Facets of neuroticism and musculoskeletal symptoms. A study of middle-aged twins

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\textbf{ABSTRACT}

Clinical and epidemiological studies have shown that both site-specific and more widespread musculoskeletal (MS) conditions are linked to anxiety and depression symptoms. However, the nature of this relationship is poorly understood, particularly in terms of underlying genetic and environmental influences. Furthermore, the personality trait neuroticism has been shown to be related to common emotional symptoms and somatic distress as well as to more serious psychiatric and medical disorders. In modern personality theory, the broad neuroticism domain is conceptualized as consisting of a set of lower-order facets, such as anxiety, hostility, and depression, which may be differentially related to various health outcome measures. So far, the role of neuroticism facets as risk factors for MS conditions has not been explored in genetically informative designs.

In the current study, the relationship between MS symptoms and six neuroticism facets was investigated in bivariate analyses and in regression models including sex, education level, and general health indices as control variables. Using multivariate twin modeling, genetic and environmental influences on the phenotypes and the associations among them were determined. The sample consisted of 746 monozygotic (MZ) and 770 dizygotic (DZ) twins in the age group of 50-65 (mean = 57.11 years, SD = 4.5). The results showed that a single factor accounted for about 50% of the overall variance in MS symptom reporting. Two neuroticism facets, N1: anxiety and N3: depression, appeared as significant in the regression analyses. Both these facets and MS symptoms were strongly influenced by genetic factors [heritability ($h^2$) = 0.46-0.54]. While there was a considerable overlap in genetic risk factors between the three phenotypes, a large proportion (71%) of the genetic variance in MS symptoms was unique to the phenotype, and not shared with the neuroticism facets.

\textbf{INTRODUCTION}

Chronic pain has been described as a “silent epidemic” (1) that affects a large proportion of the population, particularly in high-income countries, resulting in great personal suffering and societal costs in terms of sick leave and lost productivity (2). Among the most prevalent chronic or recurrent pain conditions are those affecting the musculoskeletal (MS) system. MS symptoms and disorders encompass pain and other symptoms at specific anatomical sites (e.g., low back pain, shoulder and neck pain), as well as more generalized symptoms as seen in fibromyalgia and chronic widespread pain (CWP). Chronic MS pain affects between 11% and 50% of the general population (2,3), with CWP prevalence varying between 11% and 14%. Such discrepancies in prevalence estimates are partly due to differences in the definition of MS pain and to the methods used for its assessment (2).

Except in cases of traumatic injury and certain diseases affecting MS structures, the etiological factors behind MS conditions are not fully understood and identified (1,4). However, several risk factors have been shown to be associated with disorder onset and development: (a) Demographic factors, e.g., sex, age and education level (1); (b) comorbidities such as sleep disorders, chronic fatigue, irritable bowel syndrome, and mood disorders (3,5); (c) personality traits, in particular neuroticism (6); (d) psychosocial and physical working conditions (7,8); (e) psychological states and strategies that themselves modulate pain experiences, e.g., general anxiety, catastrophizing, fear-avoidance and somatic awareness (9); and (f) genetic factors (1).

Pain problems seem to develop from an early age and tend to persist and worsen by an increasing number of pain sites during later life stages (10). Studies of adolescent populations have shown that MS symptoms are common (11), and emotional and behavioral problems appear to be strongly related to multi-site pain (12). The lifespan nature of MS symptoms and their high prevalence across age groups highlights the need to investigate the genetic and environmental factors underlying such symptoms and their correlates. Twin studies of MS pain generally indicate substantial genetic effects, with heritability estimates ranging from 30% to 68% (13). Studies of neck pain have shown that the genetic influence becomes gradually less important with increasing age, and individual-specific (non-shared) environmental factors dominate almost completely in the older age groups (14,15). Of note, in...
populations with similar environmental exposures there is still considerable individual variation in disorder occurrence and severity (4).

