Selected CSF biomarkers indicate no evidence of early neuroinflammation in Huntington disease

ABSTRACT

Objective: To investigate CSF biomarkers of neuroinflammation and neurodegeneration in Huntington disease (HD) gene-expansion carriers compared to controls and to investigate these biomarkers in association with clinical HD rating scales and disease burden score.

Methods: We collected CSF from 32 premanifest and 48 manifest HD gene-expansion carriers and 24 gene-expansion negative at-risk controls. We examined biomarkers of neuroinflammation (matrix metalloproteinase 9, C-X-C motif chemokine 13, terminal complement complex, chitinase-3-like-protein 1 [CHI3L1], and osteopontin [OPN]) and neurodegeneration (microtubule-associated protein tau, neurofilament light polypeptide [NFL], and myelin basic protein [MBP]). The study was approved by the Ethics Committee of the Capital Region of Denmark (H2-2011-085) and written informed consent was obtained from each participant before enrollment.

Results: NFL was the only biomarker that increased in premanifest stages and no evidence of early involvement of neuroinflammation in HD was found. However, we found that the biomarkers for neurodegeneration, MBP and tau, increased during the disease course in manifest HD gene-expansion carriers and were associated with an increase of the neuroinflammation biomarkers CHI3L1 and OPN. Tau was also increased in all gene-expansion carriers with psychiatric symptoms compared to gene-expansion carriers without psychiatric symptoms.

Conclusions: Neuroinflammation, which seems not to be an early event in our cohort, may be secondary to neurodegeneration in late HD. NFL is a possible disease burden correlate in HD, reflecting neuronal loss even before motor symptom onset, and may be useful as a dynamic biomarker in intervention studies.

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GLOSSARY

CAP = CAG age product; CHI3L1 = human chitinase 3-like 1 protein; CRP = C-reactive protein; CXCL13 = C-X-C motif chemokine 13; HD = Huntington disease; IgG = immunoglobulin G; MBP = myelin basic protein; MMP9 = matrix metalloproteinase-9; NFL = neurofilament light polypeptide; NOx = nitric oxide and nitrite/nitrate; OPN = osteopontin; OR = odds ratio; Tau = microtubule-associated protein tau (total); TFC = total functional capacity; TMS = total motor score; UHDRS = Unified Huntington’s Disease Rating Scale.

Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder caused by an expanded CAG repeat in the huntingtin gene. HD is characterized by involuntary movements, psychiatric disturbances, and cognitive decline. Despite intensive research, the pathogenesis of HD remains unknown; however, the mutated huntingtin protein results in neuronal dysfunction and eventually neuronal death. Several pathophysiologic mechanisms have been suggested, including a neuroinflammatory component.

Multiple studies conducted on postmortem HD brain tissue and mouse models of HD have found altered expression of immunologically active molecules in the CNS. One study reported...
increased levels of clusterin in CSF from manifest gene-expansion carriers,\(^8\) and imaging studies using the PK11195 ligand indicated increased microglial activity in manifest and premanifest HD gene-expansion carriers.\(^9,10\) The huntingtin gene is ubiquitously expressed, and the pathologic changes are not limited to the CNS as systemic abnormalities, including an altered peripheral immune profile, are also described. Biomarkers of inflammation have been shown to be increased in plasma from HD gene-expansion carriers and the upregulation has been observed up to 16 years before predicted onset,\(^4,5,8\) although in a recent study these findings were not confirmed.\(^11\)

In this study, we measured biomarkers in 104 CSF samples, drawn and handled under standardized conditions, from HD gene-expansion carriers and HD gene-expansion negative controls. No evidence for early neuroinflammation was found. We found, however, that biomarkers of neurodegeneration increased in manifest disease, which was also associated with an increase in biomarkers of neuroinflammation.

