Circulating oxysterols in Alzheimer’s disease: a systematic review and meta-analysis

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Abstract

Despite decades of research, the cause and series of events underlying the advancement of Alzheimer's disease (AD) have not yet been established. Lipid, especially cholesterol, levels have been proposed to be implicated in AD. Several studies have been undertaken and many are ongoing in different directions looking at the importance of circulating cholesterol and oxidised cholesterol in AD with inconsistent methods and results. This meta-analysis aims to systematically analyse available data describing the involvement of oxidised cholesterol in mild cognitive impairment (MCI) and AD. We conducted a systematic literature search of six databases MEDLINE (PubMed), BIOSIS (Web of Science), EMBASE (Elsevier), PsycNET, Scopus and Cochrane library for studies measuring oxysterols (24-hydroxycholesterol (24OHC); 26-hydroxycholesterol (26OHC) and 7-oxycholesterols) in serum or plasma from MCI/AD patients compared to age- and gender-matched cognitively normal controls. Data were analysed using the inverse variance and standard mean difference with random-effect analysis model at 95% CI for association between oxysterols and MCI/AD in Review Manager (RevMan) software version 5.4.1. Between January 2000 and April 2022, 175 studies were identified by two independent researchers out of which 14 met the inclusion criteria and were analysed with a total of 957 controls, 469 MCI cases and 509 AD cases. The standard mean differences between MCI/AD participants and controls did not show any difference in the oxysterol levels except for 26OHC level which was higher in AD but not statistically significant.

Introduction

Alzheimer’s disease (AD) is the most common type of dementia where affected individuals suffer progressive cognitive decline and cognitive impairment. It has been estimated that AD sufferers worldwide will reach 81 million by 2040 with most of the sufferers being old-age adults (Ferri et al. 2005). Over 9.9 million new cases of dementia are predicted each year worldwide and is forecast to be the major societal health challenge of the 21st century (World Alzheimer Report 2021). It is widely recognised that AD has an extended preclinical stage before presenting cognitive decline and neuropathological changes in middle to older adults. Therefore, it is vital to understand preclinical biomarkers and underlying mechanisms of its progression to predict and apply to successful prevention trials.

The discovery of the genetic association of apolipoprotein E (ApoE) ε4 allele with sporadic and familial late-onset AD suggested the possibility of dysfunction in the lipid metabolism and lipid transport in the brains of AD subjects (Minagawa et al. 2009). ApoE is produced by astrocytes and glial cells, and it is a primary
transporter of cholesterol involving lipoprotein particles in the brain. The key role of ApoE is to redistribute lipids through receptor-mediated uptake for neurite growth (Minagawa et al. 2009). In addition to the identification of genetic risk factors for vascular dementia and familial and sporadic AD, multiple lines of evidence suggested a strong relationship between lipid homeostasis and vascular changes in the brain of AD subjects (Papassotiropoulos et al. 2000, Vaya & Schipper 2007, Mutembei et al. 2016). These include epidemiologic studies that link environmental vascular risk factors to dementia; evidence from stroke studies (Leduc et al. 2010, Hughes et al. 2013), interaction with amyloid deposition (Loera-Valencia et al. 2019) and Tau phosphorylation (Papassotiropoulos et al. 2003) in a cholesterol-rich environment, microvascular abnormalities in AD and changes to blood-brain barrier (BBB) functions in hypercholesterolemic subjects (Loera-Valencia et al. 2019). Lipids are at the core of AD pathology due to their involvement in various cellular functions in the brain including the energy balance, myelination, membrane remodelling, signalling cascades, inflammation and resolution of inflammation. Based on these observations, the relationship between lipids, especially cholesterol, and AD has been extensively investigated in epidemiological studies in the past decade (Ferri et al. 2005, Barnes & Yaffe 2011, Dias et al. 2015). Previous meta-analysis compared the levels of lipids or lipoproteins in the blood, which include low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG) (Sáiz-Vázquez et al. 2020). This meta-analysis showed that there is an association between the effect of cholesterol in AD where LDL-C has a significant impact on the development of AD pathologies.