Numerous epidemiological and clinical studies have shown that a clear majority of patients with chronic MS pain or other pain conditions are women, and this sex bias appears to correspond to actual sex differences in laboratory pain sensitivity (9). Thus, compared to men women generally have a higher sensitivity and lower tolerance to a range of experimental pain stimuli (e.g., cold and heat pain, muscle pain), in addition to reporting higher pain ratings (9). Furthermore, both functional somatic disorders (e.g., chronic fatigue, irritable bowel syndrome) and internalizing psychiatric disorders (e.g., generalized anxiety disorder, major depression) are more prevalent in women than in men (16), and anxiety and depression frequently occur together with chronic pain in both general population and patient samples (17,18). Importantly, the added burden of depression and anxiety with chronic MS pain is strongly associated with more severe pain, greater disability, and poorer health related quality of life (19,20). Thus, negative affect symptoms, which are related to sex (6), appear to play a crucial role in the development and chronicification of MS pain and other pain conditions.

Accumulated research has documented that anxiety/depression symptoms are moderately to strongly associated with the personality trait neuroticism (21), and twin studies indicate a common genetic predisposition (22). In addition, a couple of twin studies have shown that associations between neuroticism and functional somatic disorders can be attributed to shared genetic and individual-specific environmental factors (23,24). Vassend et al. (25) showed that in a sample of young twins (aged 23-35 years) the relationship between neuroticism and general (non-clinical) somatic complaints could to a large extent be accounted for by a common genetic factor. Moreover, a substantial proportion of the variance in somatic complaints was due to unique genetic and individual-specific environmental influences unrelated to neuroticism. Similar findings have been reported by Hansell et al. (24) in a study of adolescent twins. However, to our knowledge these findings have not been replicated, and it is an open question whether they apply to MS symptoms specifically and to what extent they can be generalized to older individuals.

An additional question, not addressed in previous research in this area, pertains to the facet structure of personality domains and whether the facets or sub-scales of neuroticism are differentially related to health indices such as MS symptoms. According to Costa and McCrae’s five-factor theory of personality (26,27), the neuroticism domain comprises six facets, among them anxiety and depression. In twin studies of the relationship between neuroticism and psychiatric and somatic symptoms (22,24,28), facet information has not been utilized. Although anxiety and depression symptoms are obviously relevant to an adequate understanding of the development and consequences of various pain conditions, it is still an unsettled question which of the neuroticism facets will be most strongly associated with MS symptoms, particularly when adjusting for demographic variables and general health indices.

In the current study, we explored the relationship between MS symptoms and the six neuroticism facets in bivariate analyses and in regression models including sex, education level, and general health indices as control variables. The sample comprised middle aged twins (50-65 years) and were thus older than the participants in the two twin studies of neuroticism and somatic complaints referred to above (24,25). Using a multivariate twin design, we then investigated to what extent common genetic or environmental liability factors contribute to the covariance between neuroticism facets (identified as significant in the regression analyses) and MS symptoms.

**METHODS**

**Sample**

Twins were recruited from the Norwegian Twin Registry (NTR). The registry comprises several cohorts of twins (29), and the current study is based on a random sample from the cohort born 1945-1960. In 2011, questionnaires were sent to a total of 2136 twins. After reminders, 1516 twins responded, yielding a response rate of 71%. Of the participants, 1272 individuals were pair responders, and 244 were single responders. Zygosity has previously been determined based on questionnaire items and has been shown to classify correctly 97-98% of the twins (30). The cohort, as registered in the NTR, consists only of same-sex twins, and the study sample consisted of 290 monozygotic (MZ) male twins, 247 dizygotic (DZ) male twins, 456 MZ female twins and 523 DZ female twins. Age range of the sample was 50-65 (mean = 57.11, SD = 4.5). The study was approved by the Regional Ethical Committee, and informed consent was obtained from all participants.

**Measures**

Neuroticism facets were assessed using a Norwegian version of the NEO Personality Inventory Revised (NEO-PI-R) (26,31). The inventory consists of 240 items and measures five broad domains (i.e., extraversion, neuroticism, agreeableness, openness to experience, and conscientiousness) as well as six facets subsumed under each domain. The neuroticism domain comprises the facets N1: anxiety, N2: hostility, N3: depression, N4: self-consciousness, N5: impulsiveness, and N6: stress vulnerability. Each facet is measured by six items, and Cronbach’s alpha for the Norwegian version varies from 0.60 to 0.84 (31).

