pain in 2001. In addition only co-morbid depression and not the occurrence of prior recent MUS-pain at baseline, remained a significant ($P<.05$) predictor, increasing the likelihood of having *recent* MUS-pain at follow-up threefold.

The prognosis of MUS-pain is relatively good, except for a small group (mainly women) prone to chronicity. Clinicians should examine for depression when confronted with MUS-pain patients and be aware of the increased twofold risk for women compared with men for persistent MUS-pain over a long time.

4.3 Paper III

Leiknes KA, Finset A, Moum T, Sandanger I.
Overlap, comorbidity and stability of somatoform disorders, and the use of current versus lifetime criteria. Psychosomatics [in press, accepted 2006].

This paper presents results from the Oslo-Lofoten study at baseline (1990) and at follow-up (2001) pertaining to diagnoses of SDs, and the use of *current* versus *lifetime* criteria. The sample comprised 421 respondents (242 (57.5%) women and 179 (42.5%) men) interviewed with the CIDI somatoform section in 1990 and again in 2001. Seven disorders within the SDs category were examined; SDz, SDud, HC, PD, Abridged somatoform disorder (SSI-3/5), SDnos and MSD. Disorders were pooled into lifetime (Sdz, SDud, HC, PD) and current (SDnos and MSD) SDs.

The aims of this paper were

- to examine the extent of overlap of individual SDs, the comorbidity of SDs with anxiety and depression and the stability of SDs over time
- to find predictors of pooled "lifetime SDs" and "current SDs" at follow-up

Overlap for many individual SDs, was very high >90% with r* close to 1.0. Clear distinctions between individual disorders were not possible to find, except for a slight distinction being revealed when the SDs were pooled into "current SDs" and "lifetime" SDs according to the recency of the underlying MUSs criteria. Comorbidity by OR ranged from 2.9 to 5.1 for depression and from 2.0 to 2.5 for anxiety. Comorbidity was somewhat more pronounced for current SDs compared to lifetime SDs, and current SDs were 4 times more likely to occur among depressed respondents. For current SDs, diagnostic stability by retrospective consistency was 42% compared to only 33% for lifetime SDs. The highest estimate of agreement by kappa occurred for current SDs and must be considered fair (κ =0.214, P<.001). Among those individuals with a SD at baseline, 54% to 67% fulfilled the criteria of *any* SD at follow-up. Women <50 years of age with SD at baseline tended to show a stable (chronic) course over time.

Prior depression and physical disease were risk factors for current SDs, whereas only prior anxiety was a significant predictor for lifetime SDs. Clinical attention should be focused on young women, who are at risk for having debilitating symptoms over a long time. SDs should be merged and future criteria should be based on *current* symptoms.

4.4 Paper IV

Leiknes KA, Finset A, Moum T, Sandanger I.
Current somatoform disorders in Norway: prevalence, risk factors and co-morbidity with anxiety, depression and musculoskeletal disorders. [submitted].

This paper presents results from the Oslo-Lofoten cross-sectional survey in 2001. Respondents were interviewed with the updated computerized CIDI (electronic DIA-X/WHO-CIDI version 1.2) (Wittchen, Lachner *et al.* 1998). In order to eliminate selection bias connected with the CIDI interview sampling in 1990, all respondents from 1990 who were interviewed again in 2001 (N=421) were excluded, leaving a total of 1,247 respondents in the subsequent data analyses. Altogether 633 out of 1,247 (50.8%) were women and 554 out of 1,247 (44.4%) lived in Oslo.

The aims of the article were:

- to investigate the prevalence of current SDs in Norway
- to examine whether current SDs should be regarded as mental or physical conditions by i) inspecting risk factors of severe current SDs, anxiety/depression and musculoskeletal disorders, and ii) assessing psychological distress, utilization of health care and medication in co-morbid subclasses of severe current SDs.

The overall pooled prevalence rate for severe current SDs (MSD and SDnos pooled, with psychosocial impairment applied) was 10%. Prevalence rates were generally twice as high for women. The main risk factor associated with severe current SDs was anxiety. Co-morbidity of severe current SDs with anxiety/depression and/or musculoskeletal disorders was 69%. Psychological distress in the only severe current SDs subclass (without co-morbidity) was significantly higher ($P < .05$) than among respondents without disorders. Mental healthcare utilization among those with current SDs depended on co-morbid anxiety/depression, not on the SD diagnosis alone.

Co-morbid symptoms of anxiety/depression rather than medically unexplained symptoms per se, should qualify the patient for a psychiatric diagnosis.

5. Discussion

This thesis covers the examination of physical symptoms and SDs by the CIDI in two epidemiological studies, i) a follow-up study (1990/2001 Follow-up, Papers I-III) and ii) a cross-sectional study (2001 Sample, Paper IV). Various sources of error that may be present in the studies and possibly have influenced the data will be discussed in the following sections.

5.1 Methodological issues

Methodological issues of this thesis will be considered from the two main forms of *error* (Rothman 2002), first i) *systematic* error, referred to as *bias* and secondly ii) *random* error.

5.1.1 Systematic error (bias)

Bias relevant to the studies of this thesis will be discussed in three main areas, i) selection bias, ii) information bias and iii) confounding bias.

5.1.1.1 Selection bias

Selection bias is the error arising from procedures used for finding and including respondents into the two samples of this thesis, i) 1990/2001 Follow-up and ii) 2001 Sample, and from other factors influencing study participation. Generally the question of selection bias has to do with sample representativity and the possibility of drawing valid inferences regarding the source population.

The source population for both these samples were inhabitants living in two different geographical areas in Norway, i) the northern west coast Lofoten region and ii) the Holmlia suburb in Oslo. Proportion respondents from Lofoten in the 1990/2001 Follow-up (Paper I-III) were 55.8% and in the 2001 sample (Paper IV) 55.6%. One reason for the slightly better recruitment from Lofoten might be a better thoroughness among the Lofoten interviewers. Another reason could be that Lofoten community traditions might also have facilitated the finding and contacting of respondents a second time. Compared to Holmlia, Oslo, where community traditions are still young and perhaps still not so established, Lofoten has been influenced by a coastal fishing industry over many generations.

