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ORIGINAL ARTICLE

Association between clusterin concentration and dementia: a systematic review and meta-analysis

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Abstract

Studies have showed that high clusterin (CLU) concentration was associated with increased risk of dementia. However, the results based on small samples remained controversial. The aim of our study was to determine the relationship between CLU concentration and the late-life cognitive outcomes including mild cognitive impairment (MCI), Alzheimer's disease (AD), vascular dementia (VAD), Parkinson's disease related dementia (PDD), Lewy body dementia (DLB) and frontotemporal dementia (FTD). A comprehensive search was conducted to screen the eligible studies in online database *PubMed*, *Web of Science* and *Embase* from 1950 to January 2017 according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist. The CLU concentration data in brain tissue, cerebrospinal fluid (CSF), serum and plasma was collected to determine the strength of this association. The results were presented with standard difference of the mean (SDM) with 95% confidence intervals (CIs). A total of 28 studies were identified to calculate the association between CLU concentration and dementia. The results showed that the CLU concentration in the plasma (SDM = 0.73, 95% CI 0.26–1.19, $P = 0.002$) and brain tissue (SDM = 0.71, 95% CI 0.10–1.32, $P = 0.022$) was increased in dementia compared to normal control. Subgroup analysis showed that the plasma CLU concentration was significantly increased only in the AD group (SDM = 1.85, 95% CI 0.84–2.85, $P < 0.001$), but not in MCI or other dementias. No association was found between serum and CSF clusterin concentration and dementia. This meta-analysis indicates that high CLU concentration in the plasma and brain is associated with dementia, especially in AD.

Keywords Clusterin · Mild cognitive impairment · Dementia · Alzheimer's disease · Meta-analysis

Introduction

Dementia is a broad category of brain diseases with a wide range of symptoms associated with a long-term decline of memory, then affecting a person's daily function (Prince et al. 2013). Despite the increasing prevalence of dementia, there are still no effective therapy measures available for these diseases. Thus, to find the risk factors involved in the development of dementia might be a better strategy to predict and prevent the development and progression of dementia (Solomon and Soininen 2015). The apolipoprotein E type 4 (*ApoE4*) has been widely confirmed as the important risk gene for AD risk, but it only contributes to 50% of the genetic susceptibility of Alzheimer's disease (AD) (Ossenkoppele et al. 2013). Thus, other gene variants might be implicated in the risk for AD. Accumulated genetic evidences have suggested that *clusterin* (*CLU*) polymorphisms were associated with increased risk of cognitive impairment (Ferrari et al. 2012; Lu et al. 2014). The following meta-analysis confirmed this association in three polymorphisms (rs11136000, rs2279590 and rs9331888) on *CLU* gene (Shuai et al. 2015; Zhang et al. 2015; Du et al. 2016). However, whether there was a relationship between CLU concentration and dementia risk remain

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elusive. Although multiple studies have been performed to determine this association, unfortunately, the relationship between clusterin concentration and dementia was not concordant (Cai et al. 2016; Hakobyan et al. 2016; Vishnu et al. 2016).

Clusterin, also previously called as the apolipoprotein J, is a vital molecular chaperone implicated in correct folding of secreted proteins and responsible for the clearance of accumulated peptides (Trougakos 2013). It is well known that beta-amyloid deposition in the brain is a hallmark pathological characteristic in AD, the most common type of dementia (Villemagne et al. 2013). It is suggested that enhancing the clearance of β-amyoid (Aβ) deposition is deemed to attenuate the development and progression of AD (Liu et al. 2016). Evidences showed that CLU could inhibit the formation of fibrillar β-amyloid (fAβ) and ameliorate fAβ-induced neurotoxicity (Yerbury et al. 2007). In addition, CLU also exerted a role in modulating inflammation and apoptosis, both of which are the common pathological changes in dementia (Savkovic et al. 2007).

Due to the alternative splicing of *CLU* gene, there are two isoforms of CLU, including secretory CLU (sCLU) and nuclear CLU (nCLU) (Bettens et al. 2015). The sCLU, with full length of CLU mRNA, is a glycosylated heterodimeric protein containing α and β chains. The nCLU isoform, which lacks exon 2 or exon 5, could not target to the endoplasmic reticulum and locate in the nucleus (Kim and Choi 2011). In the brain, the sCLU is mainly secreted by the neurons and astrocytes and is widely distributed in the brain tissue and CSF (Nuutinen et al. 2009). sCLU was suggested to directly combine with Aβ and involved in the metabolism and clearance of Aβ (Desikan et al. 2014). Results from genetic studies have demonstrated that the protective CLU variants in dementia were associated with increased expression of CLU (Tan et al. 2016). Evidences from clinic data also suggested that the CLU concentration in the CSF and plasma was significantly increased in the dementia patients as compared to that in the normal controls (Mullan et al. 2013). Though numerous studies have been performed to explore the association between CLU concentration and the susceptibility of dementia (Silajdzic et al. 2012; Mullan et al. 2013; Hughes et al. 2014; Desikan et al. 2014; Mukaetova-Ladinska et al. 2015), unfortunately, the results remain inconclusive. Therefore, we performed this meta-analysis to summarize the controversial data and to determine the association between CLU concentration and dementia.

Methods and materials

Literature search

This meta-analysis was performed on the basis of the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist (http://www.prismastatement.org/statement.htm). To identify eligible studies evaluating the CLU concentration and dementia risk, published articles were searched in the PubMed, Web of Science and Embase electronic databases. The following retrieval strategy was applied: clusterin, apolipoprotein J, cognitive disorders, dementia, cognitive deficit, cognitive decline, mild cognitive impairment, Alzheimer's disease. The analyzed data covered those from 1950 to January 2017 without language limitation.

Inclusion criteria and study selection

The inclusion criteria and quality of the selected studies were confirmed by all the participated investigators. Studies meeting the following inclusion criteria were selected: a) with normal control; b) data of CLU concentration are available; c) human studies. If studies contained overlapping data, only the one with larger sample sizes was included. Articles with incomplete data were excluded from this meta-analysis.