Oxidative stress and oxidative modifications to macromolecules are one of the earliest events in AD pathology (Nunomura et al. 2001, Bai et al. 2022). Among the lipid oxidation observed in AD, cholesterol can be oxidised via non-enzymatic reactions and enzymatic oxidation, thus resulting in oxysterols. While peripheral cholesterol metabolism is kept independent of the brain, there are evidence to suggest that oxysterols can transfer to and from the brain via BBB. Polar oxysterols that can proficiently pass the lipophilic BBB have obtained substantial recognition as a potential connection between serum cholesterol, modified brain cholesterol metabolism and brain pathophysiology (Iuliano et al. 2011, Hughes et al. 2013, Dias et al. 2014b). Non-enzymatic oxidation to cholesterol can occur through reactions initiated by free radical species arising from the superoxide, hydrogen peroxide and hydroxyl radical system. These reactions oxidise the seventh position of the cholesterol main ring deriving 7-oxysterols (7α-hydroxycholesterol, 7β-hydroxycholesterol and 7-ketocholesterol) and epoxy cholesterol (Iuliano et al. 2011). The susceptibility of cholesterol to non-enzymatic oxidation and increased oxidative stress observed in AD has raised considerable interest in the function of these oxysterols as biological effectors and potential biomarkers in AD (Mahalakshmi et al. 2021).

Conversion of excess brain cholesterol to 24-hydroxycholesterol (24OHC) by the neuron-specific enzyme CYP46A1 is one of the main routes by which excess cholesterol is removed from the brain (Gamba et al. 2021). Cholesterol is also enzymatically converted to 26-hydroxycholesterol (26OHC, also identified as 27-hydroxycholesterol) via 27-hydroxylase (CYP27A1) in neurons and other cell types. The 26OHC is produced mainly by peripheral tissues, although a small amount is also generated by the brain. Brain-derived 26OHC is then transferred to the blood and catabolized towards bile acids in the liver by oxysterol 7α-hydroxylase (CYP7B1). As the most abundant oxysterol in peripheral circulation, 26OHC is found to be associated with the cholesterol content in atherosclerotic lesions and the severity of coronary artery disease (Vaya et al. 2001). In vivo studies demonstrated that mutations in several HDL genes could redistribute 26OHC levels in HDL and plasma, as well as specific changes in the esterification of 26OHC (Karuna et al. 2011). Administration of 26OHC through the tail vein negatively affected cognitive function and cholesterol metabolism in rats (Zhang et al. 2015). These observations led to later case–control studies that demonstrated a strong association between high plasma levels of 26OHC and mild cognitive impairment (MCI) (Liu et al. 2016). These observations suggest that oxysterols could act as a link between hypercholesterolemia and AD. Considering this background, the aim of this study is to provide an updated systematic review and meta-analysis of available data on oxysterols and the risk related to the development of AD.

**Methods**

**Data acquisition and criteria**

This review included a search of six databases: MEDLINE (PubMed), BIOSIS (Web of Science), EMBASE (Elsevier), PsycNET, Scopus and Cochrane for studies measuring oxysterols (24 hydroxycholesterol; 26 hydroxycholesterol/27 hydroxycholesterol and
7-oxycholesterols) in serum or plasma from MCI/AD patients compared to age- and gender-matched cognitively normal controls published between January 2000 and April 2022. The Boolean terms used were (plasma OR serum OR blood) AND (oxysterols) AND (Alzheimer’s disease) NOT review. Authors performed the initial searches and eliminated duplicates, and articles that satisfied the inclusion criteria were selected independently and checked for full text availability. Figure 1 summarises the inclusion and exclusion criteria.

**Study selection**

Inclusion criteria are:

1. studies on human subject, published between January 2000 and April 2022;
2. case-control study design that reported quantitative measurement of total cholesterol and oxysterols (24OHC, 26OHC and 7-oxycholesterols) in serum or plasma of MCI/AD patients and age- and gender-matched cognitively normal controls.

Studies that provide data on at least one of the classes of lipids to be analysed were used and there was no limitation based on quantification methodology.

Exclusion criteria are:

1. lack of control groups;
2. other forms of dementia and not AD;
3. intervention studies;
4. review papers, letters, editorials, conference papers or other non-original research articles.

Studies in any of the listed categories were excluded from the meta-analysis.