All individuals were randomly selected from the National Population Register, by Statistics Norway, and given that all resident Norwegian citizens are in fact included in the register - selection bias arising from self-selection were avoided, beyond that arising from a

refusal to participate in the study. However, some factors influencing the study samples in the direction of having a better or worse health than the source population must be taken into account. Since all respondents that the investigators classified as demented or physically too ill to undergo an interview were excluded, this may have resulted in the 1990/2001 Follow-up (Paper I, II and III) and 2001 Sample (Paper IV) being in better health than the source population. Additionally immigrant respondents who did not speak Norwegian were excluded, resulting in a very low proportion of immigrant respondents.

Although supported and funded by several sources, the Oslo-Lofoten study was similar to other long term cohort studies in being restricted by a limited budget. Not only did limits in resources and time influence the training of lay interviewers, but also the number of interviews it was possible to undertake. A clear example of this is the pre-selection of respondents by the HSCL-25 score for further CIDI interviewing, in 1990. Since the HSCL-25 yields a significantly higher proportion of women than men with scores ≥1.55 (Sandanger 1993), this necessarily caused the baseline CIDI sample to be gender biased and "sicker", i.e. having a higher proportion with psychological distress and a female preponderance (57.5% women in the 1990/2001 Follow-up) than the general source population.

On the other hand since most diseases affect only a small proportion of the population, thus requiring a very large number of respondents to be investigated in order to give reliable estimates of caseness, it can also be argued that the pre-selection by HSCL-25 served as an efficient and resource reducing case discriminator (Sandanger, Moum *et al.* 1998; Sandanger, Moum *et al.* 1999). In previous prevalence rate reports by the Oslo-Lofoten study from the 1990 data, the use of probability weights correcting for the differential representation of the sample is extensively described (Sandanger, Nygard et al. 1999).

In order to eliminate all pre-selection bias by the HSCL-25 in the 2001 Sample (Paper IV), respondents interviewed again from 1990 (N=421) were excluded. Even after excluding the 421 follow-up respondents, the 2001 Sample was still large (1,247 respondents included), and a large sample size in itself contributes to reducing error.

When applying the Bonferroni post hoc test on groups lost to follow-up, significant differences were found in number of lifetime MUS and MES at baseline (Paper I). For number of MES (but not for number of MUS) the difference was also significant ($P<.05$) between those who were interviewed again and those lost to follow-up other than death (see 3.2.2.2). A possible explanation for this could be that those lost to follow-up for reasons other than death were physically "sicker" and less able to participate.

Other reasons for non-response can only be conjectured. For example, when the respondent is initially contacted and the interviewer explains the nature and procedure of interview, including that interviewing could take about two three hours of their spare time, either during the day or evening, which ever the most convenient, this clearly appears to be quite lengthy. In our modern time jam, respondents might also have considered the procedure far too time-consuming, as well as feeling uncomfortable with the person to person interview situation and the disclosure of personal information.

All procedures aiming at reducing the amount of systematic error, secure not only precision in measurement and estimation, but also strengthen the study's internal and external validity (generalizability). In other words, the possibility of being able to draw inference to the source population (internal validity) and also to those outside the population (generalizability) is thereby created. Compared to the Norwegian population (see Table 8) the overall gender distribution was the same (51 %) in the 2001 Sample. However, as for the age groups some over representation in the 2001 Sample is found for the middle age groups (35 – 49 years) and some under representation in the highest (66 years and above) for both genders, which must be taken into account when considering the external validity (generalizability) of the results in Paper IV.

5.1.1.2 Information bias

Information bias is the error stemming from flawed information being collected about the study or from the study subjects. All information collected in studies based on self-report, could be affected by information bias, also referred to as *misclassification*. For example the answers given might be affected by "socially desirable responding" or "yea-saying", giving rise to answers being too much of the kind or too little, resulting in faulty or skewed data. Depending on the mechanism of misclassification, misclassification is often referred to as *differential* or *non-differential*. If the the error is correlated with or depends on the value of other variables then the misclassification is *differential* but if the error is not correlated with or not dependent on the value of other variables, the misclassification is *non-differential*.

Recall bias is a common form of information bias and differential misclassification. The problems related to faulty recall of lifetime MUS and MES are extensively dealt with in Paper I. Many respondents had completely forgotten previous recorded symptoms. The interchange of the MUS and MES categories over time also revealed not only a large degree of symptom variability but also a large degree of misclassification.

All interviewers in the Oslo-Lofoten study, both lay interviewers and the study's participating physicians, underwent CIDI interview training, but even doctors have been found to err when diagnosing symptoms as MES and not MUS when the consultation interaction is perceived as negative (Nimnuan, Hotopf *et al.* 2000). Although the CIDI has been used by many (Rubio-Stipec, Canino *et al.* 1993) and is a well validated diagnostic instrument (Wittchen 1994; Wittchen, Lachner *et al.* 1998), probing extensively to find out if the symptom can be accounted for by a reasonable or plausible cause, i.e. either by a physical disease or substance/alcohol abuse, or by what the doctor has said, and accordingly classified as MES, a large degree of misclassification of symptoms can still arise.

A limitation of the CIDI could lie in its use of lay interviewers, a factor which might have affected the temporal instability of symptoms over time. For a lay interviewer various medical terms used by the patient or referred to as what the doctor had said, for example lumbago or fibromyalgia, could easily lead to an underestimation of MUS. For example, clinically significant back pain for men was very rarly recorded as medically unexplained (Paper I). A reason for this could be that all mention of lumbago was recorded as MES-back pain when some rightly should have been classified as MUS-back pain, a misclassification directly affecting the occurrence of PD and also other SDs to be lower. An example of the opposite, i.e. symptoms being wrongly classified as MUS when they apparently should have be classified as MES, seem to be those related to the female reproductive organs, such as excessive menstrual bleeding and irregular menstruation. A reason for this could be the unclear communication between respondent and interviewer, but it could also be a sign of lack in gynaecological knowledge. Thus the complexity of the CIDI probe questions in itself leading to difficulties in answering might have resulted in some response bias (Knauper, Wittchen 1994). Yet another reason for the overlap of the MUS/MES categories could be that both physical and psychiatric causes actually contribute to the symptom (Kroenke, Lucas *et al.* 1992). However, since all diagnostic computation of SDs in DSM-IV and ICD-10 is based on the occurrence of clinically significant MUS, misclassification of MUS is an error which must be taken into account. Most likely the error has resulted in symptoms being more often registered as explained, thereby leading to an underestimation of SDs prevalence rates based on these symptoms, in Paper II, III, IV.

In spite of no obvious outliers being found among our interviewers and earlier reports of the CIDI showing a good inter-rater reliability (Wittchen 1994; Von Korff, Ustun 1995) the validity of the classification of a symptom as MES and MUS could still be quite low.

