Scope on triglyceride levels in elderly patients with dementia versus controls: a systematic review and meta-analysis

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Abstract

Introduction: Triglyceride levels vary among elderly patients with dementia. In this study, triglyceride levels were examined to demonstrate whether they increase or decrease in elderly dementia patients and other elderly individuals, whether there is a difference between elderly individuals with different forms of dementia and controls, and whether that difference is considered significant.
Materials and Methods: This analysis was performed via searching in Scopus, Web of Science, and PubMed. A PRISMA checklist was followed to conduct the systematic review. The quality assessment was assessed by the Newcastle-Ottawa for case-control studies. Meta-analysis was performed by SPSS, Version 28.
Results: Twenty-five studies consisting of 18943 cases and 212144 controls were included in the final analysis. Eighteen studies showed that the triglyceride levels in both patients and controls did not exceed the normal range (1.7 mmol/L or 150 mg/dl). A meta-analysis was also performed for the seven studies that revealed that triglyceride levels exceeded the normal range and no significant difference was found between the cases and controls (p-value =0.18, 95% CI).
Conclusion: Triglyceride levels may not be a serious factor that should be considered in dementia, which differs from other areas of medicine, such as cardiovascular diseases.

Keywords: Triglyceride levels, elderly, dementia, systematic review

Introduction

Dementia is defined as a neurocognitive disorder. It is associated with advancing age. It appears in different forms, such as Alzheimer's disease, vascular dementia, and frontotemporal dementia. The severity of cognitive impairment varies from mild to severe. It interrupts normal daily activities and affects patient behavior. Risk factors were studied to understand what accelerates dementia and how to address it. Attention was given to metabolic syndrome, which consisted of elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure, and elevated fasting plasma glucose. Many studies have considered it a risk factor in dementia, as is the case for other complicated diseases, especially cardiovascular diseases.[1]

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The effect of triglyceride levels, which is one component of metabolic syndrome, is controversial, and recent studies present a different view than the usual concept.

The usual concept states that biomarkers of metabolic syndrome, including elevated plasma TG/HDL-C ratios, are associated with cognitive decline in dementia patients.[2]

Another study suggests that four or five metabolic components are significantly associated with dementia.[3]

On the other hand, the findings of a large cohort study of 254,575 women and 214,891 men in the UK Biobank revealed that high triglyceride levels were associated with increased dementia risk in individuals aged <60 years, but the inverse was observed for those aged ≥60 years.[4]

The recent paper by Zhou Z. et al., published in a prospective cohort study, suggests that higher levels of triglycerides may be associated with a lower risk of dementia and a slower rate of cognitive decline over time, compared to individuals with lower triglyceride levels. This could be explained by the fact that testosterone reduces triglyceride levels. Prolonged low testosterone levels in aging may lead to "higher triglyceride levels within the normal to high-normal range."[5]

Additionally, an interesting trend in which triglyceride levels were screened in adults in the USA from 2001 to 2012 revealed that the percentage of adults with elevated triglycerides (150 mg/dL or more) in different categories (aged >20 years, men and women, aged >60 years) had a decrease in elevated triglyceride levels in 2009-2012 than in 2001-2004. This trend was detected only for triglyceride levels and was not related it to other conditions, such as dementia.[6]

This study aimed to shed light on triglyceride levels to demonstrate whether they increase or decrease in elderly patients with dementia and other elderly, whether there is a

difference between the elderly individuals with different forms of dementia and controls, and whether that difference is considered significant.

Methods and Materials

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[7]

Search methods for the identification of studies

A search was conducted on November 26, 2023, via Scopus, Web of Science, and PubMed using the search terms "triglycerides," "high triglycerides," "hypertriglyceridemia," and "dementia."

Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: (1) Only case-control studies were included. (2) Participant who had dementia or developed dementia during the study, and dementia or cognitive impairment were screened by a well-defined and approved scale or criteria. (3) All the patients and controls from the elderly population. (4) In all the studies, triglyceride levels were measured clearly, and the laboratory results were clarified and mentioned.

The excluded studies were not published in English, were conducted in animals, had designs other than case-control studies, were duplicates, had restricted free full texts, had screening scales for dementia not identified, and laboratory results of triglyceride levels not clarified.

Study selection

The eligibility of the search results was assessed via two steps: title and abstract screening, followed by full text screening.

Data extraction

The data that were extracted involved author name, year of publication, country where the study was conducted, journal that published the study, mean age in years, gender (female%), dementia form, scale that was used to assess cognition, total number of enrolled participants, number of cases and controls, and triglyceride levels in mmol/l in both cases and controls (i.e., other units, mg/dl, were converted to mmol/l).

Risk of bias

The quality assessment was assessed by the Newcastle-Ottawa Scale for case-control studies.[8] The maximum number of gained stars is eight. A score less than 4 stars was considered to indicate poor quality, and 4 or more was considered to indicate moderate to high quality (Table S1).