**Data extraction and assessment**

Two independent reviewers performed the search and collected the data. The mean, s.d. and s.e., as well as the adjusted oxysterol levels, were extracted. We explored the year, country of study design, use of quality control, criteria for AD diagnosis, mean age, gender, type of sample, assay method, laboratory kit used, collection process, sample storage, sample preparation and blinding of personnel were assessed for each study. Variables extracted from each of the 14 studies shortlisted for meta-analysis are shown in Table 1 and include mean and s.d. We used the formula $SD = SE*\sqrt{n}$ to calculate s.d. for data reported as s.d., where $n$ is the number of participants.
Data analysis

Statistical analyses were performed using the Review manager (RevMan) version 5.4.1 (provided by www.cochrane.org). The meta-analysis compared the mean differences and standard deviations within the study groups using inverse variance for the continuous data. Chi-square test was used to investigate heterogeneity within the studies, and sensitivity analysis was used to identify the source of heterogeneity. A random-effects model was used for analysis with heterogeneity ($P \leq 0.1$, $I^2 \geq 50\%$). We used the standardised mean difference (SMD), and 95% CI was calculated to analyse statistical data effectiveness for the continuous data. The difference was statistically significant when $P < 0.05$.

We categorised the studies into three groups for separate meta-analyses: (i) total 24OHC composition of plasma/serum in studies comparing AD or MCI to cognitively normal individuals; (ii) 26OHC composition of plasma/serum in studies comparing AD or MCI to cognitively normal individuals; (iii) 7-oxycholestrol composition of plasma/serum in studies comparing AD or MCI to cognitively normal individuals. We performed a total of 1935 meta-analyses (957 control vs 469 MCI...
and 509 AD). Oxysterol summary including all units and sources is shown in Table 1. The overall effect results of meta-analysis were accepted as statistically significantly different if they have \( P \leq 0.05 \).

**Results**

**Literature search results**

The flow diagram of the literature searches and study selection is shown in Fig. 1. Overall, 175 studies between January 2000 and April 2022 were identified by two independent researchers. Finally, 14 observational studies met the inclusion criteria and were included in the meta-analysis. Sample size ranged from 10 to 140 subjects and analysed with a total of 957 controls, 469 MCI and 509 AD cases. Populations in the included studies were from Pittsburgh (USA), Germany, Spain, Tunisia, China, Brazil, India and Sweden. Data of the included studies are summarised in Table 1. The full list of plasma/serum levels of oxysterols reported in each paper is in the Forest plot summary tables. Only studies reporting MCI and dementia of the Alzheimer’s type were used for meta-analysis. Highly specific mass spectrometric approaches (either LCMS or GCMS) were used for the analysis of oxysterols in all the studies except for Roy et al. (2019) who used sandwich ELISA.

**Studies on oxysterols and MCI**

To understand the relationship between circulating 24OHC, 26OHC and 7-oxycholesterols in disease progression, first, we investigated data from subjects with MCI (Fig. 2). The data used in the meta-analysis were calculated and converted from the original data. Among seven studies included in this analysis, no change was reported for 24OHC levels in four studies (Iuliano et al. 2010, Hughes et al. 2012, Liu et al. 2016). While Hughes et al. (2012) and Popp et al. (2012) reported increased levels of circulating 24OHC in MCI, Mateos et al. (2011) reported decreased levels. For 26OHC, Hughes et al. (2012) and Popp et al. (2012) reported decreased circulating levels in MCI but Liu et al. (2016) and Zuliani et al. (2011) reported 26OHC is higher in MCI plasma.

Overall, 24OHC showed no difference between control and MCI; the standardised mean difference was 0.07 (95% CI: −0.12 to 0.26, \( P = 0.47 \), Fig. 2). No statistical heterogeneity was found (\( \chi^2 = 7.82, P = 0.25, I^2 = 23\% \)). Likewise, 26OHC
showed no difference between control and MCI; the standardised mean difference was 0.20 (95% CI: −0.41 to 0.81, P = 0.53, Fig. 2). However, statistical heterogeneity was found (χ² = 108.48, P < 0.00001, I² = 94%). Subgroup analysis (not shown) did not show statistical significance for 24OHC and 26OHC either. 7-oxycholesterols showed no difference between control and MCI; the standardised mean difference was 0.09 (95% CI: −0.16 to 0.34, P = 0.49, Fig. 2). No statistical heterogeneity was found (χ² = 0.47, P = 0.49, I² = 0%).