MS symptoms were measured using the Giessen Symptom Checklist (GSCL) (32,33). This GSCL sub-scale comprises 6 items, reflecting symptoms at various
body sites: (1) Pains in joints or limbs, (2) backache,  
(3) pain in neck and shoulders, (4) headaches, (5) heaviness or tiredness in the legs, and (6) head-pressure.  
The participants were asked to rate the degree to which  
they ‘generally’ suffered from the complaints, using a  
5-point scale: 1 – not at all; 2 – slightly; 3 – somewhat; 4 – considerably; and 5 – strongly. In the original  
development of the scale Brähler and Scheer (32)  
decided to include additional symptoms (i.e., items 4-6)  
that are commonly associated with MS pain symptoms  
proper (i.e., items 1-3). Principal components analysis  
of the six items yielded only one component with an  
eigenvalue >1 in two sub-samples comprising, respecti-  
vely, the first and the second member of the twin pair.  
The first/second eigenvalues in the two sub-samples  
were 2.92/0.95 and 3.08/0.87, respectively. The factor  
loadings were in the 0.50-0.80 range. This common  
factor explained about 50% of the variance in MS  
symptoms in both sub-samples. Chronbach’s alpha  
values for the full and the shortened (items 1-3) scale  
were 0.80 and 0.76, respectively, and the correlation  
between the two scales was 0.93 (p < 0.001). In the  
present study, in which MS symptoms in the broader  
sense constitute the main study variable, results based  
on the original full scale (i.e., the mean of all the 6  
measures) will be reported.

As noted, the demographic variables included in the  
study were sex and education (5 levels). A set of general  
health indices was adopted from previous large-scale  
Norwegian health surveys (6,34). These were (1)  
presence of medical disease (yes/no), (2) presence of  
lasting functional impairment (yes/no), and (3) reduced  
activity or days in bed due to illness (acute or chronic)  
or injury for the last two-week period (yes/no), before  
completing the questionnaire.

Analyses

Descriptive statistical analyses were performed to  
examine means (SD) or score distributions of the vari-  
ables. Bivariate associations between the neuroticism  
facets and the MS symptoms index were assessed using  
Pearson correlation analysis. Regression analysis was  
then performed to examine the independent effects of  
the neuroticism facets on the MS symptoms index in  
models including the neuroticism facets alone or to-  
gether with demographic and general health variables.  
Because regression analysis needs to reflect the paired  
structure of the data when the complete sample is  
examined, Generalized Estimating Equations (GEE)  
was used (35).

Based on the results from the regression analysis,  
we conducted a set of biometric analyses to estimate  
the genetic and environmental contributions to the  
associations between neuroticism facets and MS symp- 
toms in the best-fitting model. All models were run  
with OpenMx (36). Standard Cholesky models (37-39)  
were used to estimate the genetic and environmental  
contributions to variance in and covariance between  
the three phenotypes. The Cholesky model specifies as  
many latent genetic and environmental factors as vari-  
ables (phenotypes) in a triangular decomposition (for  
illustration see Figure 1). The estimates of genetic and  
environmental effects is based on a comparison of  
resemblance in MZ twins (who share all segregating  
genetic material) and DZ twins (who share on average  
half of their segregating genetic material). Generally,  
bio metric modeling allows for estimating three major  
sources of variance, i.e., additive genetic factors (A),  
common environment (C) and individual-specific or  
non-shared (E) environment. In addition, non-additive  
 genetic effects (D) may be tested, but are only  
indicated if the observed MZ-correlations are greater  
than twice the DZ-correlations. Models are constrained  
so that latent A-factors correlate perfectly among MZ  
twins, and at 0.5 among DZ-twins. C-factors are corre- 
lated at unity for both zygosity groups, and E-factors  
are by definition uncorrelated. Several nested models  
were compared in order to identify the best-fitting one  
according to the minus2LogLikelihood difference test  
(Δ-2LL) and the Akaike Information Criterion (AIC)  
(40). Thus, an ACE model was compared to an AE  
model, and the consequences of constraining the  
parameters to be equal across sex in a given model  
were assessed. In investigating potentially sex-limited  
effects of genetic and environmental factors using the  
Cholesky model, the approach outlined by Neale et al.  
(39) was adopted. In same-sex twin samples only so- 
called scalar sex limitation can be assessed, i.e., it is  
presupposed that the same factors cause variation in  
males and females, but they may do so to a different  
extent. Since the factors are the same across sex, they  
can correlate with each other to the same extent.  
Hence, the genetic and environmental correlation  
matrices must be constrained to be equal for males and  
females. The model with the lowest AIC represents the  
best balance of goodness-of-fit and parsimony.