Data synthesis and analysis

The meta-analysis was performed with SPSS, version 28. The numerical values of triglyceride levels were presented in mean and standard deviation for both the patients and controls and were processed in the final analysis. The final analysis was conducted with a 95% confidence interval (CI) and a p-value of 0.05 and by using the standard mean difference (SMD).The heterogeneity between the studies was assessed by the I2 index, which showed significant heterogeneity, although a random effect model was used. This high heterogeneity in the study results reflects the controversial levels of triglycerides among the elderly people. Sub-group analysis was performed for only studies that showed elevated triglyceride levels to levels higher than the normal levels (1.7 mmol/L or 150 mg/dl) for cases or controls. The I2 index reached 54%. The final results are displayed in forest and funnel plots.

Results

The initial search identified 608 studies from Web of Science, 607 from Scopus, and 366 from Pubmed. A total of 576 studies were excluded because they were duplicates. Sixty-eight studies were non-English studies. A total of 946 studies were screened in the title-abstract step; 84 studies were reviews; 85 studies were conducted in animals; 11 studies were case reports and case-series studies; 568 studies were irrelevant to outcomes; and 7 studies had restricted full text. 191 studies were eligible for the full text screening step, and 149 studies out of 191 were irrelevant to the outcome. The final number of included studies was 25, after the exclusion of 17 studies that were irrelevant to the outcome (Figure 1).

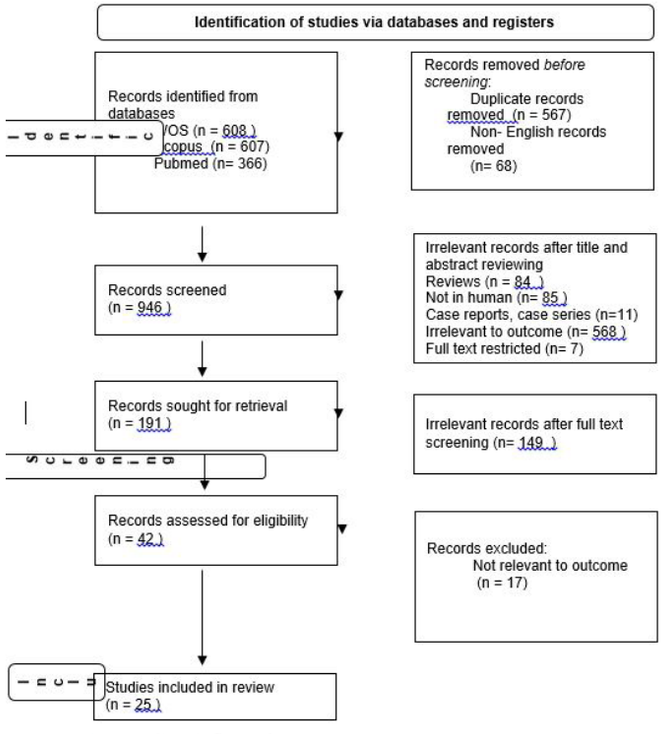

Figure 1. PRISMA flow diagram

Characteristics of the included studies and summary of findings

Twenty-five studies9-33 consisting of 18943 cases and 212144 controls, were included in the final analysis. It was published from 2007 to 2023. The largest number of included studies according to the inclusion criteria was found in 2020 (6 studies). The studies were conducted in several countries, but the largest number of studies were conducted in China (9 studies). All the studies were published in considerable journals. Although all the studies were conducted on elderly individuals, in most (21 studies), the mean age exceeded 60 years; in 4 studies (study

1, 4, 11, and 25), the mean age exceeded 50 years; and in one study (study 17), the mean age was 85.8±12. The percentage of females varied between studies and ranged from 31% to 70.8%. Although all the studies concerned the elderly population in general, two studies (study 4 and study 19) were conducted on diabetic patients. The studies included different forms of dementia, but Alzheimer disease was in the top by 10 studies (study 6, 7, 9, 11, 13, 14, 15, 20, 21, and 25), and that finding is consistent with the theory that Alzheimer disease is considered the most common type of dementia.34 The other studies assessed other types of dementia, such as vascular dementia, frontotemporal dementia, dementia associated with Parkinson disease, and cognitive impairment, which was described in some studies as mild or early and in others as poor cognitive functions (Table S2). Study 6 was split into 2 studies for mild cognitive impairment and Alzheimer disease; Study 11 was split into 2 studies for Alzheimer disease and frontotemporal dementia; and Study 23 was split into 2 studies for males and females. The total number of cases in the included studies ranged from 23 to 10732, and the total number of controls ranged from 33 to 167854, which indicates high variation between studies. Additionally, the percentage of cases compared to controls largely varied between studies. In some studies, the number was closed, and in others, the number of controls was extremely high in comparison to the number of patients.