**METHODS** HD gene-expansion carriers and controls. CSF samples from 3 groups were analyzed: premanifest gene-expansion carriers, manifest gene-expansion carriers, and gene-expansion negative individuals. Participants’ recruitment, exclusion and inclusion criteria, and investigation program is reported elsewhere.\(^12\) Participants were classified according to the Unified Huntington’s Disease Rating Scale (UHDRS) total motor score (TMS)\(^13\) with a UHDRS-TMS of \(\geq 5\) defined as motor manifest HD gene-expansion carriers. If the score was \(\leq 5\), indicating no substantial motor signs, they were classified as premanifest HD gene-expansion carriers. Participants were categorized based on the evaluation of psychiatric symptoms and performance on cognitive testing as described in Vinther-Jensen et al.\(^14\) Disease burden was calculated as CAG age product (CAP) score: CAP = ([CAGn - 33.66] \times age).\(^15\)

The study was approved by the Ethics Committee of The Capital Region of Denmark (H2-2011-085) and written informed consent was obtained from each participant before enrollment.

**CSF studies.** CSF samples were obtained by lumbar puncture and processed as previously described.\(^12\) Blood samples were drawn for corresponding blood biochemistry including leukocyte count and C-reactive protein (CRP) to control for possible infections. The following ELISAs were used to measure CSF biomarkers: C-X-C motif chemokine 13 (CXCL13), Quantikinine ELISA Kit (R&D Systems, Minneapolis, MN); matrix metalloproteinase-9 (MMP9), QuantiKinikine ELISA Kit; total nitric oxide and nitrite/nitrate (NO\(_x\)) assay; human osteopontin (OPN) and human chitinase 3-like 1 protein (CHI3L1), QuantiKinikine ELISA Kit; neurofilament light polypeptide (NFL), ELISA (Uman Diagnostics, Umeå, Sweden); myelin basic protein (MBP) ELISA (Beckman Coulter, Sharon Hill, PA); TCC ELISA Kit (Hyycult Biotech, Uden, Netherlands); and microtubule-associated protein tau (total) (Tau) human ELISA Kit (Life Technologies, Napru, Denmark). ELISAs were performed according to the manufacturers’ instructions. Samples were measured in duplicate and the mean intra-assay variability was 22.4% for CXCL13, 7.7% for MMP9, 5.5% for NO\(_x\), 3.2% for OPN, 4.7% for CHI3L1, 3.5% for NFL, 4.9% for MBP, 5.5% for TCC, and 2.9% for Tau.

**Statistical analysis.** Data are shown as mean and SD or as median and range. Biomarkers were corrected for skewed levels with logistic function prior to analysis. All measured concentrations of the values were adjusted for age and sex; regression coefficients \(b\) and \(p\) values are annotated. Adjustments for age and sex were calculated from a regression analysis that included age, sex, and group as covariates. The adjustments were based on an assumption that the age effect was the same in the 3 groups; this assumption was tested in a regression analysis with an interaction between age and group. Comparisons of concentration levels between the groups were performed using linear regression with adjustment for age and sex, corrected for multiple comparisons with Bonferroni correction. Determination of the individual biomarkers’ association with traditional disease progression scales and cumulative CAG toxicity expressed as CAP score was tested with linear regression analysis including age, sex in all gene-expansion carriers, and UHDRS total functional capacity (TFC)\(^16\) and UHDRS-TMS scores in manifest gene-expansion carriers. Correlations and partial correlations (after CAP score adjustment) between the individual biomarkers were performed using Pearson \(r\), while \(p\) values were Bonferroni-corrected. The levels of the biomarkers in relation to gene-expansion carriers with psychiatric symptoms or cognitive impairment were tested using multiple regression analysis including the adjusted values of the biomarkers as the dependent variable, and CAP score and a dichotomous variable indicating symptom group as independent variables. To test that the effect of the CAP score was the same in the 2 groups, a regression analysis with an interaction between CAP score and symptom group was applied.

**RESULTS** CSF samples were drawn from 121 individuals, 104 of whom were included in the analysis. The remaining samples from 3 gene-expansion negative controls and 8 premanifest and 6 manifest gene-expansion carriers were excluded due to high erythrocyte count (>500 cells/mL). The included participants were 24 HD gene-expansion negative controls and 32 premanifest and 48 manifest gene-expansion carriers. Participant characteristics are shown in table 1 and further described in earlier publications from our group.\(^12,14\) Immunoglobulin G (IgG) index was not significantly different in the 3 groups \((p = 0.224)\) and the distribution of individuals who had an IgG index above normal (>0.67) did not differ in the 3 groups \((p = 0.294)\) either. CSF oligoclonal bands were detected in 3 gene-expansion negative controls, in 3 manifest HD gene-expansion carriers, and in 9 premanifest gene-expansion carriers. CSF leukocyte counts were not significantly different in the 3 groups \((p = 0.392,\) Kruskal-Wallis). All participants had normal blood leukocyte count and CRP.

