The disturbance of cholesterol synthesis and metabolism described in Alzheimer’s disease (AD) may be either a contributor to the pathogenesis, or a consequence of the neurodegenerative process, or both. These putative relationships and their underlying mechanisms are not well understood.

The aim of this study was to evaluate the relationship between cerebral and extracerebral cholesterol synthesis and metabolism and AD pathology as reflected by AD specific cerebrospinal fluid (CSF) markers.

We determined the plasma and CSF concentrations of cholesterol, its precursors (lanosterol, lathosterol and desmosterol), and its elimination products (24S-hydroxycholesterol and 27-hydroxycholesterol) and investigated their relationships to the CSF markers for AD pathology Aβ1-42 and p-tau181 in 87 subjects with normal cognition and in 106 AD patients.

CSF desmosterol, cholesterol and 24S-hydroxycholesterol correlated with p-tau181 levels. There was no correlation between CSF lanosterol, lathosterol and 27-hydroxycholesterol or the measured plasma concentrations and CSF p-tau181. Neither CSF nor plasma concentrations of the included compounds correlated with the Aβ1-42 CSF levels. In multivariate regression tests including age, gender, albumin ratio, the number of the APOEε4 alleles, and diagnosis, p-tau181 levels independently predicted the CSF desmosterol, cholesterol and 24S-hydroxycholesterol concentrations. These associations remained significant for CSF cholesterol and 24S-hydroxycholesterol when analyses were separately performed in the AD group.

The results suggest that alterations of both CNS cholesterol de novo synthesis and metabolism are related to neurodegeneration and in particular to the cerebral accumulation of phosphorylated tau in AD.