Data extraction and quality assessment

To better present the information of the included studies, the following data was extracted by two independent investigators: name of the first author, year of publication, country of origin, ethnicity, diagnostic criteria of cognitive impairment, mean age, dementia type, female ratio, CLU concentration, clusterin measuring methods, number of patients and controls. Based on the inclusion criteria, the data was extracted and then input into *Stata* software to calculate the overall estimation. Any disagreements were discussed until reaching a consensus.

The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of included studies by two independent authors. The NOS judges the quality of the studies according to the following three aspects: selection, exposure and comparability. One score was given once an item was matched and disagreements were resolved by discussion.

Data synthesis and statistical analyses

The mean concentration of CLU and SD were used to estimate the association between the CLU concentration (brain tissue, serum, plasma and CSF) and dementia susceptibility. The heterogeneity was measured by Cochran Q test (<50%) and I-squared test ($P < 0.1$). The statistical model applied to calculate the SDM was selected according to the result of heterogeneity test. A random-effects model was utilized when $P < 0.1$, and a fixed-effects model was applied when $P > 0.1$. The publication bias was evaluated by conducting Begg's and Egger's test quantitatively. The sensitivity analysis was performed by excluding one study at a time to address the stability of the results. All statistical analyses were conducted by

STATA statistical software version 12.0. Two-sided *P* value less than 0.05 was considered to be statistically significant.

Results

Description of study characteristics

After a systematic literature search was in the online database PubMed, Web of Science, and Embase, a total of 1665 potential studies were recruited. 577 duplicate studies were removed in Endnote software. After further screening the title and abstract, 937 studies were excluded. The remained 151 articles were then screened for full-text analysis (Fig. 1), and 123 studies were excluded: 31 articles were not relevant to our meta-analysis, 45 articles were polymorphism studies, 38 articles were conferences poster or studies without presenting detailed data, 6 of them only presenting data of median without 95% CIs, and three of them with overlapped data. A total of 28 studies were included in this meta-analysis (Harr et al. 1996; Lidstrom et al. 1998; Lidstrom et al. 2001; Puchades et al. 2003; Nilselid et al. 2006; Thambisetty et al. 2010; Ijsselstijn et al. 2011; Schrijvers et al. 2011; Schurmann et al. 2011; Chen et al. 2012; Silajdzic et al. 2012; Song et al. 2012; Thambisetty et al. 2012; Xing et al. 2012; Mullan et al. 2013; Hughes et al. 2014; Richens et al. 2014; Desikan et al. 2014; Jongbloed et al. 2014, 2015; Meng et al. 2015; Mukaetova-Ladinska et al. 2015; Cai et al. 2016; Deming et al. 2016; Dukic et al. 2016; Gupta et al. 2016; Hakobyan et al. 2016; Vishnu et al. 2016). There were 3 studies including clusterin concentration data for both plasma and CSF sample in this meta-analysis (Richens et al. 2014; Jongbloed et al. 2014; Deming et al. 2016). Finally, the number of studies for plasma, serum, CSF and brain tissue were 19, 2, 7 and 3, respectively.

The detailed description for each selected study was presented in Table 1. Nineteen studies containing 2970 dementia patients and 5976 controls were included to evaluate the association between plasma CLU concentration and dementia. Among the 19 studies, 12 of them were performed in the AD, 11 were conducted in the MCI, and two in other dementias. For the CLU concentration in the CSF, 7 studies with 891