Results

Symptom score distributions and prevalence of symp-  
tomatic individuals are shown in Table 1. Pain and  
other symptoms in the extremities and in the head,  
neck and back region were reported commonly, with a  
prevalence of 16.9-60.0%. MS pain symptoms (i.e.,  
items 1-3) were the most prevalent, and a fairly large  
proportion of the respondents (8-15%) indicated that  
they suffered ‘considerably’ or ‘strongly’ from their  
complaints.

As expected, medical problems were common in this  
middle-aged twin sample (Table 2). A large number of  
the respondents (41%) reported that they had at least  
one medical condition, and about 11% reported having  
been ill or injured during the last two weeks. All  
demographic and general health variables were signifi- 
cantly associated with MS symptoms when they were  
entered simultaneously with the neuroticism facets in  
regression analysis (Table 2). The phenotypic correla-


were set equal for men and women, yielded additional
models. Model 1 included A, C and E factors, and
symptoms index. Table 3 shows the fit of the different
environmental effects in model 2 did not result in a
improvements in fit, with the AE model having lowest
Figure 1 shows the Cholesky parameters of the model. A genetic factor (A1) accounted for all the
genic variance in N1: anxiety, plus 37% of the total
ance (81% of the genetic variance) in N3: depression,
third column), and and after adjustment for sex, education and general health indices (fourth column). ** p < 0.01; *** p < 0.001.

Table 1. Score distributions for the six symptoms included in the MS index, and prevalence of symptomatic individuals (i.e., with a score equal to or greater than 2; Slightly).

<table>
<thead>
<tr>
<th>Model</th>
<th>-2 log likelihood</th>
<th>df</th>
<th>∆-2LL (Δdf)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ACE (sex-specific parameters)</td>
<td>14891.35</td>
<td>9018</td>
<td>-</td>
<td>-3144.65</td>
</tr>
<tr>
<td>2. AE (sex-specific parameters)</td>
<td>14894.57</td>
<td>9030</td>
<td>3.22 (12)</td>
<td>-3165.43</td>
</tr>
<tr>
<td>3. AEC (equal standardized parameters across sex)</td>
<td>14899.27</td>
<td>9027</td>
<td>7.92 (9)</td>
<td>-3154.73</td>
</tr>
<tr>
<td>4. AE (equal standardized parameters across sex)</td>
<td>14900.23</td>
<td>9033</td>
<td>8.88 (15)</td>
<td><strong>-3165.77</strong></td>
</tr>
</tbody>
</table>

and the MS symptoms index on the other, varied be-
tween 0.12 and 0.34 (all coefficients significant at the
p < 0.05 level). N1: anxiety and N3: depression was found to be significant in a regression analysis includ-
ing only the six facets as independent variables (Table 2).

We next tested a set of trivariate Cholesky models
including N1: anxiety, N3: depression, and the MS
symptoms index. Table 3 shows the fit of the different
definitions. Model 1 included A, C and E factors, and
allowed estimates to vary across sex. Dropping shared
environmental effects in model 2 did not result in a
significant reduction in fit (i.e., ∆-2LL = 3.22, Δdf = 12, ns.) and produced a lower AIC value. Furthermore,
model 3 and 4, in which the standardized path
coefficients for both environmental and genetic effects
were set equal for men and women, yielded additional

Table 2. Descriptive statistics (second column) and estimates of regression coefficients based on generalized estimating equations, representing statistical effects of neuroticism facets on MS symptoms (third column), and

Table 3. Model fitting results (best-fitting model shown in bold). A – Additive genetic effects; C – common environmental effects; E – non-shared environmental effects; AIC – Akaike’s Information Criterion.
were found, indicating that interactions between symptoms at different anatomical sites report biometric modeling. In congruence with present sample, was used in regression analyses and (32,33).

The relationship of neuroticism facets with MS symptoms in primarily two ways. First, our study contributes to the research on psychological D

0.12 (95% CIs were 0.05-0.19, and 0.40-0.60, respectively). The corresponding environmental correlations were also of equal magnitude, i.e., 0.12 (95% CIs were 0.05-0.19, and 0.06-0.19, respectively).