5.1.1.3 Confounding bias

Confounding is a statistical concept referring to the confusion or mixing of effects. Confounding bias is present when the apparent effect on one's outcome measure from a putative cause (exposure) is due to a common underlying cause, the confounder. There are two main methods to prevent erroneous conclusions due to confounding; one is *randomization* and another *restriction*. Restriction, i.e. the selecting of homogenous subjects (for example same age, same sex, same genotype) to the study, as undertaken in experimental animal laboratory studies, the effect of which prevents confounding, increases the study validity, enhancing the ability to make scientific inference. This is a strategy that cannot easily be used in epidemiological surveys, and it has not been employed in the papers of this thesis. However, statistical controls in many cases may be attained by stratifying one's data according to levels at the suspected confounding variable. Randomization or random assignment of study subjects to experimental groups is also not used in the studies of this thesis, thus leaving only the method of statistically controlling for possible confounding effects in the data analysis. The *statistical control* for possible confounding effects is undertaken in all regression analyses of papers I-IV and described in each paper accordingly.

Generally a confounder must be associated with both the outcome (disorder/disease) and exposure under examination, and fulfil three criteria; i) be a risk factor for the disorder/disease ii) be associated with the exposure under examination in the source population and iii) not be affected by (caused by) the exposure or disease (i.e. it should not be an intervening variable between the exposure of interest and the outcome). For example in Paper I, a model for symptoms lost to recall and possible confounding effects are given (Paper I, Fig. 3). When statistically controlling for number of MUS at baseline, men tended to lose more symptoms, i.e. forget more than women. For respondents reporting high levels of MUS at baseline the propensity to lose more symptoms also increased with increasing age. Confounders influencing the outcome of symptoms lost to recall could be physical morbidity and psychological distress.

5.1.2 Random error (precision) and statistical analyses

Random error is the variability in the data arising from hidden (unknown) causes that are statistically unrelated both to the outcome and the independent variables investigated. Random error can also give rise to misclassification. *Precision* in measurement and estimation corresponds to the lack of random error. Precision can be affected by the study size, and the

negative effects of random error can be diminished by a large sample size, most importantly by reducing the risk of Type-II errors. The cross-sectional sample of 1,247 respondents (2001 Sample) interviewed with the CIDI somatoform section is large and even the follow-up study size of 421 persons (1990/2001 Follow-up) interviewed in 1990 and 11 years later, is quite considerable. The inevitable attenuation of correlations between variables as a result of random errors thus could be counteracted and the risk of Type-II errors reduced. Reducing random error by creating additive summary scales with sufficient internal consistency was done in the case of the HSCL (in Paper IV Cronbach's alpha for total HSCL-25 score 0.91, HSCL-25 anxiety sub-score 0.78, and HSCL-25 depression sub-score 0.88).

5.1.3 Study designs

5.1.3.1 Longitudinal prospective

Strengths of the 1990/2001 Follow-up and its longitudinal prospective study design are the possibility of studying course over time. The general population sample examined in this thesis, from baseline 1990 to follow-up 2001, is exceptional with respect to the long 11 year time span (Paper I, II, III). Two sets of data on the same individuals in 1990 and 2001 made the examination of course over time, assessment of risk factors influencing prognoses and the identification of predictors possible. To the best of my knowledge no other study in Norway, nor any other recent international study has examined the phenomena of MUS and their associated SDs syndromes over such a long time interval. In this respect the results presented in this thesis are unique.

The finding again of respondents in 2001 interviewed before in 1990 was achieved with diligence and the final response rate (70%) was high, ensuring validity of the 1990/2001 Follow-up sample (Paper I, II and III). However, some bias associated with the non-response (other than death) being in poorer health at baseline must be taken into account, an aspect which might have caused the prevalence of disorders among respondents followed up to be rather low.

5.1.3.1 Cross-sectional

Strengths of the 2001 Sample study lie in the random general population selection from two geographical areas in Norway, ensuring a sample largely representative of the source population, and thereby allowing for valid inferences. A further strength in the 2001 study was the revised Oslo-Lofoten Interview Schedule and Self-questionnaire, containing more

specific updated questions of for example musculoskeletal disorders and use of medication (anti-depressives). In addition the WHO-CIDI version 1.2 also contained a revised somatoform section, with a larger number of symptoms examined than the previous CIDI version 1.0 utilized in the 1990 baseline survey. The use of the computerized CIDI interview in 2001 allowed direct data entry and minimized errors arising from incorrect data entry.

However, a limitation of the cross-sectional or prevalence study design is its descriptive nature. Associations and risk factors found in Paper IV are therefore descriptive in character and not so much explanatory.

5.2 Empirical issues

Empirical issues dealt with in the studies of medically unexplained symptoms and their related SDs (Paper I-IV) of this thesis are many, difficulties of classification and lifetime versus current symptom criteria, prevalence, diagnostic overlap and comorbidity, course over time and risk factors.

5.2.1 Diagnostic difficulties, diagnostic validity, reliability and utility

Criterion sets and classification of mental disorders have largely been put together on the basis of consensus and expert opinion (Beauchaine, Beach 2006). The DSM as a whole is also based on a descriptive and pragmatic foundation rather than an empirical foundation or theories about pathogenesis (Follette, Houts 1996; First 2005). By the application of criterion sets and development of structured interviews, the diagnostic reliability of psychiatric disorders, including SDs, has been very much improved (Beauchaine, Beach 2006), even though many empirical questions still remain. Whether SDs really are sufficiently validated to defend them being treated as well-founded "taxa" in psychopathology and thus belonging to the future DSM-V, is the matter in question.

Doubt about the reliability and validity of the MUS/MES differentiation and the MUS category on which the disorders of the SD category are based, is raised in this thesis (Paper I). Although the said dichotomy might be useful in some respects, the results of Paper I reveal that the distinction between explained and unexplained is very unreliable, affected to a large degree by recall bias. Nevertheless, future recommendations, for example regarding the PSD, are still based on assessing *not fully explainable* symptoms according to a 15-item symptom list (see Table 3 and Appendix 2).