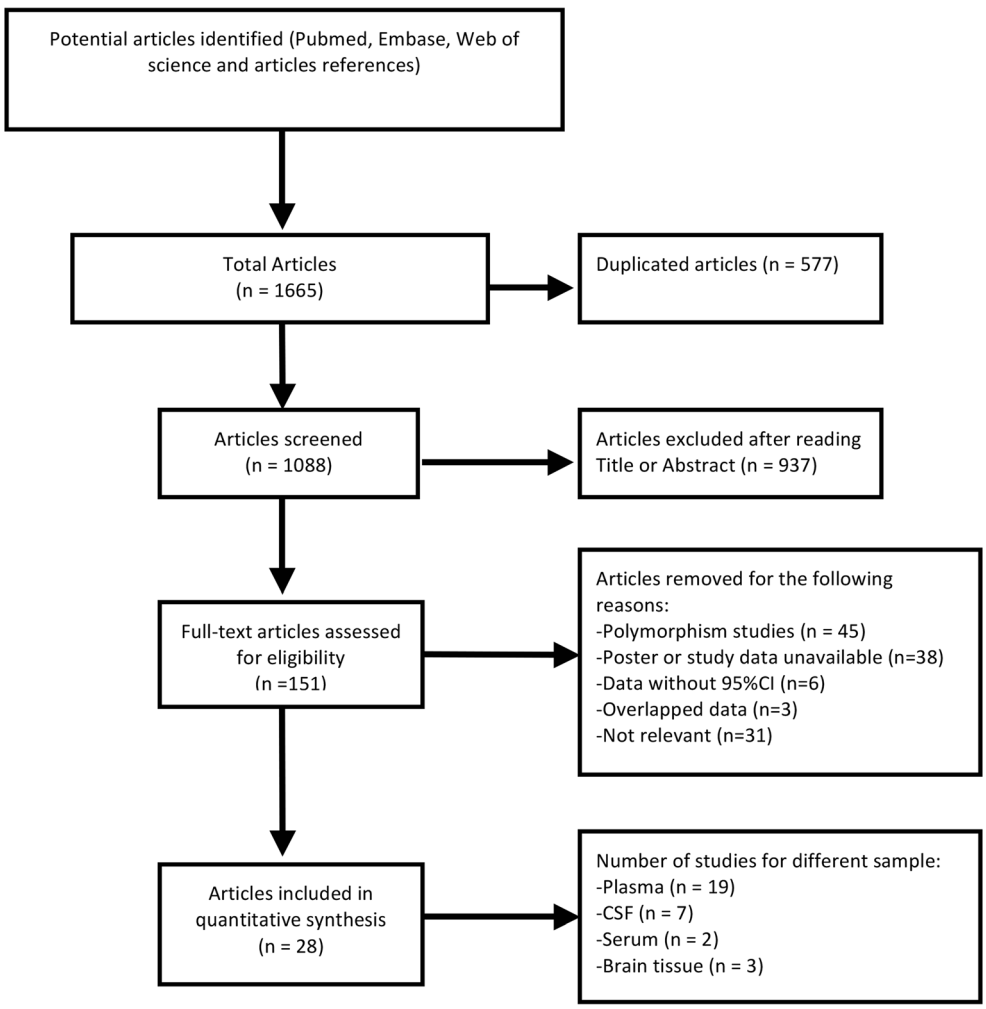

Fig. 1 Flow diagram of studies included in this meta-analysis

Table 1 Characteristics of the included studies

Author	Year	Ethnicity	Country	Disease types	Samples	Dementia			
						Mean age(year)	Sizes	Mean(ug/ml)	SD
Chen et al. (frontal cortex)	2012	Caucasian	USA	AD	Brain tissue	80.2	6	39.1	9.1
Chen et al. (temporal cortex)	2012	Caucasian	USA	AD	Brain tissue	79.6	6	28	8.4
Lidstrom et al. (AD-frontal cortex)	1998	Caucasian	Sweden	AD	Brain tissue	78 ± 9	19	1.5	0.36
Lidstrom et al. (AD-hippocampus)	1998	Caucasian	Sweden	AD	Brain tissue	78 ± 9	19	1.79	0.58
Lidstrom et al. (AD-cerebellum)	1998	Caucasian	Sweden	AD	Brain tissue	78 ± 9	19	1.04	0.25
Lidstrom et al. (VAD-frontal cortex)	1998	Caucasian	Sweden	Others	Brain tissue	79 ± 7	6	1.3	0.46
Lidstrom et al. (VAD-hippocampus)	1998	Caucasian	Sweden	Others	Brain tissue	79 ± 7	6	1.7	0.78
Lidstrom et al. (VAD-cerebellum)	1998	Caucasian	Sweden	Others	Brain tissue	79 ± 7	6	1.02	0.21
Harr et al.	1996	Caucasian	USA	AD	Brain tissue	74.3 ± 9.4	23	720	247
Jongbloed et al.	2014	Caucasian	Netherlands	MCI	CSF	65.4 ± 7.8	67	8.7	3.3
Jongbloed et al.	2014	Caucasian	Netherlands	MCI	CSF	67 ± 8	206	9.4	3.4
Desikan et al.	2014	Caucasian	USA	MCI	CSF	75.1 ± 0.7	150	1.42	0.01
Nilselid et al.	2006	Caucasian	Sweden	AD	CSF	77.3 ± 5.9	99	7.17	2.43
Puchades et al.	2003	Caucasian	Sweden	AD	CSF	80 ± 5	7	4240	1294
Lidstrom et al. (AD)	2001	Caucasian	Sweden	AD	CSF	77 ± 6.6	32	6.5	1.9
Lidstrom et al. (VAD)	2001	Caucasian	Sweden	Others	CSF	83 ± 7.9	20	6.6	1.6
Deming et al.	2016	Caucasian	USA	AD	CSF	76.68 ± 7.18	300	24.74	0.56
Richens et al.	2014	Caucasian	UK	AD	CSF	NA	10	7.38	1.19
Hakobyan et al.	2016	Caucasian	UK	AD	Plasma	NA	106	387.6	113.9
Cai et al.	2016	Asian	China	MCI	Plasma	62.56 ± 8.53	126	115.67	31.59
Gupta et al. (MCI)	2016	Caucasian	Australia	MCI	Plasma	75.84 ± 7.31	93	327.33	41.41
Gupta et al. (AD)	2016	Caucasian	Australia	AD	Plasma	77.89 ± 7.66	150	347.17	42.09
Meng et al.	2015	Asian	China	MCI	Plasma	72.3 ± 1	47	115.27	4.3
Jongbloed et al.	2015	Caucasian	Netherlands	MCI	Plasma	68 ± 9	50	87	24
Jongbloed et al.	2014	Caucasian	Netherlands	MCI	Plasma	67 ± 8	206	187	30
Mukaetova-Ladinska et al.	2015	Caucasian	UK	AD	Plasma	78.08 ± 1	25	68.78	4.47
Hughes et al.(Aβ+)	2014	Caucasian	USA	MCI	Plasma	NA	25	390	110
Hughes et al.(Aβ-)	2014	Caucasian	USA	MCI	Plasma	NA	12	340	80
Mullan et al. (AD)	2013	Caucasian	Northern Ireland	AD	Plasma	77.9 ± 7.1	154	193.6	58.2
Mullan et al. (MCI)	2013	Caucasian	Northern Ireland	MCI	Plasma	73.7 ± 8.8	111	222.3	61.3
Silajdzic et al. (AD)	2012	Caucasian	Sweden	AD	Plasma	75(56–87)	127	33.3	3.9
Silajdzic et al. (DLB)	2012	Caucasian	Sweden	Others	Plasma	75(54–85)	34	33.2	4.4
Silajdzic et al. (FTD)	2012	Caucasian	Sweden	Others	Plasma	61(45–75)	17	33.3	2.1
Silajdzic et al. (VAD)	2012	Caucasian	Sweden	Others	Plasma	76(56–87)	19	35	4.5
Silajdzic et al. (PDD)	2012	Caucasian	Sweden	Others	Plasma	72(62–81)	12	34.1	3.4
Xing et al.	2012	Asian	China	AD	Plasma	80.20 ± 5.57	104	162.74	10.03
Thambisetty et al. (MCI)	2012	Caucasian	USA	MCI	Plasma	77.0 ± 7.1	16	134.5	42
Thambisetty et al. (AD)	2012	Caucasian	USA	AD	Plasma	86.0 ± 6.36	17	106.3	23.7
Schrijvers et al.	2011	Caucasian	Netherlands	AD	Plasma	83.4 ± 7.3	60	129	29
Schurmann et al.	2011	Caucasian	Germany	AD	Plasma	85.3 ± 3.7	67	158.5	45.3
Thambisetty et al. (MCI)	2010	Caucasian	UK	MCI	Plasma	NA	222	77.6	22.5