The genetic correlations between MS symptoms on the one hand, and N1: Anxiety and N3: depression on the other, were both 0.52 (95% CIs were 0.44-0.60, and 0.43-0.60, respectively). The corresponding environmental correlations were also of equal magnitude, i.e., 0.12 (95% CIs were 0.05-0.19, and 0.06-0.19, respectively).

DISCUSSION

Our study contributes to the research on psychological aspects of MS symptoms in primarily two ways. First, the relationship of neuroticism facets with MS symptoms was investigated, for the first time we assume, in a genetically informative design. Second, a composite MS index, based on previous psychometric research (32,33) and psychometric results obtained in the present sample, was used in regression analyses and biometric modeling. In congruence with the findings reported by Williams et al. (41), significant associations between symptoms at different anatomical sites were found, indicating that a single, common factor accounts for much of the liability to report MS symptoms.

As expected, our results showed that MS symptoms were commonly reported in this population-based sample of middle-aged twins. Furthermore, demographic and general health variables were significantly associated with MS symptoms when entered simultaneously as independent variables in multiple regression analyses. Of note, women evidenced a higher MS complaint level than men, even after adjustment for education, general health indices, and neuroticism facets. This finding is in keeping with accumulated research on sex differences in chronic pain conditions, suggesting the existence of a female-specific pain psychobiology (9). Of significance, however, the best-fitting biometric model did not include any sex-specific parameters. Thus, while there are systematic sex differences in pain symptom levels (9) and neuroticism scores (26), the underlying genetic and environmental variance-covariance structures do not appear markedly sex-specific.

The heritability estimates of MS symptoms and neuroticism facets were broadly consistent with those reported in previous studies (4,42,43). Cholesky modeling furthermore revealed significant and non-trivial genetic cross-effects from N1: anxiety to N3: depression and MS symptoms, but not from N3: depression to MS symptoms. However, the genetic correlations between N1: anxiety and N3: depression on the one hand, and MS symptoms on the other, were substantial (i.e., 0.52), as was the genetic correlation between the two N facets (i.e., 0.90). Hence, which of these facets are put in the first position in the Cholesky.
model is more or less arbitrary, the essential finding being that the phenotypic correlations are significantly influenced by common genetic factors. In the model shown in Figure 1, a strongly influential common genetic factor was identified, accounting for nearly 50% of the total variance in N1: anxiety and around 81% and 27% of the genetic variance in N3: depression and MS symptoms, respectively. This factor may reflect a general susceptibility to psychological and somatic distress (44), which is a core characteristic of the neuroticism trait (i.e., depression, hostility, and stress/anxiety related psychophysiological activation).

Accumulated research across decades has documented the consistent association between neuroticism and the presence of somatic complaints and illnesses (44, 45). Researchers have offered a variety of explanations, including both spurious and causal relationships, when describing these neuroticism-health associations. A first possibility is that neuroticism is associated with a greater internal self-focus and a tendency to worry/ rumination, resulting in an exaggerated preoccupation with physical symptoms and therefore a greater symptom report bias (44). However, several large-scale longitudinal studies have documented that initial neuroticism levels are predictive of somatic and psychiatric morbidity assessed several decades later (23,46). Furthermore, the employment of various statistical control procedures, such as adjustment for simultaneous neuroticism scores, indicates that such longitudinal findings are unlikely to be the result of manifest psychiatric disorder or reporting bias. Of significance, individuals with higher neuroticism levels are vulnerable to a broad range of mental disorders (i.e., anxiety, depression, schizophrenia, personality disorders), higher levels of comorbidity, medically unexplained somatic symptoms, and general health problems, including cardiovascular disease, irritable bowel syndrome, and chronic widespread pain (23,47).

For these reasons, neuroticism may not reflect just a symptom perception and report bias, but is in all likelihood also linked to symptom generating neurobiological processes. The significant genetic correlations that emerged in the present study indicate that a common genetic vulnerability may explain the neuroticism-MS symptoms association. In light of the research referred to above, it appears unlikely that common genes and mechanisms are restricted to exert their effects solely on symptom perception and symptom reporting processes.