**Age and sex effects on the CSF biomarkers.** NFL and MBP were associated with both age and sex (expressed
Table 1 Participants’ background data

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>M/F</th>
<th>Age, y</th>
<th>CAG repeat length</th>
<th>CAP score</th>
<th>Albumin ratio</th>
<th>IgG index</th>
<th>Oligoclonal bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifest gene-expansion carriers</td>
<td>48</td>
<td>29/19</td>
<td>50 (30-74)</td>
<td>43 (40-53)</td>
<td>468.0 (101.8)</td>
<td>5.45 (2.36)</td>
<td>0.54 (0.09)</td>
<td>3</td>
</tr>
<tr>
<td>Premanifest gene-expansion carriers</td>
<td>32</td>
<td>19/13</td>
<td>36 (20-54)</td>
<td>43 (39-48)</td>
<td>319.3 (99.3)</td>
<td>5.05 (2.56)</td>
<td>0.58 (0.22)</td>
<td>9</td>
</tr>
<tr>
<td>HD gene-expansion negative</td>
<td>24</td>
<td>13/11</td>
<td>42 (26-68)</td>
<td>18 (17-26)</td>
<td>NR</td>
<td>4.92 (1.43)</td>
<td>0.53 (0.23)</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: CAP = CAG age product; HD = Huntington disease; IgG = immunoglobulin G index; NR = not relevant.

Data are presented as mean (SD) or median (range). (a) CAP score = [(CAGn – 33.66) × age].
(b) Albumin ratio = (CSFalbumin/Palbumin) × 1,000.
(c) Number of participants with oligoclonal bands.

as male compared to female participants (b = 0.009, p < 0.0001, age and 13.2% higher levels in male participants, p = 0.030, for NFL; and b = 0.006, p < 0.001, age and 8.1% higher levels in male participants, p = 0.004, for MBP). Associated with age but not sex were Tau (b = 0.003, p = 0.027, age and 8.8% higher levels in male participants, p = 0.135); CHI3L1 (b = 0.007, p < 0.0001, age and 8.8% higher levels in male participants, p = 0.104); TCC (b = 0.011, p = 0.001, age and 8.6% higher levels in male participants, p = 0.385); NOx (b = 0.003, p = 0.001, age and 9.2% higher levels in male participants, p = 0.073); and OPN (b = 0.006, p < 0.0001, age and 9.2% higher levels in male participants, p = 0.165).

Concentration differences between the groups. Figure 1 shows the adjusted levels for the 7 biomarkers in the 3 groups.

Subsequently, interaction analyses between age and group were performed to investigate if the age effect differed significantly among the 3 groups. Only Tau showed different effects of age in the 3 groups (p < 0.001) and was dependent on age solely in manifest gene-expansion carriers. As a result, Tau was only adjusted for sex and not age in subsequent analyses.

MMP9 was only detected in 3 samples (all with increased IgG index and oligoclonal bands), while CXCL13 was detected in 7 (3 with increased IgG index and 4 with oligoclonal bands). Neither the pattern of detection (p = 0.914 [MMP9], p = 0.938 [CXCL13]) nor the risk, expressed as odds ratio (OR), of having a detectable sample differed significantly in the 3 groups (OR 0.670, p = 0.786 for MMP9; OR 0.818, p = 0.838 for CXCL13) when comparing gene-expansion negative controls with manifest gene-expansion carriers and when comparing gene-expansion negative controls with premanifest gene-expansion carriers (OR 0.962, p = 0.962 for MMP9; OR 0.703, p = 0.529 for CXCL13).