Table 1 (continued)

Thambisetty et al. (AD)	2010	Caucasian	UK	AD	Plasma	NA	336	82.4	25.6
Deming et al.	2016	Caucasian	USA	AD	Plasma	77.65 ± 7.51	521	285.05	3.12
Song et al.	2012	Caucasian	Australia	MCI	Plasma	78.8 ± 4.7	257	51	119.98
Richens et al.	2014	Caucasian	UK	AD	Plasma	NA	10	5.93	1.31
Vishnu et al. (Alzheimer type)	2016	Asian	India	Others	Plasma	NA	34	65.44	28.32
Vishnu et al. (Vascular type)	2016	Asian	India	Others	Plasma	NA	12	51.77	18.92
Dukic et al. (AD)	2016	Caucasian	Croatia	AD	Serum	74(69–79)	70	42.2	15
Dukic et al. (VAD)	2016	Caucasian	Croatia	Others	Serum	78(74–80)	67	37	14.7
Dukic et al. (MCI)	2016	Caucasian	Croatia	MCI	Serum	72(68–76)	48	41.8	16.3
Ijsselstijn et al.	2011	Caucasian	Netherlands	AD	Serum	78 ± 6.5	43	62.7	13.9

Author	Dementia	Control					Test methods	Diagnosis
	Female(%)	Mean age(year)	Sizes	Mean(ug/ml)	SD	Female(%)		
Chen et al. (frontal cortex)	66.7	87.3	6	25.4	4.4	50	Mass spectrometry*	NA
Chen et al. (temporal cortex)	0	83.5	6	29	7.9	0	Mass spectrometry*	NA
Lidstrom et al. (AD-frontal cortex)	63.2	72 ± 16	7	1	0.07	28.6	Western blots*	CERAD criteria
Lidstrom et al. (AD-hippocampus)	63.2	72 ± 16	7	1	0.22	28.6	Western blots*	CERAD criteria
Lidstrom et al. (AD-cerebellum)	63.2	72 ± 16	7	1	0.1	28.6	Western blots*	CERAD criteria
Lidstrom et al. (VAD-frontal cortex)	16.7	72 ± 16	7	1	0.07	28.6	Western blots*	NA
Lidstrom et al. (VAD-hippocampus)	16.7	72 ± 16	7	1	0.22	28.6	Western blots*	NA
Lidstrom et al. (VAD-cerebellum)	16.7	72 ± 16	7	1	0.1	28.6	Western blots*	NA
Harr et al.	NA	63.3 ± 18.1	13	848	256	NA	Western blots*	NA
Jongbloed et al.	38.8	60.4 ± 8.7	76	8.5	3	39.5	ELISA	Petersen
Jongbloed et al.	42.2	61 ± 9	223	8.9	3.3	41.3	ELISA	Petersen
Desikan et al.	33%	76 ± 0.6	91	1.39	0.02	51%	Multiplex immunoassay	NA
Nilselid et al.	64.6	69.5 ± 9.7	39	5.73	2.09	69.2	ELISA	NINCDS
Puchades et al.	57.1	66 ± 6	7	7711	2210	42.8	Mass spectrometry	NINCDS-ADRDA
Lidstrom et al. (AD)	53.1	70 ± 5.5	11	5.6	1.1	63.6	ELISA	NINCDS
Lidstrom et al. (VAD)	50	70 ± 5.5	11	5.6	1.1	63.6	ELISA	NINCDS-AIREN
Deming et al.	40.33	73.77 ± 6.92	373	19.92	0.36	58.98	Multiplex immunoassay	NINCDS-ADRDA
Richens et al.	NA	NA	18	7.14	1.02	NA	Immunoassays	CERAD criteria
Hakobyan et al.	NA	NA	186	295	128.5	NA	ELISA	DSM-IV and NINCDS-ADRDA
Cai et al.	47.6	58.71 ± 7.97	105	104.24	32.01	39	ELISA	EADC
Gupta et al. (MCI)	56	70.72 ± 6.9	590	283.76	38.98	57	ELISA	NINCDS-ADRDA
Gupta et al. (AD)	59	70.72 ± 6.9	590	283.76	38.98	57	ELISA	NINCDS-ADRDA
Meng et al.	53.2	69 ± 1.5	35	120.32	6.87	62.8	ELISA	Petersen
Jongbloed et al.	40	64 ± 8	67	76	12	64.1	ELISA	Petersen
Jongbloed et al.	42.2	61 ± 9	223	188	35	41.3	ELISA	Petersen
Mukaetova-Ladinska et al.	40	70.81 ± 1.98	26	61.13	3.95	69	ELISA immunoassay	NINCDS-ADRDA
Hughes et al.(Aβ+)	NA	NA	71	380	100	NA	ELISA	Winblad criteria
Hughes et al.(Aβ-)	NA	NA	66	380	80	NA	ELISA	Winblad criteria
Mullan et al. (AD)	59.1	74.5 ± 8.6	142	178.6	52.3	59.2	ELISA	NINCDS-ADRDA
Mullan et al. (MCI)	60.4	74.5 ± 8.6	142	178.6	52.3	59.2	ELISA	Winblad criteria

Table 1 (continued)