Some of the main issues of diagnostic validity addressed in this thesis (Papers II-IV) are those of the Feighner Phases 4, follow-up study/predictable course (Paper I, II and III) and

Feighner Phase 3, delimitation from other disorders (Paper III and IV) (for Feighner Phases, see Table 1). Antecedent validators (predictors and risk factors) are also addressed by the regression analyses in Papers I-IV and predictive validators concerning diagnostic consistency over time, relapse and recovery (Paper II and III). The issues of course, relapse and recovery of SDs, at the one symptom level (by current MUS-pain), are addressed in Paper II. The extensive diagnostic overlap of SDs subtypes (SDud, HC, PD, SSI-3/5, SDnos and MSD) with the only possible differentiation being between pooled "current SDs" and "lifetime SDs" is dealt with in Paper III, as well as the superior consistency (stability) of pooled "current SDs" compared to "lifetime SDs". Although the use of symptoms lists to count ensures higher diagnostic reliability, the question of utility remains. Viewed from a primary care perspective, the more complex the amount and type of symptoms for which it is necessary to examine, including the combination of symptom types to fulfil the diagnostic criteria (as in SDz), the lower the diagnostic utility seems to be.

5.2.2 Symptom lists and symptom counting

The quandary associated with unexplained symptom counting and the threshold required for diagnosing a disorder, either being very low (at the one symptom level) or very high (at 6 for ICD-10 and 8 for DSM-IV) is reflected in Paper II and IV. In spite of DSM-III-R introducing the new disorder SDud due to the symptom count dilemma of SDz, this does not seem to have solved the problem. In order to comply with the DSM-IV and ICD-10 diagnostic criteria, the symptom screening in the older CIDI 1.0 Somatoform section 41-item symptom list (see Appendix 3) in the WHO-CIDI 1.2 was changed to a 43-item symptom list (see Appendix 4). However, nearly all symptoms in the CIDI somatoform section lists are clearly taken from the original 59-item symptom list of Hysteria (Feighner, Robins et al. 1972) based on the work by Perley and Guze, in 1962 (Perley, Guze 1962) (see Appendix 1). In this respect the symptom lists used today appear very much unchanged (see Table 4), and symptoms seem to have just "survived" when they are in fact out-dated. An example of this is also seen in the symptom "feeling sickly" - since it was not regarded as a symptom *per se* it was excluded, in all Papers I-IV. Other symptoms, such as menstrual irregularities, excessive menstrual bleeding and vomiting during the whole pregnancy, can also very much be questioned as to their legitimacy for being on today's symptom lists used for diagnosing SDs. Similar to the exclusion of amenorrhea (see Appendix 1) in later symptom lists, it can be argued that these symptoms should also have been excluded. However, since this was not done and since these gender-

related gynaecological symptoms are still part of the diagnostic criteria, they were not omitted in the papers of this thesis. However, in order for symptoms to be directly comparable at baseline (1990) and follow-up (2001) in Papers I-III, only 38 symptoms could be used in the 41-item CIDI 1.0 (see Appendix 3) and 43-item CIDI 1.2 (see Appendix 4) symptom lists. Likewise, the disorders in Paper II and III had to be computed directly from the 38 unexplained symptom CIDI raw data by diagnostic algorithms according to DSM-IV criteria in order to be directly comparable at the two time points. Since diagnoses obtained from the CIDI computerized diagnostic program did not contain MSD, the diagnoses of SDs in Paper IV also had to be computed directly from the CIDI raw data, which examined for recency of MUS in three pooled categories. In effect the computation of MSD in this thesis (Paper III and IV), is an adaptation of the original MSD by the PRIME-MD study (Kroenke, Spitzer et al. 1997). A difference in methodology, which might have influenced the differences in report of prevalence rates of MSD, originally reported 8% (Kroenke, Spitzer et al. 1997) and by others 24 % (Lynch, McGrady et al. 1999) and in this thesis (Paper IV) as 14% in 2001 (Paper IV)

5.2.3 Prevalence

Even though reports the existing literature of prevalence rates of SDs are quite abundant, most studies are based on lifetime exploration of MUS and only a few are based on current symptom criteria (Kroenke, Spitzer *et al.* 1997; Lyles, Hodges *et al.* 2003; Hiller, Rief *et al.* 2006). Wide variations in reported prevalence ranges, (Faravelli, Salvatori *et al.* 1997; Lynch, McGrady *et al.* 1999; De Waal, Arnold *et al.* 2004) could be due to differences in methodology and a wide variety definitions (Creed, Barsky 2004; Creed 2006a). For example, for SDud it is apparent that some studies define this category according to the abridged SSI-4/6 or SSI-3/5 criteria (Escobar, Rubio-Stipec et al. 1989; Rief, Heuser et al. 1996) whereas others define it as a disorder at the one MUS level (Lynch, McGrady et al. 1999). Even figures from different epidemiological studies in the same country, for example Norway (Sandanger, Nygard *et al.* 1999; Kringlen, Torgersen *et al.* 2001; Kringlen, Torgersen *et al.* 2006) are not directly comparable due to diverging methodologies.

Nevertheless, comparisons of prevalence rates within the same survey having a repeated cross-sectional design, such as the Oslo-Lofoten study are considered more trustworthy (Sandanger, Nygard *et al.* 2006). The overall 10.2% six-month prevalence rate of pooled SDs according to *current* MUS criteria presented in Paper IV may be seen as comparable to the

two-week 5.9 % prevalence rate of SDs previously reported from the Oslo-Lofoten study. Even so the comparison has some shortcomings since the CIDI 1.0, 41-item symptom list of 1990 is somewhat different from the CIDI 1.2, 43-item symptom list of 2001 and since disorders examined in the SDs category were more numerous in 2001 (for example SDnos was not examined by the CIDI diagnostic algorithms in 1990).

Although it is argued that the introduction of "clinical significance" in DSM-IV has reduced prevalence rates of any mental disorder (anxiety, depression and substance abuse) in the adult population (over 18 years) from an earlier 28.1% down to 18.5% (Regier, Narrow 2002), this does not seem to be the case for SDs. In contrast, the 18.7% - 22% size and burden of SDs according to newer studies, also based on current criteria (Wittchen, Jacobi 2005; Hiller, Rief et al. 2006), give the impression of an increased prevalence rate tendency. When compared with previous two week 5.9% prevalence rate of SDs the Oslo-Lofoten study from 1990, the overall 10.2% rate of *severe* current SDs (Paper IV) does not support an increased prevalence rate tendency. Although the use of severity, i.e. employing the disability dimension to reduce number of false-positive disorder cases, has been criticized (Wakefield, Spitzer 2002), it can be argued that this practice does have a practical utility purpose, when also considering the policy implications of epidemiologic data. When applying the severity criterion, the pooled prevalence rate of current SDs dropped from 24.6% to 10.2% (Paper IV).