A second explanation, related to the discussion of the symptom perception hypothesis, maintains that chronic emotional instability and psychophysiological activation trigger off pain enhancing, inflammatory and other physiological processes, resulting in wear and tear in the body, increased symptom levels, and illness liability. In a longitudinal twin study, Charles et al. (23) showed that the likelihood of having a somatic conditions (e.g., chronic fatigue syndrome, ulcers, coronary heart disease, chronic widespread pain) was related to higher levels of neuroticism assessed 25 years earlier. Neuroticism exerted the strongest effects for conditions involving systemic pain. Many researchers (48,49) maintain that higher levels of neuroticism and negative affect symptoms such as anxiety and depression may disturb normal pain responding and over time cause pain sensitization and other disabling effects. As documented in numerous pain experiments, repeated exposure to noxious stimulation may lead to amplified pain response (sensitization) or diminished pain response (habituation), and these phenomena seem to involve both peripheral and central processes (50). Recently, Nakamura et al. (51) showed that participants in an experimental pain study on average showed amplification (sensitization) of pain report over trials. Of note, the personality traits neuroticism and conscientiousness contributed to the variance in pain amplification. However, the statistical effects were rather modest, and the authors were careful to point out that their results do not indicate that personality traits explain clinical pain conditions characterized by central sensitization. Moreover, while personality traits and negative affect symptoms appear, depending on pain modality, essentially unrelated to or only weakly related to sensory pain sensitivity (28), they are evidently more strongly associated with the affective-motivational dimensions of pain in both clinical and non-clinical populations (52,53).

For example, in a study of fibromyalgia patients (54), depressive symptoms and anxiety correlated with pain catastrophizing and subjective rating of general health, but did not correlate with pressure pain sensitivity or cerebral processing of pain as assessed by functional magnetic resonance imaging (fMRI).

Altered immune function should also be considered as a possible mechanism underlying neuroticism and somatic complaints. One recent and potentially important insight from psychoneuroimmunological research is the discovery that components of the immune system that mediate inflammation may be intimately involved in negative affect symptoms (55). Normally, inflammatory activity is provoked by physical stimuli such as infections or injuries. There is now substantial evidence that stress/negative affect can trigger significant increases in inflammatory activity (i.e., in the absence of physical injury/infection). Amplified inflammation can in turn influence pain perception and induce symptoms such as fatigue, depressive symptoms and social-behavioral withdrawal (56). Notably, some studies have reported significant associations between personality traits and inflammation markers. A population-based study, including nearly 5000 participants, showed that high neuroticism and low conscientiousness were both associated with higher levels of the pro-inflammatory cytokine interleukin-6 (IL-6) (57). However, the associations were weak (i.e., correlations in the 0.04-0.07 range), and some studies have failed to find an association between neuroticism and IL-6 (58).

A third general explanation for the neuroticism-
health relationship is that either the somatic condition or its treatment may give rise to rather than result from negative affect symptoms and elevated neuroticism. Generally, life events including acute and chronic illnesses are unrelated to or only weakly related to neuroticism or the other personality domains within the five-factor framework (27). It is worth mentioning, however, that a recent longitudinal study of long-time consequences of chronic, serious diseases such as cancer, stroke and heart disease on personality traits has indeed documented significant effects (59). However, the effects were weak to moderate (i.e., T score changes on the order of 0.25-0.44), and the agreeableness trait was unaffected by chronic disease. As shown in the Cholesky analysis in the present study, the environmental influences were largely specific to each phenotype. These model parameters reflect, besides measurement error, environmental factors unique to the trait and to the individual, such as occupational risk factors, stressful life events, injuries and illnesses. Obviously, without further information it is uncertain to what extent such factors are reflected in significant E parameters in the present model.