Silajdzic et al. (AD)	71	74(62–99)	171	33.3	4.8	64	ELISA	DSM-IIIR and NINCDS-ADRDA
Silajdzic et al. (DLB)	68	74(62–99)	171	33.3	4.8	64	ELISA	McKeith et al. criteria
Silajdzic et al. (FTD)	41	74(62–99)	171	33.3	4.8	64	ELISA	McKhann et al. criteria
Silajdzic et al. (VAD)	68	74(62–99)	171	33.3	4.8	64	ELISA	DSM-IIIR and NINDS-AIREN
Silajdzic et al. (PDD)	42	74(62–99)	171	33.3	4.8	64	ELISA	NA
Xing et al.	60.6	79.32 ± 5.37	104	167.01	13.4	55.8	ELISA	NINCDS-ADRDA
Thambisetty et al. (MCI)	40.7	69.6 ± 7.4	123	117.4	44.8	43.8	ELISA	Petersen criteria
Thambisetty et al. (AD)	82.4	81 ± 7.49	4	88	7.2	50	ELISA	NINCDS-ADRDA and DSM-IV-TR
Schrijvers et al.	68	72.8 ± 7.3	926	115	25	55	Multiplex immunoassay	NINCDS-ADRDA
Schurmann et al.	70.1	83.7 ± 3.2	191	161.5	47.6	70.2	ELISA	NA
Thambisetty et al. (MCI)	NA	NA	385	82.2	23.8	NA	ELISA	NA
Thambisetty et al. (AD)	NA	NA	385	82.2	23.8	NA	ELISA	NINCDS-ADRDA
Deming et al.	38.58	74.12 ± 7.44	297	221.22	4.39	60.27	Multiplex immunoassay	NINCDS-ADRDA
Song et al.	33.03	77.9 ± 4.5	407	108.97	27.43	57	Multiplex immunoassay	Winblad criteria
Richens et al.	NA	NA	18	6.12	1.31	NA	Immunoassays	CERAD criteria
Vishnu et al. (Alzheimer type)	NA	NA	19	130.18	108.66	NA	ELISA	Dubois criteria and NIA-AA
Vishnu et al. (Vascular type)	NA	NA	19	130.18	108.66	NA	ELISA	DSM IV Criteria and NIA-AA
Dukic et al. (AD)	61	66(63–73)	50	40.5	12.8	60	ELISA	NINCDS-ADRDA
Dukic et al. (VAD)	60	66(63–73)	50	40.5	12.8	60	ELISA	NINDS-AIREN
Dukic et al. (MCI)	65	66(63–73)	50	40.5	12.8	60	ELISA	Petersen's criteria
Ijsselstijn et al.	74.4	78 ± 6.8	43	61	11.4	74.4	Nano LC-MRM MS	CAMDEX

Others: VAD, PDD, DLB and FTD

NA not available; *AD* Alzheimer's disease; *MCI* mild cognitive impairment; *VAD* vascular dementia; *DLB* Lewy Body dementia; *PDD* Parkinson's disease with dementia; *FTD* frontotemporal dementia; *SD* standard derivation; *Aβ* β-amyloid; *ELISA* enzyme-linked immunosorbent assay; *CSF* cerebrospinal fluid; *NINCDS-ADRDA* National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; *NINDS-AIREN* National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et I'Enseignement Neurosciences; *EADC* MCI Working Group of the European Consortium on AD; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders-IV; *CERAD* The Consortium to Establish a Registry for Alzheimer's Disease; *CAMDEX* Cambridge Examination for Mental Disorders; *NIA-AA* National Institute on Aging and the Alzheimer's Association.

*: The methods applied in measuring the clusterin level in brain tissue are semi-quantification without unit of measurement

dementia patients and 849 controls were included in this meta-analysis. Among the 7 studies, 5 of them were performed in the AD, 3 were conducted in the MCI, and one in other dementia type. Only three and two studies were selected to perform a meta-analysis for the association between brain tissue and serum CLU concentration and dementia, respectively.

Quantitative synthesis

Due to the significant heterogeneity (Cochran Q test, $P < 0.1$), the random-effects model was used to analysis the association between CLU concentration and dementia. There was a significant increase of plasma CLU concentration in the dementia population compared to that in the normal controls (SDM = 0.73, 95% CI 0.26–1.19, $P = 0.002$) (Fig. 2). However, the results from subgroup analysis based on disease type suggested that the plasma CLU concentration was only significantly increased in the AD population (SDM = 1.85, 95% CI 0.84–2.85, $P < 0.001$), but not in the MCI (SDM = 0.10, 95% CI -0.30–0.49, $P = 0.641$) or other dementia types (SDM = −0.18, 95% CI -0.57–0.22, $P = 0.375$) (Fig. 2).

No significant difference was found in the CSF CLU concentration between the dementia patients and normal controls (SDM = 1.45, 95% CI -0.25–3.15, $P = 0.095$) (Fig. 3). Furthermore, subgroup analysis did not found a significant association between CSF CLU concentration and dementia in all the dementia types (Table 2).

We also performed a meta-analysis to estimate the association between brain tissue CLU concentration and dementia. The result showed that the CLU concentration in the brain was significantly increased in the dementia patients as compared to that in normal controls (SDM = 0.71, 95% CI 0.10–1.32, $P = 0.022$). However, the result from subgroup analysis did not found a relationship between brain tissue CLU concentration and AD (SDM = 0.71, 95% CI -0.14–1.55, $P = 0.102$), which may be due to the limited number of the included studies. In addition, no significant association was found between the serum CLU concentration and dementia (SDM = 0.01, 95% CI -0.18–0.21, $P = 0.890$) (Table 2).

Publication bias and studies quality

The potential publication bias was assessed by Egger's and Begg's tests. No significant publication bias was observed in evaluating the association between plasma and CSF clusterin concentration and dementia. The results from Egger's test showed that P values for plasma and CSF were 0.158 (Fig. 4) and 0.473 (Supp. Fig. S1), respectively. Due to the limited number of included studies in serum and brain tissue, the publication bias analysis was not performed. The NOS was conducted and median score for plasma, CSF, serum and brain tissue were 7, 7, 6 and 6.5, respectively.

Discussion

Polymorphisms in the CLU gene have been reported to be associated with the susceptibility of dementia, which could affect the transcription and translation of *CLU* in the brain (Mullan et al. 2013; Du et al. 2016). Over the past decades, accumulated studies have been performed to evaluate the relationship between CLU concentration and dementia (Schrijvers et al. 2011; Hughes et al. 2014; Meng et al. 2015). However, due to the limit patient sizes and different sample used in clusterin quantification, the results from these studies remain inconsistent. Therefore, in order to determine the association between CLU concentration and dementia risk, we conducted this meta-analysis to address this relationship.