5.2.4 Course and stability

Longitudinal epidemiological studies concerned with SDs are not many (Creed 2006a) and validation by course over time are lacking (Robins, Guze 1970; Feighner, Robins et al. 1972; Panzetta 1974). When considering issues of diagnostic validity, marked differences in outcome suggesting a diagnostic heterogeneity must be taken into account (Dennerstein 2005). For example only a small group (mainly women) with MUS-pain are found prone to chronicity (Paper II), suggesting that the group of MUS-pain sufferers is not homogenous. Since this reveals the group of MUS-pain sufferers to be etiologically heterogeneous, it could be argued that a single symptom should not be representative of a disease or disorder entity (Dennerstein 2005). On the other hand, some mono-symptomatic physical disorders are a matter of considerable clinical concern, such as non-cardiac chest pain (Dammen, Bringager *et al.* 2006) and chronic dizziness (Staab 2006). Such disorders do in some cases obviously need to be addressed as the disease itself (Hahn 1999) based on the manifestation of the severity of the symptom.

Comparable to the overall 48% stability for the whole SDs group reported by Lieb and colleagues (Lieb, Zimmermann *et al.* 2002), stability for pooled "lifetime SDs" is found similar and highest (53%) by prospective consistency (Paper III). However, for current SDs, stability by retrospective consistency was 42% and better than for lifetime SDs (33%), and the measurement of agreement although good/fair (κ =0.214 (P<.001)) was best for current SDs (Paper III). This reflects not only an inconsistency of the CIDI instrument in detecting these disorders from baseline to follow-up, but likewise to the findings in Paper II for MUS-pain, that the course of SDs is remittent rather than chronic in nature over time. These findings are in clear contrast to the criteria and view of SDs having a chronic and recurrent course, in both the DSM-IV and ICD-10.

5.2.5 Gender

The purpose of introducing the terms medically unexplained, somatization and somatoform was to free the manifestation of unexplained symptoms from their hysteria legacy (Wool, Barsky 1994). However, this does not seem to be the result. Compared to other mental disorders, the gender differences in criteria, requiring fewer symptoms for men than for women, as in the SDz, SSI-4/6 and SSI-3/5 concepts are quite exceptional.

The symptom lists used to explore whether symptoms are medically explained or not, are by their history (Perley, Guze 1962; Feighner, Robins et al. 1972) still stuck in the mire of more female symptoms being on the list (see Appendix 2 to 4). Although not the only explanation, this bias most likely does account for some of the tendency of women to report more MUS than men (Paper I) and consequently for the prevalence rates generally being twice as high for women (Paper IV). Generally women tend to report more symptoms than men at baseline, but men tend to forget more at follow-up than women (Paper I). The forgetting of symptoms was also related to age and symptom load, and young women had an increased twofold risk compared with men for having persistent MUS-pain over a long time. Although just a few (predominantly women) are prone to chronicity of MUS-pain at the one symptom level (Paper II), it is of vital importance to all clinicians to identify those at risk and to subsequently find adequate treatment measures.

5.2.6 Overlap and comorbidity

The overlap of functional syndromes has previously been described as being so extensive that similarities outweigh the differences (Wessely, Nimnuan et al. 1999; Aaron, Buchwald 2001). In this thesis the overlap between the subtypes of disorders in the SDs category is found so substantial that a slight difference can only be found when classifying the disorder subtypes by current or lifetime criteria (Paper III). These very unclear boundaries seem to reflect not only the consensus opinion criteria roots of mental disorders, but also that arbitrary cut-off points have been superimposed on variables that are normally distributed in the population (Follette, Houts 1996; Kroenke, Rosmalen 2006).

In contrast to SDs having a three-fold increased risk of co-morbid anxiety and depression (De Waal, Arnold et al. 2004), an even higher four to five times greater likelihood of having current SDs when depressed is found (Paper III and IV). In addition a two times risk of comorbid musculoskeletal disorders is found (Paper IV). A kinship between current SDs, anxiety and depression in the sharing of risk factors is also demonstrated (Paper IV). Altogether, only 31% of those with severe current SDs were without co-morbidity (Paper IV) and in this subclass psychological distress measured by the HSCL-25 score is also found elevated compared to those without any disorders.

5.2.7 Predictors and risk factors

Not all disease pathology explains bodily symptoms and not all bodily symptoms can be explained by disease, neither can all bodily symptoms that are not explained by disease be explained by psychopathology (Sharpe, Mayou *et al.* 2006).

Considering that the psychobiology of MUSs has been linked with depression and the involvement of decreased tryptophan and other serotonergic amino acids (Rief, Pilger *et al.* 2004), and the antidepressant mianserin found as an effective agent for treatment of patients with FGID (Tanum, Malt 1996), MUS-pain, might in this respect represent a real “taxon” in psychopathology. If this be the case, then the question is whether the CIDI instrument and the methods used for identifying MUS are good enough.

Although etiological support is given in this thesis to the psychobiology of MUS being linked with depression (Rief, Pilger *et al.* 2004; Larson, Clark *et al.* 2004) (Paper I) the exact psychopathology of MUSs can not be determined. To gain such knowledge, interventions, neuroimaging and similar studies, in addition to epidemiological studies, such as the Oslo-Lofoten study, are needed. Hypothetically if MUS-pain should be a real taxon in

psychopathology, then the question is whether the CIDI instrument and the methods used for identifying MUSs are good enough.

No matter how good the identification of MUS by strict exclusion of possible medical disease causes is in the CIDI somatoform probing (Wittchen, Essau et al. 1993; Rubio-Stipec, Canino et al. 1993), this cannot make up for the fact that the presumed psychopathology behind MUSs has been hypothetically derived and is based on psychoanalytical theory (Sharpe, Mayou *et al.* 2006). In the long run, such preconceptions are scientifically very unsatisfactory, as demonstrated by the large variability in the MUS/MES distinction by Paper I.

5.3 Conceptual issues

Distinguishing disorders from non-disorders, mental from physical disorders, and the problem of a diagnostic category being either over or under exclusive involves also conceptual issues (Wakefield, Spitzer 2002; Regier, Narrow 2002; Bradfield 2006; Sykes 2006). Conceptual issues of unexplained symptoms and their related syndromes can be traced all the way back to Ancient Greek medicine in the history of Hysteria. However, modern history of SDs can be said to have its origin in the mid 19th century beginning with the influential hysteria works of Briquet and Charcot (Briquet 1859; Charcot 1987) which later, under the influence of psychoanalytical Freudian theory (Micale 1993; Marin, Carron 2002) metamorphosed into somatization and SDs of the twentieth century. The controversies of medical theory, disease explanation and causation throughout the ages and even those facing SDs today can be seen in the fascinating history of SDs.