Relationship between biomarkers and disease progression scales. Analyses of the relationship of age- and sex-adjusted biomarkers to disease progression scales were subsequently performed. In manifest gene-expansion carriers, CHI3L1, OPN, TCC, and NOx were not associated with UHDRS-TFC or UHDRS-TMS. For both NFL (p = 0.065) and MBP (p = 0.078), there was a trend towards association with the UHDRS-TFC scores. Furthermore, NFL but not MBP was associated with UHDRS-TMS (p = 0.022). Tau was not associated with UHDRS-TFC, but a trend towards association was found for UHDRS-TMS (p = 0.075). In all gene-expansion carriers, CAP scores were significantly associated with MBP (p = 0.001), CHI3L1 (p = 0.010), Tau (p = 0.01), and NFL (p < 0.0001) (figure 2).

Correlation between biomarkers. In all gene-expansion carriers, the correlation and the partial correlation of the adjusted concentration of the biomarkers showed a strong association between NFL and MBP (R = 0.509, p < 0.0001); however, the association was lost when controlling for CAP score (R = 0.301, p = 0.073) (table 2). Correlations between the adjusted levels of the biomarkers were repeated in the gene-expansion negative controls. The correlations that were significant were the same in the 2 analyses, apart from the correlations between OPN and Tau (R = 0.517, p = 0.073) and OPN and CHI3L1 (R = 0.443, p = 0.23) (data not shown).

Correlation between HD symptoms and biomarkers. Only Tau and TCC were associated with psychiatric symptoms. Tau showed different effects of the CAP score in the 2 groups, with or without psychiatric symptoms (p = 0.005). Thus, Tau only increased as a function of CAP score in HD gene-expansion carriers without psychiatric symptoms but was at a constantly higher level in HD gene-expansion carriers with psychiatric symptoms. TCC levels in HD gene-expansion carriers with psychiatric symptoms were higher than TCC levels in HD gene-expansion carriers without psychiatric symptoms (p = 0.015). NFL was the only biomarker associated with cognitive impairment, with HD gene-expansion carriers with cognitive impairment having higher levels of NFL than cognitively intact HD gene-expansion carriers (p = 0.012).
DISCUSSION In this controlled study of CSF inflammation in HD, we examined a total of 104 CSF samples from 32 premanifest and 48 manifest HD gene-expansion carriers and 24 gene-expansion negative at-risk controls. All samples were drawn, processed, and stored according to a standardized procedure. We examined several biomarkers of neuroinflammation and neurodegeneration and their correlation with motor, psychiatric, and cognitive measures. We found no evidence of early inflammatory involvement; however, we found evidence of sequential evolvement of biomarkers of neurodegeneration and neuroinflammation. The examined biomarkers fell into 2 categories. One category primarily consisted of specific inflammatory biomarkers (MMP9, CXCL13, TCC, and NOx). These biomarkers were not increased in manifest gene-expansion carriers and showed no correlation with disease burden or other biomarkers. The second category comprised biomarkers of neurodegeneration (NFL, MBP, and Tau) and the biomarker of inflammation CHI3L1. These biomarkers were increased in manifest HD gene-expansion carriers, correlated to disease burden, and showed intercorrelation with the other biomarkers in this category. OPN did not fit in either category.
group as it was marginally decreased in HD gene-expansion carriers and did not correlate with disease burden but was closely correlated with the biomarkers in the second category and therefore subsequently included there.

MMP9 and CXCL13 are considered to be biomarkers of leukocyte trafficking into the subarachnoid and perivascular space during neuroinflammation. MMP9 activity has been linked to increased blood–brain barrier permeability and CXCL13 is a B-cell chemo-attractant. Previous studies have found increased expression levels of MMP9 in postmortem HD brain tissue and increased levels of MMP9 in plasma samples from patients with HD and transgenic HD mice. Our data do not indicate a blood–brain barrier dysfunction as CSF leukocyte counts, and the albumin quotient did not differ in the 3 groups. However, CSF oligoclonal bands were found in 9 premanifest

![Figure 2](image-url)
gene-expansion carriers, which may indicate the presence of an aspect of neuroinflammation not detected by our assays that may be present in the premanifest stage.

The complement pathway is a powerful humoral component of the innate immune system. Increased levels of TCC have been measured in several studies where the complement pathway is suspected to be activated. A previous study showed an increased expression of complement activators and regulators in HD brain tissue, suggesting an activation of the complement pathway. We did not find increased TCC in HD gene-expansion carriers compared to gene-expansion negative controls, which could indicate that (1) there is no complement pathway activation, (2) the activation may be present locally on the cell surfaces in the striatum and thus not reaching the CSF, or (3) the increased expression of complement activators is limited to early activation of the complement cascade but not terminal activation with generation of TCC.