The overall effect of the oxysterols analysed between control and MCI was not significant.

**Studies on oxysterols and AD**

To explore the relationship between circulating oxysterols levels and risk of AD, next, we investigated data from subjects with AD (Fig. 2). Data of 24OHC, 26OHC and 7-oxycholesterol levels were also inconsistent in literature. Out of ten studies analysed for 24OHC, six studies reported high circulating levels (Lütjohann et al. 2000, Iuliano et al. 2010, Zuliani et al. 2011, Hughes et al. 2012, Popp et al. 2013, Zarrouk et al. 2020) and four studies reported low circulating levels (Qureischie et al. 2008, Mateos et al. 2011, Costa et al. 2018, Roy et al. 2019) in AD compared to control. For 26OHC, three studies reported high circulating levels (Iuliano et al. 2010b, Popp et al. 2013, Zarrouk et al. 2020), two studies reported low levels (Mateos et al. 2011, Hughes et al. 2012) and one study reported no change (Costa et al. 2018) compared to control. 7-oxycholesterol levels were reported as high in both studies but not statistically significant (Iuliano et al. 2010b, Zarrouk et al. 2020).

Overall, 24OHC showed no difference between control and AD; the standardised mean difference was −0.03 (95% CI: −0.58 to 0.52, P = 0.91, Fig. 3). However, statistical heterogeneity was found (χ² = 144.92, P < 0.00001, I² = 94%). 26OHC showed no difference between control and AD; the standardised mean difference was 0.07 (95% CI: −0.34 to 0.48, P = 0.73, Fig. 3). However, statistical heterogeneity was found (χ² = 24.09, P = 0.0002, I² = 79%) for 26OHC. 7-oxycholesterols showed no difference between control and AD; the standardised mean difference was 0.23 (95% CI: −0.11 to 0.56, P = 0.18, Fig. 3). No statistical heterogeneity was found (χ² = 0.36, P = 0.55, I² = 0%).

The overall effect of the oxysterols analysed between control and AD was not significant.

**24OHC**

![Figure 2](https://doi.org/10.1530/REM-22-0009)

**26OHC**

![Figure 3](https://doi.org/10.1530/REM-22-0009)

**7-oxycholesterols**

![Figure 3](https://doi.org/10.1530/REM-22-0009)

*Figure 3* Forest plots of concentration of oxysterols in plasma/serum in AD vs control meta-analyses. Random-effect model did not show significant difference in oxysterols measured in AD patients compared to healthy controls.
Discussion

Oxysterols, especially neuronal-derived 24OHC and peripheral 26OHC, have been of interest as biomarkers for neurodegeneration including AD. A large portion of the total 24OHC in the periphery is known to be produced in the brain (Björkhem et al. 1998). During brain cholesterol metabolism, 99% of brain-derived 24OHC is estimated to enter into the plasma and excreted via liver (Lütjohann et al. 1996), reflecting brain cholesterol metabolism. Plasma levels of 24OHC seem to be stable in healthy subjects regardless of the sex differences, but there are mixed results on circulating 24OHC levels in AD (Dzeletovic et al. 1995). Defective BBB permeability in AD has been suggested to increase the permeability of many brain biomarkers into the circulation including oxysterols (Dias et al. 2014b). To ascertain 24OHC as a possible biomarker for neurodegeneration, many previous studies investigated 24OHC levels in the brain as well as in the blood and the results have been reviewed before (Leoni & Caccia 2011, 2013a,b). Therefore, the aim of this study was to incorporate recent findings and to analyse available data to investigate any changes to circulating oxysterol levels in AD. This meta-analysis shows that circulating levels of 24OHC, 26OHC and 7-oxycholesterols are not changed between healthy subjects and patients with MCI or AD.