Interestingly, Hysteria was among the psychiatric disorders found sufficiently validated by means of the five Feighner phases (given in Table 1) presented in 1972 (Feighner, Robins *et al.* 1972), later to be included and modified into the SDs of DSM-III (American Psychiatric Association 1980). Although the symptomatology for SDz concerning number of symptoms has changed throughout revisions of DSM, age of onset (defined as: before 30 years for Hysteria) and the course (chronic or recurrent for Hysteria) have not. Even the screening of many of the symptoms, to date has remained the very same! It is not surprising that present-day neurologists proclaim hysteria to have *never* disappeared but to have lived on over two millennia, being seen as pseudo and psychogenic seizures in ordinary neurological practice among both women and men today (Trimble 2004). On the other hand, in light of the remnants of Hysteria and Briquet's syndrome living on in today's SDs, the controversy and

criticism of SDs not being valid enough any longer to justify their belonging to future classification of mental illness is not surprising (Mayou, Kirmayer et al. 2005; Bradfield 2006; Sykes 2006; Sharpe, Mayou et al. 2006).

Although the terms MUSs and MESs were introduced to clarify and to operationalize somatization in research (Melville 1987; Kirmayer, Robbins 1991), and to rid SDs of their hysteria legacy (Wool, Barsky 1994) the extensive gender issue connected with unexplained symptoms and SDs still remains today. Why only amenorrhea was abolished from the original 59-item hysteria symptom list (Appendix 1) and dysmenorrhoea, menstrual irregularity, excessive bleeding, vomiting during the whole pregnancy and dyspareunia kept in the later lists (Appendix 3 and 4) is a relevant question. Similar to the argument that dyspareunia should no longer be classified as a mental disorder (Spitzer 2005) because "it makes no sense", the same can be argued for all these gynaecological symptoms.

Even though application of criterion sets and the use of structured interviews, such as the CIDI, to a large extent have improved the diagnostic reliability of psychiatric disorders (Beauchaine, Beach 2006), the studies of this thesis still casts considerable doubt on both the validity and reliability of MUS and their related syndromes. The MUS criteria used today to separate SDs from other physical disorders are definitely less clear today than when they were introduced (Bradfield 2006).

5.4 Pros and cons in the DSM-V deliberations

Suggestions concerning what to do in the future are many and diverse. In spite of a collective agreement on all future changes being empirically based, increasing validity, reliability and utility of the disorder(s), strong voices have advocated a variety of outcomes, such as the disorders be lumped, split up, relocated within DSM-V and discarded altogether (Mayou, Kirmayer et al. 2005; First 2005; Kroenke 2006; Fava, Fabbri et al. 2007). In each classification revision, the number of diagnoses and pages grow substantially (Follette, Houts 1996) and new dimensions of the disorders are introduced, for example disability and distress in the DSM-IV (Wakefield, Spitzer 2002; Regier, Narrow 2002). A completely new category of "interface disorders" collecting and covering all functional disorder in a multidisciplinary fashion (Henningsen, Zipfel et al. 2007) has also been suggested as a solution to bridge the symptom in the mind versus body gap (Komaroff 2001). Views from experts concerning how to deal with these disorders in the future cannot entirely free themselves from appearing tinged by their context and being somewhat country dependent (Anglo - American - German

– Scandinavian - Italian) (Mayou, Kirmayer et al. 2005; Kroenke 2006; Henningsen, Lowe 2006; Fink, Toft et al. 2007; Rief, Isaac 2007; Fava, Fabbri et al. 2007), regarding how the field of psychosomatic medicine and research in the field is organized and funded. Although political pressure has been warned against as being determinative for changing DSM classification (Starcevic 2006), health policy issues concerning inequity in patient disability pensions if and when symptoms, distress and dysfunction are classified as mental disorders, are very central to the debate and must be taken seriously.

Although using the term "functional" rather than "medically unexplained" may be less stigmatizing (Stone, Wojcik et al. 2002) by implying a malfunctioning nervous system, it does not really solve the problem, since the precise aetiology of MUS and the mechanisms by which psychopathology causes physical symptoms still remain unclear today (Rief, Pilger et al. 2004; Sharpe, Mayou et al. 2006). The future suggested replacement of all existing SDs, under the new PSD umbrella relocated on an Axes III, general medical disorders of DSM-V (Kroenke 2006), with a cut-off level of only one *not fully explainable* symptom (see Table 3), still leaves PSD to be established by MUSs and by exclusion criteria. Even the recommended PHQ-15 physical symptom list (see Appendix 2) for confirming PSD, includes symptoms of menstrual problems/cramps for women, and still does not solve the dilemma of how many symptoms to count and how really to decipher which symptoms are not fully medically explained.

6. Conclusion and implications

Classification of mental disorders should be aimed at merging disorders sharing the same presenting symptoms, encouraging differential diagnoses and the exclusion of general medical conditions, and facilitating communication between mental health professionals and also between health professionals and patients. Co-morbid symptoms of anxiety/depression rather than medically unexplained symptoms per se, should qualify the patient for a psychiatric diagnosis.

Main conclusions of the thesis:

- Lifetime symptoms are often forgotten over time. Lifetime data elicited in community surveys by diagnostic instruments such as the CIDI should be viewed with caution. Methodological errors weakening the data credibility could lead to false impressions of true change over time.

- The medically unexplained and medically explained distinction of physical symptoms is difficult to maintain.
- A course of re-currency and remittance of MUS-pain is the rule rather than the exception. Except for a small group (mainly women) prone to chronicity, the prognosis of MUS-pain is relatively good. Clinicians should examine for depression when confronted with MUS-pain patients and be aware of the increased twofold risk for women compared to men to have debilitating pain symptoms over a long time.
- Prior depression and physical disease are risk factors for current SDs, but only prior anxiety appears to be a risk factor for lifetime SDs. However, present anxiety is a main risk factor associated with severe current SDs. Utilization of health care should be considered an outcome measure and not be part of the future SDs criteria.
- Overlap between SDs is high (up to 100%). Diagnostic stability of current SD is better than lifetime SDs. Current SDs are 4 times more likely to occur among depressed respondents and co-morbidity of severe current SDs with anxiety/depression and/or musculoskeletal disorders is 70%. The overall prevalence rate of *severe* current SDs in 2001 is 10%.