Oxidative stress has been linked to the activation of microglia, biomarkers of inflammation in other neuroinflammatory conditions, and is suspected to have a major role in the neuronal damage and degeneration in HD. We found NOx to be elevated in premanifest but not in manifest HD gene-expansion carriers compared to gene-expansion negative controls and with no correlation to disease burden in either premanifest gene-expansion carriers alone (data not shown) or all HD gene-expansion carriers. This finding implies that there is increased NO synthase activity in the preclinical stages of HD, but the pathophysiologic relevance of this finding is unclear.

NFL is an unspecific but sensitive biomarker of neuronal and axonal damage in neurodegenerative disorders. Two previous HD CSF studies have shown elevated NFL levels in CSF from HD gene-expansion carriers. The first study used CSF from 35 manifest HD gene-expansion carriers and correlated increased NFL to UHDRS-TMS but not with CAG repeat length. A recent study from Wild et al. found that NFL was associated with the level of mutant huntingtin but not to cognitive function when controlling for disease burden. In our larger independent cohort, we confirm significant correlations of NFL with both UHDRS-TMS and CAG repeat length as included in CAP score. In contrast to another study of CSF markers in HD, we found that HD gene-expansion carriers with cognitive impairment had higher CSF levels of NFL, as compared to cognitively intact HD gene-expansion carriers controlling for disease burden (CAP score), possibly indicating a more severe degree of neurodegeneration in cognitively impaired HD gene-expansion carriers. This discrepancy may arise from the fact that this study only included 12 participants in the analysis of NFL and cognitive function.

NFL was also the only biomarker that was elevated in both premanifest and manifest HD gene-expansion carriers compared to controls. These results suggest that NFL potentially reflects the neurodegeneration in HD from an early time point, long before onset of motor symptoms. NFL correlated with MBP and CHI3L1, but these correlations disappeared when controlling for disease burden, reflecting that NFL may be a biomarker of disease burden.

Tau and MBP concentrations are elevated in a variety of neurodegenerative disorders as measures of different aspects of neurodegeneration, myelin breakdown, and neuronal and axonal damage. In contrast to NFL, Tau and MBP appear to reflect later stages of the neurodegeneration in HD, since Tau and MBP concentrations were only increased and correlated with the disease burden in manifest gene-expansion carriers but not in premanifest gene-expansion carriers. Two earlier studies have investigated Tau in CSF and reported increased levels in manifest gene-expansion carriers; however, Tau was not correlated to any disease scores. In our study the levels of Tau did, however, differ in HD gene-expansion carriers with or without psychiatric symptoms. HD gene-expansion carriers with psychiatric symptoms had elevated levels of Tau in general, whereas in HD gene-expansion carriers without

### Table 2 Intercorrelation and partial intercorrelation of the adjusted markers

<table>
<thead>
<tr>
<th></th>
<th>NFL</th>
<th>MBP</th>
<th>Tau</th>
<th>CHI3L1</th>
<th>OPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP</td>
<td>0.509b</td>
<td></td>
<td>0.514d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td>0.388a</td>
<td>0.389a</td>
<td>0.471b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHI3L1</td>
<td>0.330a</td>
<td>0.389a</td>
<td>0.471b</td>
<td>0.510b</td>
<td>0.393a</td>
</tr>
<tr>
<td>OPN</td>
<td>-0.192</td>
<td>0.117</td>
<td>0.046</td>
<td>0.034</td>
<td>0.033</td>
</tr>
<tr>
<td>NOx</td>
<td>-0.155</td>
<td>0.217</td>
<td>0.086</td>
<td>0.073</td>
<td>0.037</td>
</tr>
</tbody>
</table>

**Partial correlations, controlled for CAP score**

<table>
<thead>
<tr>
<th></th>
<th>MBP</th>
<th>Tau</th>
<th>CHI3L1</th>
<th>OPN</th>
<th>NOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP</td>
<td>0.301</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td>0.227</td>
<td>0.452d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHI3L1</td>
<td>0.168</td>
<td>0.327</td>
<td>0.416a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPN</td>
<td>0.049</td>
<td>0.374</td>
<td>0.518b</td>
<td>0.390a</td>
<td></td>
</tr>
<tr>
<td>NOx</td>
<td>-0.155</td>
<td>0.217</td>
<td>0.086</td>
<td>0.073</td>
<td>0.037</td>
</tr>
</tbody>
</table>

**Abbreviations:** CHI3L1 = chitinase-3-like 1; MBP = myelin basic protein; NFL = neurofilament light polypeptide; OPN = osteopontin; NOx = total nitric oxide; Tau = microtubule-associated protein tau (total).