Some studies observed increased 24OHC at the early stage of the disease due to increased brain cholesterol turnover, but majority of the studies did not observe changes to circulating 24OHC levels in AD (Iuliano et al. 2010, Hughes et al. 2014, Liu et al. 2016). Lütjohann et al. (2000) reported significantly higher concentration of 24OHC in AD and non-Alzheimer demented patients compared to healthy controls and depressed patients. Agreeing with this, Popp et al. reported increased 24OHC in circulation (Popp et al. 2013). In contrast, several studies reported decreased levels of 24OHC in AD and MCI (Brettillon et al. 2000, Kölsch et al. 2004, Roy et al. 2019) and a correlation between severity of AD and decrease of 24OHC (Ruthirakuhan et al. 2019). Plasma 24OHC was also found to be significantly reduced in some other human neurodegenerative diseases such as multiple sclerosis (MS) (Teunissen et al. 2003) and Huntington’s disease (Solomon et al. 2009, Leoni et al. 2013). Since AD progression is coupled with loss of 24-hydroxylase-expressing neurons, brain 24OHC levels are found to be significantly lower than in healthy subjects (Testa et al. 2016, Dias et al. 2022). The reduction of neuronal cell-rich grey matter during neurodegeneration could be mirrored by a parallel reduction of peripheral 24OHC (Solomon et al. 2009). However, Solomon et al. described that 24OHC was significantly related to brain volumes in the control group but not with MCI or AD groups despite the significant decrease in plasma 24OHC levels. Previous work found a differential expression of the CYP46 enzyme in glial cells in AD (Brown et al. 2004). Abnormal induction of the cholesterol-catabolic enzyme CYP46 in glial cells may act as a compensatory mechanism in neurodegeneration masking the direct correlation between brain volume and the evolution of the disease. It is also possible that the differences observed in circulating 24OHC may be due to individual variance in hepatic clearance rates of 24OHC.

It was estimated that 24OHC is eliminated from human circulation with half-lives of 10–14 h (Björkhem et al. 1998). However, there are no data available for differential clearance of 24OHC in AD patients. Another confounder to varied levels of 24OHC would be polymorphism in 24-hydroxylase gene. Previous reports suggest that polymorphisms in CYP46A1 are associated with an increased load of amyloid beta (Aβ) or earlier onset of AD (Kölsch et al. 2002, Papassotiropoulos et al. 2003)

Hughes et al. (2014) have shown that plasma oxysterol concentrations were higher among normal individuals who progressed onto developing MCI or AD by an 8-year follow-up study. This study demonstrated that blood lipid levels were not associated with Aβ status in the non-demented elderly group. However, higher levels of oxysterols and, in particular, significantly greater ratios of 24OHC to 26OHC and cholesterol were related to Aβ deposition in individuals with MCI. This might reflect alterations in cholesterol metabolism occurring early-on in the cognitive impairment process and may be indicative for individuals experiencing cognitive deterioration. However, it was uncertain whether all the subjects with MCI would progress onto AD or if 24OHC levels were directly associated with AD pathology. Roy et al. (2019) reported that serum 24OHC does not correlate with APOE4 genotype in AD subjects. Recently, Gamba et al. (2021) discussed the ambiguity of 24OHC levels related to AD pathogenesis and the controversial role it plays in the brain.