6.2 Future research and classification

Although psychiatric and somatic disorders should be diagnosed separately, it is important to arrive at a consensus between the medical specialities concerning diagnoses. It is still necessary to base diagnoses on consensus opinion of experts, but they should also increasingly be based on empirical evidence concerning, reliability, validity and utility. Future diagnostic criteria of SDs should be based on *current* symptoms, and not on lifetime. The criteria should also be based on positive symptomatology, and not on exclusion criteria. The same should apply to other outcome measures such as utilization of health care. The criteria for women and men should be the same. Follow-up studies and further validation of recently suggested multidimensional and multidisciplinary functional somatic syndromes criteria for SDs are clearly needed.

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Appendix

Appendix 1. Hysteria (Briquet's syndrome) and 59-item physical symptoms list

Diagnostic criteria [a] - both criteria A and B are required:	
A. A chronic or recurrent illness beginning before age 30, presenting with dramatic, vague or complicated medical history.	
B. At least 25 symptoms for "definite" diagnosis and 20 to 24 symptoms for a "probable" diagnosis in at least 9 of the following groups:	
Group 1	
1. Headaches	32. Diarrhea
2. Feeling sickly most of life	33. Constipation*
Group 2	**Group 6**
3. Blindness	34. Abdominal pain
4. Paralysis	35. Vomiting
5. Anesthesia	
6. Aphonia	**Group 7**
7. Fits or convulsions	36. Dysmenorrhea
8. Unconsciousness	37. Menstrual irregularity
9. Amnesia	38. Amenorrhea*
10. Deafness	39. Excessive bleeding
11. Hallucinations (in absence of psychosis)*	
12. Urinary retention	**Group 8**
13. Trouble walking	40. Sexual indifference
14. Other conversion symptoms	41. Frigidity
	42. Dyspareunia
Group 3	43. Other sexual difficulties
15. Fatigue*	44. Vomiting during all nine months of pregnancy or hospitalized for hyperemesis gravidarum
16. Lump in throat	
17. Fainting spells	**Group 9**
18. Visual blurring	45. Back pain
19. Weakness	46. Joint pain
20. Dysuria	47. Extremity pain
	48. Burning pains of the sexual organs, mouth, or rectum
Group 4	49. Other bodily pains
21. Breathing difficulty	
22. Palpitation	**Group 10**
23. Anxiety attacks*	50. Nervousness*
24. Chest pain	51. Fears*
25. Dizziness	52. Depressed feelings*
	53. Need to quit working or inability to carry on regular duties because of feeling sick*
Group 5	54. Crying easily*
26. Anorexia*	55. Feeling life was hopeless*
27. Weight loss*	56. Thinking a good deal about dying*
28. Marked fluctuations in weight*	57. Wanting to die*
29. Nausea	58. Thinking of suicide*
30. Abdominal bloating	59. Suicide attempts*
31. Food intolerances	
C. No other diagnosis can be made to explain the symptoms	

[a] Diagnostic criteria by Feighner et al. in 1972 (Feighner, Robins *et al.* 1972) based on the work by Perley and Guze, 1962 (Perley, Guze 1962)

* Eliminated symptoms in the DSM-III list (American Psychiatric Association 1980)

Appendix 2. Patient Health Questionnaire 15-Item Somatic Symptom Severity Scale (PHQ-15)

During the past 4 weeks, how much have you been bothered by any of the following problems?	0 Not bothered at all	1 Bothered a little	2 Bothered a lot
1. Stomach pain			
2. Back pain			
3. Pain in your arms, legs or joints (knees, hips, etc.)			
4. Menstrual cramps or other problems with your periods [women only]			
5. Headache			
6. Chest pain			
7. Dizziness			
8. Fainting spells			
9. Feeling your heart pound or race			
10. Shortness of breath			
11. Pain or problems during intercourse			
12. Constipation, loose bowels or diarrhea			
13. Nausea, gas or indigestion			
14. Feeling tired or having low energy			
15. Sleeping trouble			
Total score (from 0 to 30) [a]:			

[a] Severity of symptoms score, ranging from 0 to 30. The PHQ-15 is a somatic symptom subscale derived from the full 20-item self-administered Patient Health Questionnaire (PHQ) of the PRIME-MD (Pfizer Inc, New York, NY) a brief instrument developed for making criteria based diagnoses of mental disorders in primary care (Spitzer, Williams *et al.* 1994).

Appendix 3. CIDI 1.0 Somatoform section, 41-item physical symptoms list

i) Pain [a]**:**	
1. abdominal pain	21. numb feeling in arm/leg
2. back pain	22. paralysis
3. joint pain	23. lost voice
4. leg/arm pain	24. seizure
5. chest pain	25. faint
6. headache	26. unconscious
7. painful menstruation*	27. amnesia
8. urination pain	**iii) Sexual and other symptoms** [c]**:**
9. genital pain	28. double vision
10. other place pain	29. short breath
ii) Gastrointestinal and pseudo-neurological [b]**:**	30. weakness
11. vomiting	31. blotchy skin
12. continuous vomiting during pregnancy*	32. bad taste in mouth
13. nausea	33. urinate too often
14. diarrhoea	34. unable to urinate
15. excessive gas	35. numbness
16. food intolerance	36. lump in throat
17. blindness	37. irregular menstruation*
18. blurred vision	38. excessive menstrual bleeding*
19. deafness	(39. dizziness) [d]
20. trouble walking	(40. heart pounding, beating hard) [d]
	[41. often felt sickly] [e]

[a] 1. Pain category, pooled for recency of MUS(s); last month, last six months, over six months ago and within last year, over one year ago.

[b] 2. Gastrointestinal and pseudo-neurological, pooled for recency of MUS(s) as in [a].

[c] 3. Sexual and other symptoms, pooled for recency of MUS(s) as in [a].