Analyzed by Pearson correlation. The p values are one-sided, Bonferroni corrected.

*Only sex-adjusted.

b.p < 0.0001.

c.p < 0.05.

d.p < 0.001.

* p < 0.01.

fCAG age product (CAP). The directions of all the correlation were characterized by increases in both biomarkers and CAP score.
The dynamics of CSF biomarkers over time are illustrated for gene-expansion negative controls (medium-toned lines) and the changes from gene-expansion negative controls to gene-expansion carriers are illustrated by dark-toned lines. Light-toned lines: * illustrates level of microtubule-associated protein tau (total) (Tau) in HD gene-expansion carriers with psychiatric symptoms; ** illustrates level of neurofilament light polypeptide in HD gene-expansion carriers with cognitive impairment. CHI3L1 is human chitinase 3-like 1 protein; MBP = myelin basic protein; NFL = neurofilament light polypeptide; OPN = osteopontin.

The dynamics of CSF biomarkers in Huntington disease (HD) are illustrated by microglia and astrocytes, respectively. These cells are hypothesized to be involved in HD pathogenesis. However, we cannot exclude that non-inflammatory processes may alter the expression of OPN or CHI3L1 in astrocytes, microglia, or other CNS cells in HD and that the increased level of CHI3L1 is not an indication of neuroinflammation per se. Indeed, OPN and CHI3L1 may play physiologic roles in tissue regeneration and repair. OPN was decreased in the premanifest group but not the manifest group, which might indicate an early but not late malfunction of microglia. More markers of microglia/macrophage function should be measured to investigate this further. There are several isoforms of OPN and the different commercial ELISA kits do not take this into account; hence the results of OPN measurements should be interpreted with caution.

Figure 3 presents a hypothesized model on the dynamics of the investigated CSF biomarkers.

We found that NFL may be a relevant correlate of disease burden in all HD gene-expansion carriers reflecting neuronal loss even before motor symptom onset, and may be useful as a dynamic biomarker in future intervention studies.

Although our cohort is relatively large, our study is exploratory and needs validation, ideally also including a positive control group as, e.g., multiple sclerosis. Furthermore, measurements of the relevant markers in plasma or serum are needed to investigate a possible relation between CSF and blood levels of the markers. Despite those limitations, our study does not provide evidence of neuroinflammation in early HD pathogenesis and the increased CSF concentrations of CHI3L1 in manifest HD gene-expansion carriers are not substantiated by other inflammatory biomarkers and may reflect other pathologic processes in HD. However, the fact that 9 presymptomatic gene-expansion carriers did have oligoclonal bands deserves attention in future studies and additional cross-sectional and longitudinal studies on more CSF biomarkers of inflammation and neurodegeneration are necessary to fully clarify the contribution of neuroinflammation in HD pathogenesis.

**AUTHOR CONTRIBUTIONS**

T. Vinther-Jensen: research project conception, organization, and execution; statistical analysis design, execution, review, and critique; writing of the first draft; and manuscript review and critique. L. Børnsten: research project conception and execution, writing of the first draft, and manuscript review and critique. E. Budtz-Jørgensen: statistical analysis design, execution, review, and critique. C. Ammitzbøll: research project execution and manuscript review and critique. I.U. Larsen: research project organization and execution and manuscript review and critique. L.E. Hjermind: research project conception and organization, statistical analysis design, execution, review, and critique; and manuscript review and critique. E. Budtz-Jørgensen: statistical analysis design, execution, review, and critique; and manuscript review and critique. F. Sellebjerg: research project conception and organization, statistical analysis design, execution, review, and critique; and manuscript review and critique.
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