Of the potentially important individual-specific environmental effects on MS conditions, psychosocial working conditions and physical workloads should be mentioned in particular (8). In a meta-analysis, Hauke et al. (60) concluded that working conditions characterized by low social support, high job demands, low job control, low decision authority, and low job satisfaction were associated with risk for MS pain in the low back, the neck/shoulder, and the upper extremities. However, as pointed out by several authors (7,60), much research in this area is to a large extent inconclusive and is often focused on a circumscribed body region, such as neck/shoulder or low back pain. For example, Clausen et al. (7) hold that most studies have failed to adjust for physical workload or different types of negative affectivity, both of which may be important confounders. In their own prospective study, Clausen et al. (7) showed that psychosocial working conditions such as emotional demands, role conflicts and work influence predicted low back pain for between 1 and 30 days in the past year at follow-up after adjustment for sociodemographic variables, health behaviors, and physical workload. However, most associations became statistically insignificant when adjusted for depressive symptoms at baseline. The authors maintain that depressive symptoms will cause over-reporting of both adverse psychosocial working conditions and MS pain, which implies that the observed associations between independent and dependent variables may be spurious. Similar results were reported in a study (61) of anxiety/depression symptoms in shift workers, using neuroticism as the main control variable. In a series of simple regression models, most of the psychosocial work factors were significantly related to anxiety/depression symptoms, controlling for age, sex, and education level. When neuroticism was included in the regression models, several of these associations were no longer significant, and due to the strong statistical effect of neuroticism the amount of explained variance in the dependent variables increased substantially. Thus, one important implication of these studies is that the perception and appraisal of environmental characteristics are inherently linked to stable and heritable personality traits.

The present study has notable strengths such as using a genetically informative sample of twins that can be considered representative of a large segment of the Norwegian general population. Additionally, all the measurement instruments have established psychometric properties and have been used in previous epidemiological research and in twin studies (6,25). Nevertheless, some limitations should also be noted. First, our assessment was based on self-reports, without physical examinations or other objective data. Thus, clinical conditions that may cause MS symptoms were not assessed, and the results may not be directly comparable to those based on clinical samples. For example, in a twin study of the role of disc degeneration (assessed by lumbar MRI) in low back pain (62), significant genetic correlations were found for disc height narrowing and different definitions of back pain, such as duration of the worst back pain episode and disability in the previous year from back pain. The heritability estimate was 0.51 for disc height and in the 0.31-0.37 range for the various definitions of low back pain. However, as noted by Williams et al. (41) and others, there is often a lack of correspondence between (subjective) clinical pain and objective findings such as radiographic change. It can furthermore be argued that pain reporting is significant and valid in its own right as it represents the symptoms with which patients present to their physicians. Lastly, the genetic and environmental structure underlying subjective vs. objective aspects of MS symptoms are evidently very different so one should not be used as a substitute for the other (41).

Second, the data were obtained on only one occasion. Life-course epidemiology points to the need for longitudinal research designs to investigate the course of both somatic and psychiatric conditions. Cross-sectional study designs tend to mix single-episode cases with recurrent and chronic cases, which are known to differ with regard to the extent of comorbidity, disability, and possibly etiology (63). It should be emphasized, however, that the relationship between neuroticism, negative affect symptoms, and somatic complaints appears highly robust and has been demonstrated across developmental phases, from childhood to old age (45). Nevertheless, there is an obvious need for longitudinal, genetically informative studies in this research area.

A third limitation may be the conceptualization of neuroticism facets and subjective somatic symptoms as distinct phenotypes, given the relative lack of empirical data to support a clear separation (24). For example,
Watson and Pennebaker (44), in their pioneering studies, maintained that the systematic associations among numerous negative affect and somatic complaints measures were due to an underlying ‘somato-psychic distress factor’. Additionally, various symptom clusters such as functional somatic syndromes (16), together with anxiety and depression, may be considered part of a broader spectrum of internalizing disorders (64). Still, comprehensive factor analytic studies indicate a clear separation (65-67). Of particular note, our own findings as well as previous research (16,24) have demonstrated that while neuroticism, anxiety/depression symptoms, and somatic complaints are related, they are also distinct in terms of underlying genetic and environmental factors.

In summary, our results indicate that a substantial part of the variance in symptom reporting at different anatomical sites can be accounted for by a single underlying factor. This generalized symptom susceptibility is furthermore phenotypically linked to the neuroticism facets N1: anxiety and N3: depression, and to sex, education level and indices of general health condition. Cholesky modeling indicated substantial unique genetic and non-shared environmental influences on each phenotype, whereas genetic sources accounted for most of the associations among the three phenotypes. How these findings should be accounted for in terms of underlying genetic architecture and psychobiological mechanisms, must still be regarded as an open question. There are probably several causes and processes involved such as central pain modulation and inflammatory activity. The clinical implications of the relationship between pain, anxiety and depression have been emphasized by many authors (19). The present study contributes to this discussion by showing that the neuroticism trait facets N1: anxiety and N3: depression are genetically linked to MS symptoms.

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