This meta-analysis showed that the plasma CLU concentration in the AD patients was significantly higher than that in normal controls. However, no significant alternation was found in the MCI patients. Though sCLU acted as a protective protein in the pathology of AD, the study from Schrijvers et al. suggested that the plasma clusterin concentration was positively correlated with the severity of the disease and brain atrophy (Schrijvers et al. 2011). This result suggests a compensatory function of clusterin in the development and progression of AD (Bertrand et al. 1995). The negative results for plasma clusterin concentration and MCI may be contributed to the slight pathological alternation in MCI patients, since there was a trend of the association between CLU concentration and severity of AD (Thambisetty et al. 2010). Furthermore, it was also reported that higher CLU concentration was associated with lower risk of dementia in younger participants, but with higher risk in older participants (80–89 years old) (Weinstein et al. 2016). Unexpectedly, there was no significant association between serum CLU concentration and AD or MCI. It is worth noting that the clusterin was also expressed in the platelet (Macaulay et al. 2005), a potential source of clusterin in the serum (Mukaetova-Ladinska et al. 2012). As the platelet secreted many peptides in the blood coagulation process, the negative results from serum analysis may be resulted from the mixture of platelet-derived clusterin (Golebiewska and Poole 2015). Therefore, it is better to collect the plasma rather than serum to measure the CLU concentration in blood.

Data from the brain tissue analysis also suggested an increased CLU concentration as compared to that in normal controls. Clusterin was reported to combine with Aβ and locate in the senile plaque in the AD patients' brain (Desikan et al. 2014). Though we found that the CLU concentration in the brain tissue was significantly increased in the dementia patients, some limitations should be clarified. First, only three studies with 9 data sets (obtained from different brain region) were included in the analysis (Harr et al. 1996; Lidstrom et al. 1998; Chen et al. 2012). Second, the methods applied in measuring clusterin in the brain tissue were not consistent and all

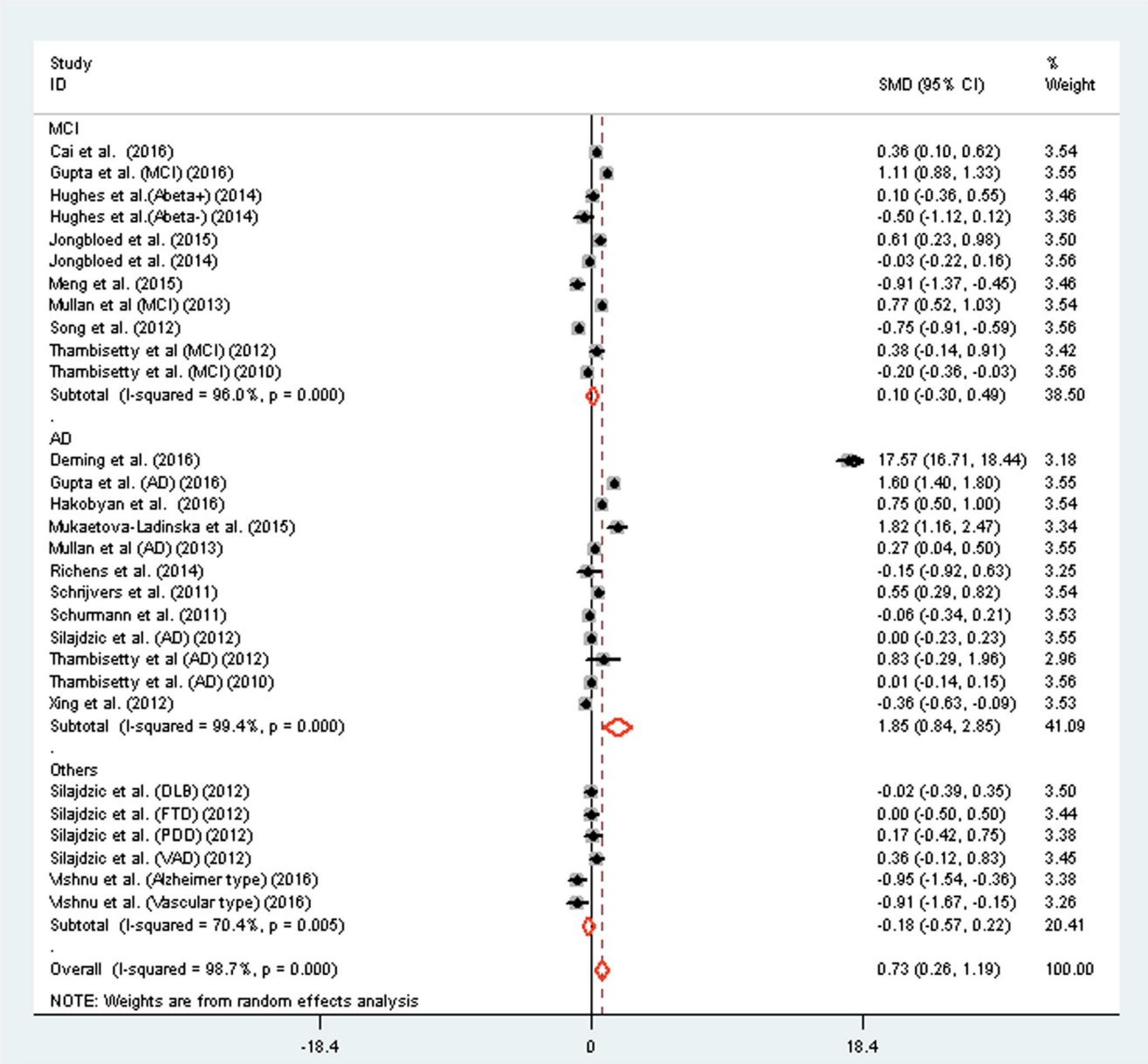

Fig. 2 Forest plot of plasma clusterin concentration and dementia risk. The plasma clusterin concentration was significantly increased in the dementia group compared to controls (SDM = 0.73, 95% CI 0.26–1.19, $P = 0.002$). Subgroup analysis base on dementia type showed that the plasma clusterin concentration was only significantly associated with AD subgroup (SDM = 1.85, 95% CI 0.84–2.85, $P < 0.001$)

the data were semi-quantification. Thus, further studies with concordant measurement method and large sample sizes were eager to confirm the above results in our meta-analysis.