[d] Not in A2, 2001 list

[e] Symptom excluded

* Women only

Appendix 4. WHO-CIDI 1.2 Somatoform section, 43-item physical symptoms list

i) Pain [a]**:**	
1. abdominal pain	22. paralysis
2. back pain	23. lost voice
3. joint pain	24. seizure
4. leg/arm pain	25. faint
5. chest pain	26. unconscious
6. headache	27. amnesia
7. painful menstruation*	**iii) Sexual and other symptoms** [c]**:**
8. urination pain	28. double vision
9. genital pain	29. short breath
10. other place pain	30. weakness
ii) Gastrointestinal and pseudo-neurological [b]**:**	31. blotchy skin
11. vomiting	32. bad taste in mouth
12. continuous vomiting during pregnancy*	33. urinate too often
13. nausea	34. unable to urinate
14. diarrhoea	35. numbness
15. excessive gas	36. lump in throat
16. food intolerance	37. irregular menstruation*
17. blindness	38. excessive menstrual bleeding*
18. blurred vision	(39. sexual problems/impotence) [d]
19. deafness	(40. sexual indifference) [d]
20. trouble walking	(41. pain during sexual intercourse) [d]
21. numb feeling in arm/leg	(42. sex not enjoyable) [d]
	[43. often felt sickly] [e]

[a] 1. Pain category, pooled for recency of MUS(s); last month, last six months, over six months ago and within last year, over one year ago.

[b] 2. Gastrointestinal and pseudo-neurological, pooled for recency of MUS(s) as in [a].

[c] 3. Sexual and other symptoms, pooled for recency of MUS(s) as in [a].

[d] Not in A1, 1990 list

[e] Symptom excluded

* Women only

Appendix 5. Hopkins Symptom Checklist (HSCL-25) anxiety and depression subscales

The respondent is requested to assess how much, on a scale from (1) not at all to (4) very much, she/he has been bothered with the following symptoms (during the last week, including at present):	
Anxiety subscale items (1–10)	Depression subscale items (11–25)
1. Suddenly scared for no reason	11. Feeling low in energy
2. Feeling fearful	12. Blaming oneself for things
3. Faintness, dizziness or weakness	13. Crying easily
4. Nervousness or shaking inside	14. Loss of sexual interest or pleasure
5. Heart pounding or racing	15. Poor appetite
6. Trembling	16. Difficulty falling asleep or staying asleep
7. Feeling tense or keyed up	17. Feeling hopeless about the future
8. Headaches	18. Feeling blue
9. Panic attacks or spells of fear	19. Feeling lonely
10. Feeling restless, unable to sit still	20. Thoughts of ending your life
	21. Feeling of being trapped or caught
	22. Worrying too much about things
	23. Feeling no interest in things
	24. Feeling everything is an effort
	25. Feelings of worthlessness

Appendix 6. Fifteen-item physical disorders list, in 1990/2001 Follow-up

Disorders recorded in 1990 and 2001as present or not [a]:
15-item physical disorders list:
1. Diabetes
2. Heart stroke, angina, hypertension
3. Stroke, cerebral haemorrhage
4. Bronchitis, asthma, hay fever, allergic eczema
5. Psoriasis
6. Rheumatic disease, arthritis, ankylosing spondylitis
7. Arthrosis
8. Tendonitis, muscle knots
9. Lumbago, sciatic back pain
10. Epilepsy, neurological disorder
11. Gastrointestinal disorders, stomach ulcer, gastritis
12. Blood diseases, anaemia
13. Kidney, liver, bile/gall bladder disease
14. Cancer
15. Other physical diseases

[a] 1990/2001 Follow-up (Paper I, II, III) – in 2001 only disorders with impairment (2) moderate to (3) severe were included

Appendix 7. Thirteen-item physical disorders list and four-item musculoskeletal disorders list, in 2001 Sample

The respondent is requested to assess how much, on a scale from (1) a little (2) moderate to (3) severe she/he has been affected (impaired in daily life, activities, work) by the following disorders (during the last year) [a]:	
13-item physical disorders list:	**4-item musculoskeletal disorders list:**
1. Diabetes	1. Tendonitis, muscle knots
2. Heart stroke, angina, hypertension	2. Fibromyalgia, chronic fatigue
3. Stroke, cerebral haemorrhage	3. Neck/shoulder myalgia, including whiplash
4. Bronchitis, asthma, hay fever, allergic eczema	4. Lumbago, sciatic back pain/myalgia
5. Psoriasis	
6. Rheumatic disease, arthritis, ankylosing spondylitis	
7. Arthrosis	
8. Epilepsy, neurological disorder	
9. Gastrointestinal disorders, stomach ulcer, gastritis	
10. Blood diseases, anaemia	
11. Kidney, liver, bile/gall bladder disease	
12. Cancer	
13. Other physical diseases	

[a] 2001 Sample (Paper IV) – only disorders with impairment (2) moderate to (3) severe included

Appendix 8. Fifty-two item Stressful Life Events Scale

Report of events 12 months preceding the interview and affected by the event (1) a little (2) moderately (3) severely [a].

1. Large changes in duties at work	29. Spouse/living partner with emotional problems
2. Conflict at work	30. Spouse/living partner with alcohol or narcotic problems
3. Large business problems	31. Serious conflict with children
4. Dismissed from work	32. Separation or divorce in children
5. Without employment, laid off	33. Conflict with neighbour
6. Spouse or living partner laid off	34. Significant conflict with another (not neighbour or cohabitant)
7. Started an education	35. Seriously ill friend
8. Broken off an education	36. Seriously ill grandchild
9. Serious financial difficulties	37. Seriously ill child
10. Serious illness or accident (own)	38. Seriously ill parent
11. Admitted to hospital (own)	39. Seriously ill relative
12. Abortion or miscarriage	40. Seriously ill spouse/living partner
13. Menopause	41. Married or become cohabitant
14. Given birth	42. Relationship problems, in marriage or with living partner
15. Something of great importance lost or destroyed	43. Separated, divorced or broken up living partner relationship
16. Death of close friend	44. Unfaithful (self or spouse/living-partner)
17. Death of close relative	45. Abused
18. Death of grandchild	46. Become separated from persons of significance (other than death)
19. Death of child	47. Housing/residential problems
20. Death of father	48. Change of housing/residence
21. Death of mother	49. Retired, resigned or on welfare pension
22. Death of spouse/living partner	50. Home residence suddenly ruined
23. Moved, migrated	51. Started new job
24. In trouble with the law	52. All other events of importance
25. Other legal difficulties	
26. Children moved out of home	
27. Children with emotional problems	
28. Children with alcohol or narcotic problems	

[a] In 1990, severity of life events from (1) to (3) was not recorded. The 52-item list is a reduced and adapted version of Paykel and Mangan' s 63-item schedule (Paykel, Mangen 1980)