Enzymatically derived 26OHC is mainly produced in peripheral tissues and transported to the brain via BBB. This transport may be limited in healthy people due to intact BBB but could be increased during compromised BBB functions in AD. Therefore, multiple research studies have investigated the potential role of increased 26OHC in brain cell activity. Generally, 26OHC levels in the brain are about ten-fold less than that of 24OHC (Hughes et al. 2013). Even though the low-abundant 26OHC might
not severely influence the brain cholesterol metabolism, there is copious evidence to suggest its neuronal toxicity (Gamba et al. 2014, Dias et al. 2015). At low concentrations, 26OHHC induced neuronal cell oxidative stress and increased Aβ production (Dias et al. 2014a, Gamba et al. 2014). Animal studies also indicated that 26OH levels alter synaptic potentiation and could lead to dysfunction of fine-tuned processing of information in hippocampal circuits resulting in cognitive impairment (Loera-Valencia et al. 2021). These studies confirmed neuronal toxicity exerted by 26OHHC at high concentrations. Leoni et al. investigated the possibility of using 24OHHC and 26OHHC to inform differences between different conditions that affect neuronal damage (MS, AD, viral meningitis, chronic demyelinating polyneuropathies and subarachnoid haemorrhage) (Leoni et al. 2004). The study concluded no significant change to plasma levels of 24OHHC and 26OHHC, but neuronal damage and demyelination could increase oxysterol levels in cerebrospinal fluid (CSF) (Leoni et al. 2004). These studies clearly show that there is oxysterol involvement in neuronal cell damage in the brain but less likely that oxysterol levels would mirror this effect in the circulation. A meta-analysis to investigate 24OHHC and 26OHHC as surrogate biomarkers in CSF demonstrated both 24OHHC and 26OHHC are increased in MCI and AD (Wang et al. 2016). Altered cholesterol metabolism and increased cholesterol levels in CSF during MCI (Papassotriopoulos et al. 2002, Mateos et al. 2011) may account for increased oxysterols found in CSF and compromised BBB functions may explain the accumulation of oxysterols at later stage. This data suggested along with Aβ, total tau and phospho-tau, CSF 24OHHC and 26OHHC could be appropriate biomarkers for AD screening.

In contrast to the brain cholesterol metabolism, peripheral cholesterol metabolism is greatly influenced by diet, physical activity and medications. Therefore, levels may be variable between and within individuals during sampling. As a result, circulating 26OHHC levels affected by these confounders may complicate the use of it as a disease biomarker. Hence, interpretation of 26OHHC levels in biomarker studies should be carefully considered. A recent randomized controlled trial suggests that reducing serum 26OHHC levels by managing lifestyle and vascular factors over 2 years is beneficial for improving cognitive function related to memory (Sandebring-Matton et al. 2021). The study suggested that the intervention is beneficial to reduce 27OHCHC, particularly in individuals with the highest 27OHHC levels and younger age. This suggests that managing oxysterol levels from young is beneficial to improve cognition, but it is possible that increased oxidative stress in ageing and neurodegeneration may overcome the benefits of managing vascular and lifestyle factors. Therefore, we also compared autooxidised circulating 7-oxycholesterol levels between healthy, MCI and AD. However, these were not significantly different in our meta-analysis. In a systematic analysis of oxysterols in the brains of patients with different stages of AD development, they identified increased levels of oxysterols including 7-oxycholesterol, 4β-hydroxycholesterol, 5α,6α-epoxycholesterol and 5β,6β-epoxycholesterol (Testa et al. 2016). Toxicity of 7-oxycholesterols on neuronal cells is well documented in both in vivo and in vitro studies (Okabe et al. 2013, Debbabi et al. 2017, Yammine et al. 2020). In addition, 7-ketocholesterol levels have been reported to increase in AD CSF (Iriondo et al. 2020). However, it is not clear if circulating 7-oxycholesterols would transfer through BBB to add oxidative stress burden in the brain.

### Conclusions

In summary, this meta-analysis does not show significant changes in circulating oxysterols between healthy individuals and people with MCI and AD. One important factor comparing biomarker results across decades is the changes to the classification between MCI and AD. While early studies were mainly based on clinical examinations, later studies included other biomarkers such as Aβ or Tau to categorise disease groups. This will have significant impact on reported data on oxysterols. Another confounding factor for oxysterol data could be the level of medication between healthy controls and AD patients. While most of the studies that enrol healthy controls do not undergo medications, AD patients could be on many different types of medications to control cognitive functions such as neuropsychiatric drugs, vitamins, anti-hypertensive agents or statins. These drugs may have confounding effects on oxysterol levels. In addition, diet and physical performance play important role in peripheral cholesterol levels that will affect cholesterol metabolites. The context of this data and evidence from previous work suggest that the use of oxysterols as biomarkers in AD is a complex process and it may need careful analysis and modelling to find trends to predict AD risk.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

https://rem.bioscientifica.com
https://doi.org/10.1530/REM-22-0009

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Funding
I H K D would like to acknowledge funding from Alzheimer’s Research UK grant ARUK-PGP2020A-019. O S A would like to acknowledge funding from University of Derby Knowledge Exchange Impact Accelerator fund.

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Received 25 June 2022
Accepted 28 June 2022