No statistically significant association was found between CSF clusterin concentration and dementia, neither in the subgroup analysis (AD, MCI and other dementias). As clusterin in the CSF can bind to Aβ, the concentration of Aβ in the CSF may influence the amount of clusterin in the CSF (Golabek et al. 1995). In fact, the study from Desikan et al. (2014) indicated that the CSF clusterin concentration was only significantly associated with CSF Aβ1–42-positive individuals, but not CSF Aβ1–42-negative patients (Desikan et al. 2014). Due to the CSF Aβ1–42 data was unavailable in most of the included studies, we could not perform a subgroup analysis based on Aβ1–42 distribution. Therefore, to further determine the effect of CSF Aβ1–42 on the CSF clusterin concentration is essential to evaluate the predictive function of CLU on AD, and to fully understand the role of clusterin in AD. Though no significant relationship was found between CSF clusterin concentration and dementia, a significant association was found in the plasma and brain sample (Thambisetty et al. 2012). This results indicating plasma CLU concentration could partially reflect the CLU concentration in brain tissue, and plasma CLU concentration could be used as a biomarker for dementia.

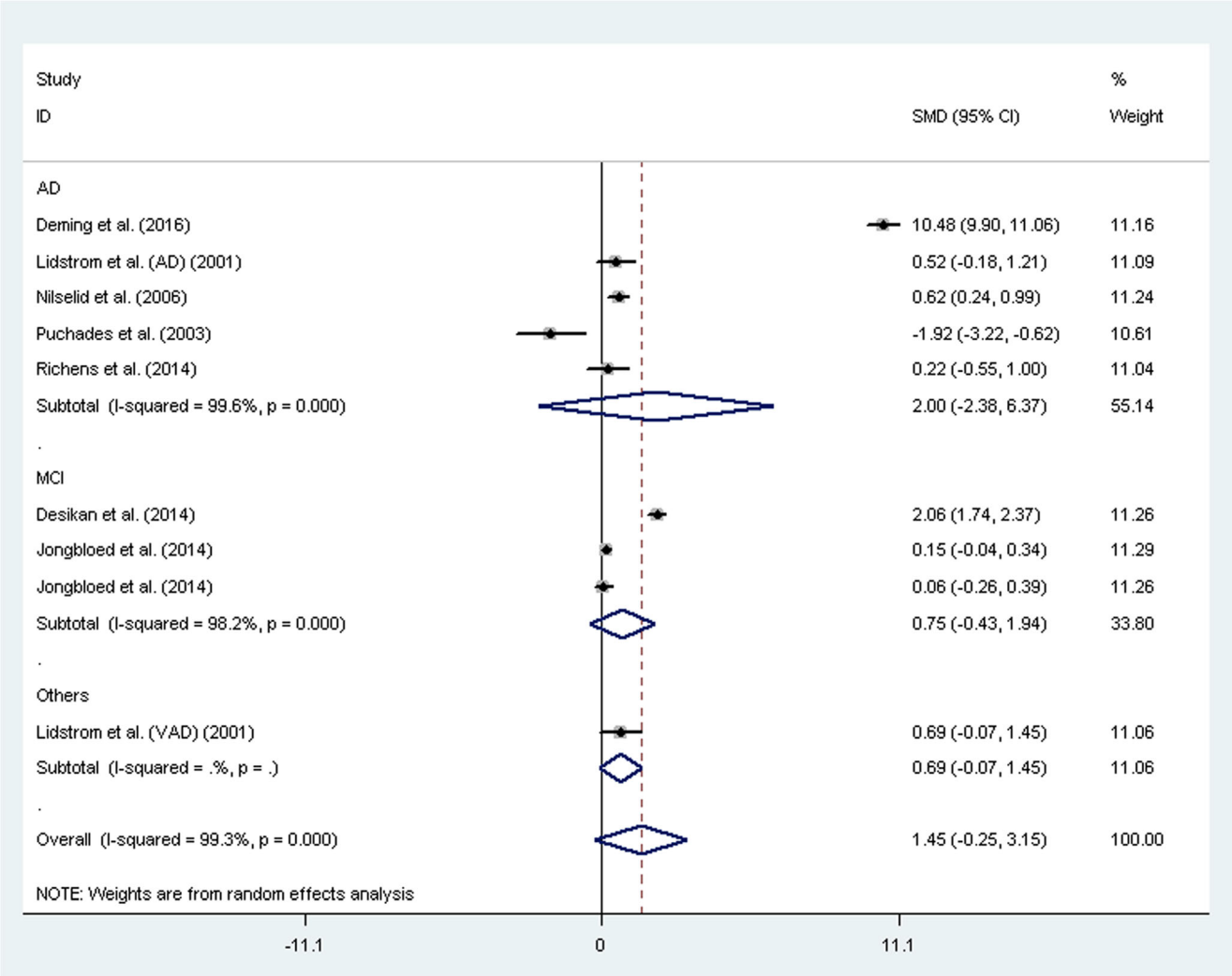

Fig. 3 Forest plot of CSF clusterin concentration and dementia risk

The genetic type in CLU gene was indicated to influence its expression, and various alleles were found to be associated with different CLU concentration (Xing et al. 2012). The study from Mullan et al. (2013) suggested that in rs11136000, the CLU concentration in the TT allele was significantly lower than that in the TC or CC allele individuals (Mullan et al. 2013). In addition, it was reported that people carrying TT genotype or T allele of rs11136000 (C/T) polymorphism were associated with a lower risk of AD (Du et al. 2016). There are also other polymorphisms (like rs2279590 and rs9331888) in CLU gene reported to be associated with AD (Shuai et al. 2015; Zhang et al. 2015). However, whether these polymorphisms are involved in the CLU expression and concentration need to be further confirmed. Furthermore, other gene (like APOE4) variants may be also implicated in modulating the function of clusterin (DeMattos et al. 2004), so to clarify the effect of these genes on clusterin function is need in the future studies. Since the limited information of the included studies, we could not conduct a subgroup analysis to determine the influence of APOE4 on clusterin function and concentration.

