INTRODUCTION
Cerebral microbleeds are primarily a marker of small vessel disease and have been demonstrated to occur in higher frequency in populations with dementia, compared with healthy controls. The two main reasons for microbleeds are cerebral amyloid angiopathy, causing microbleeds in lobar regions of the brain, and hypertensive angiopathy, causing microbleeds in deep and infratentorial regions of the brain. Both aforementioned diseases are common in dementia. Consequently, the current hypothesis on microbleeds is that they may be an important marker in the dementia disease process.

One way of directly investigating the impact of microbleeds on the brain is by analysing routine cerebrospinal fluid biomarkers used in dementia investigation, and their relation to microbleeds. Altered amyloid beta (Aβ42), total tau (T-tau) and tau phosphorylated at threonine 181 (P-tau) levels, and perhaps also cerebrospinal fluid/serum albumin ratios, as a marker of disrupted blood brain barrier integrity, would suggest an impact on dementia by microbleeds.

MATERIAL AND METHODS
1039 patients undergoing dementia investigation (mean age 62 (±10), 53% female) were included in this study. Diagnoses were set according to the ICD-10, and focus in this study was put on a continuum of cognitive impairment, with analysis made on the whole cohort (n=1039), Alzheimer’s disease (n=281) and mild (n=308) and subjective cognitive impairment (n=270) cognitive impairment. All patients underwent lumbar puncture, and an MRI scan, as part of the dementia investigation. The MRI scan was done on 1.5-3.0T with SWI and/or T2* sequences added to the general MRI dementia protocol. Microbleeds were analyzed according to the microbleed anatomical rating scale, while matter hyperintensities according to the Fazekas scale, and lacunar infarctions were defined as 3-15mm of size, with cerebrospinal fluid signal on FLAIR, T2 and T1. Cerebrospinal fluid samples were analysed for Aβ42 (Innotest β-Amyloid1-42), T-tau (Innotest hTau-Ag), P-tau (Innotest Phospho-tau181P) and cerebrospinal fluid/serum albumin ratios. All biomarkers were log transformed due to their non-parametric distribution.

RESULTS
Multivariate linear regression analyses were performed to assess microbleed topography and associations with cerebrospinal fluid biomarkers. Biomarkers were used as dependent variables, with the topographies (deep, infratentorial and lobar) as independent variables in one model. All topographies were dichotomous variables, and all analyses were adjusted for white matter hyperintensities, lacunar infarctions, age, MRI field strength and microbleed sequence (SWI/T2*). Analysis was made for the whole cohort (n=1039), Alzheimer’s disease (n=281) and mild (n=308) and subjective (n=270) cognitive impairment. Values are presented below as the regression coefficient, standardized beta, if significant.

CONCLUSION
Aβ42 is routine cerebrospinal fluid biomarker mainly associated with microbleeds in cognitive impairment, and there is an accumulative effect with increasing number of microbleeds.

A disrupted blood brain barrier seen with increasing number of microbleeds may be due to accompanying microvascular changes with microbleeds, such as white matter hyperintensities.

We confirm the differing pathogenesis of lobar and deep microbleeds, showing that lobar microbleeds are associated with lower Aβ42 levels, and deep and infratentorial microbleeds with lower tau levels. Our findings suggest that lobar microbleeds may be associated with dementia pathology, but not deep.