As mentioned above, CLU has two different subtypes sCLU and nCLU. It is reported that these two subtypes play opposite roles in AD development (Yu and Tan 2012). sCLU is thought to exert a anti-apoptotic function in AD. Opposed to the protective function of the sCLU form, the nCLU is reported to be involved in cytotoxicity by binding to bridging integrator 1 (BIN1) or Bcl-XL (Kim et al. 2012; Zhou et al. 2014). Though our results show that the CLU concentration is increased in AD patients, it seems failed to impede the progression of the AD. The controversial roles of sCLU and nCLU may partially explain that intrigued phenomenon. Since no specific antibody is available now to measure plasma sCLU and nCLU concentration, the ratio of sCLU and nCLU in blood sample from AD patients remains unknown. Thus, further studies are needed to clarify the association between plasma sCLU or nCLU and AD.

Table 2 Meta-analysis results for clusterin levels and dementia

Samples	Dementia type(s)	SMD (95%CIs)	*P* value	Heterogeneity test	
				I^2(%)	*P* value
Plasma	AD	1.85 (0.84–2.85)	< 0.05	99.4	< 0.05
	MCI	0.10 (−0.30–0.49)	> 0.05	96.0	< 0.05
	Others	-0.18 (−0.57–0.22)	> 0.05	70.4	< 0.05
	Total	0.73 (0.26–1.19)	< 0.05	98.7	< 0.05
CSF	AD	2.00 (−2.38–6.37)	> 0.05	99.6	< 0.05
	MCI	0.75 (−0.43–1.94)	> 0.05	98.2	< 0.05
	Others	0.69 (−0.07–1.45)	> 0.05	NA	NA
	Total	1.45 (−0.25–3.15)	> 0.05	99.3	< 0.05
Serum	AD	0.13 (−0.15–0.40)	> 0.05	0	0.962
	MCI	−0.25 (−0.62–0.12)	> 0.05	NA	NA
	Others	0.09 (−0.31–0.49)	> 0.05	NA	NA
	Total	0.01 (−0.18–0.21)	> 0.05	0	0.426
Brain tissue	AD	0.71(−0.14–1.55)	> 0.05	78.3	< 0.05
	MCI	–	–	–	–
	Others	0.74 (0.06–1.42)	< 0.05	4.2	0.352
	Total	0.71 (0.10–1.32)	< 0.05	68.6	0.001

Others: VAD, PDD, DLB and FTD

SDM standard difference of the mean; *CSF* cerebrospinal fluid; *NA* not available; *AD* Alzheimer's disease; *MCI* mild cognitive impairment.

Some potential limitations in this meta-analysis should be addressed. First, The clinical criteria for diagnosis of dementia, gender and therapies of participant, specimen collection and storage and methods used in measuring CLU were different across all the selected studies, which could contribute to variability. However, due to the limited detailed information, it is hard for us to perform a further analysis according to above variables. Second, the variants in the CLU gene were reported to affect the expression of clusterin, but whether the variants in CLU gene were involved in the association between CLU concentration and dementia could not be estimated due to limit data. Third, there was a significant heterogeneity in this meta-analysis, indicating a low quality of the included studies. Fourth, the method applied in clusterin quantification from the brain tissue obviously differed among the included studies, which may weaken the strength of this meta-analysis. Fifth,

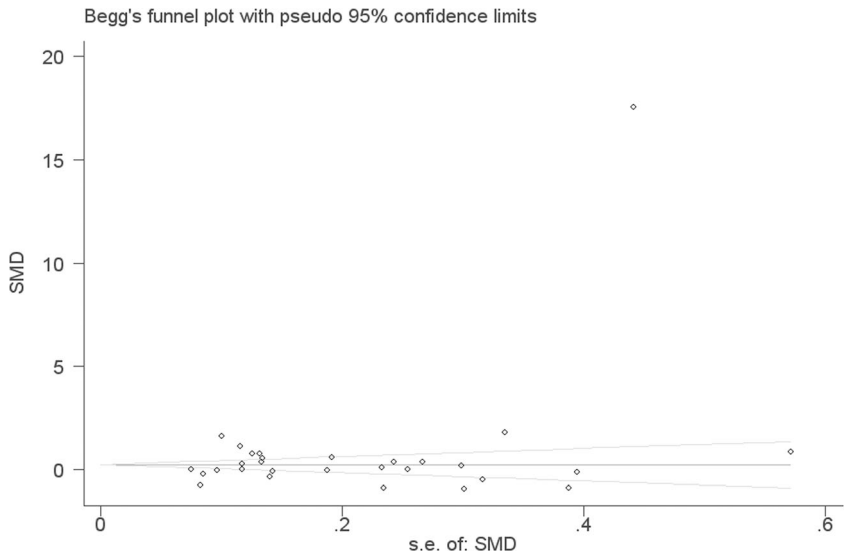

Fig. 4 Funnel plot for the association between plasma clusterin concentration and dementia in evaluating the publication bias

the gene-gene (APOE4) interactions could not be evaluated due to the unavailable data for APOE4. Finally, due to the significant heterogeneity in the meta-analysis, both positive and negative results in this meta-analysis should be interpreted cautiously.

Conclusion

Our meta-analysis demonstrated that the plasma CLU concentration was significantly increased in the AD patients, but not in the MCI or other dementias. More original studies with large samples are warranted to confirm the association between CLU concentration and AD.

Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

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