When examining the triglyceride levels for the individual studies that were included in the final analysis, the mean triglyceride levels were found to be widely varied. For the dementia group, it ranged from 0.79 to 1.88 mmol/l, with standard deviations ranging from 0.02 to 1.86, and for the control group, it ranged from 1.04 to 1.83 mmol/l, with standard deviations ranging from 0.03 to 1.05 (Table 1). The wide variation displays major heterogeneity between individuals in the same study and between studies. The large standard deviation, which sometimes exceeds the mean triglyceride levels, indicates excessive outliers in both the patients and controls. Eighteen studies showed that the mean triglyceride levels in both cases and controls did not exceed the normal range (1.7 mmol/L or 150 mg/dl); however when the standard deviation was taken into consideration given the difference in number between cases and controls, the p-value mentioned in some studies was significant (study 2, 3, 9, 10, 13, 17, and 25), indicating that even if the mean triglyceride levels did not exceed the normal level, there was a significant difference between cases and controls. In seven studies (study 4, 6, 12, 14, 16, 19, 24), the mean triglyceride levels were greater than the normal range; the p-value mentioned was sometimes significant and in others, it was non-significant. The meta-analysis was performed with caution due to the large difference observed between studies, as clarified above.

Table 1. Triglyceride levels in cases versus controls

study ID	TN D*	TG D**	SD+	TN C¶	TG C‡	SD	outcome
study 1	217	1.39	0.81	259	1.18	0.72	p-value= .347
study 2	160	1.63	0.54	340	1.27	0.28	p-value < 0.001
study 3	2128	1.4	0.85	26358	1.36	0.93	p-value < 0.001
study 4	458	1.7	0.54	820	1.63	0.76	p-value= 0.045
study 5	32	1.07	0.69	41	1.48	0.52	PDD& patients had lower levels of triglyceride, The average ages of PDD patients were significantly higher than the HC@ group
study 6 for MCI	339	1.75	1.62	190	1.59	0.9	Significant association
study 6 for AD	160	1.78	1.12	190	1.59	0.9	Significant association
study 7	400	1.37	0.61	289	1.45	1.05	p-value= 0.17
study 8	468	1.35	0.02	4163	1.41	0.03	p-value= 0.070
study 9	10732	1.57	0.8	167854	1.53	0.8	p-value < 0.0001
study 10	361	1.24	0.66	2385	1.31	0.77	p-value = 0.018
study 11 for AD	63	1.26	0.54	33	1.37	0.54	p-value= 0.172
study 11 for FD	30	1.54	0.98	33	1.37	0.54	p-value= 0.172
study 12	384	1.88	1.12	347	1.81	1.04	p-value= 0.478
study 13	40	0.79	0.4	40	1.25	0.87	p-value < 0.0001
study 14	38	1.83	1.29	33	1.8	0.78	p-value= 0.9
study 15	785	1.3	0.6	3140	1.2	0.6	No significant case-control differences
study 16	112	1.67	0.3	115	1.77	0.32	p-value= 0.018
study 17	630	0.9	0.49	1370	1.04	0.7	p-value <0.01

study 18	140	1.55	1.86	457	1.6	1.01	p-value= 0.117
study 19	23	1.83	0.95	238	1.41	0.77	p-value= 0.015
study 20	51	1.6	0.77	42	1.67	0.67	p-value = 0.638
study 21	150	1.19	0.35	320	1.17	0.32	P = .48
study 22	81	1.39	0.7	738	1.48	0.96	P = .43
study 23 males	87	1.19	0.59	141	1.25	0.54	p= 0.88
Study 23 females	322	1.23	0.65	159	1.28	0.87	p= 0.88
study 24	502	1.84	0.93	1974	1.83	0.99	p-value= 0.19

*TN D total number of dementia group
**TG D mean triglyceride levels in dementia group mmol/l
+SD standard deviation
¶TN C total number of control group
‡TG C mean triglyceride levels in control group mmol/l
&PDD Parkinson disease dementia
@HC healthy cognition

Meta-analysis for the included studies

The meta-analysis was conducted using the standard mean difference (SMD) method to determine the overall results of the included studies. Despite efforts to lessen it by using random effects model, notable heterogeneity was observed. The overall effect is expressed by a p-value = of 0.58, which is non-significant. There was no significant difference between the cases and controls based on the mean triglyceride levels, with a slight tendency towards the dementia group (Figure S1). The Egger test and funnel plot were conducted (p-value = 0.03) (Figure S2). Sub-group analysis was subsequently performed for only studies in which the mean triglyceride levels exceeded the normal level.

Meta-analysis for studies with high triglyceride levels

A sub-group analysis was conducted on seven studies (study 4, 6, 12, 14, 16, 19, 24) that reported mean triglyceride levels exceeding the normal level. The heterogeneity decreased to 54% (I2 = 54%, p-value = 0.02) with the random effects model. The overall effect is expressed by a p-value of 0.18, which is non-significant. There was no significant difference between the cases and controls based on the mean triglyceride levels, and this non-significant difference slightly goes forward to the dementia group (Figure S3). Additionally, Egger test and funnel plot were conducted (p-value = 0.587), suggesting no publication bias (Figure S4).

Table S1. Newcastle-Ottawa Scale (NOS) for case-control studies

Study		Selection			Comparability		Outcome	Total score
Case definition		Representation	Control selection	Control definition	Controlled for cofounders	Measured clearly	Same method of measurement	
1	*	*		*	*	*	*	6
2	*	*		*	*	*	*	6
3	*	*		*	*	*	*	6
4	*	*		*	**	*	*	7
5	*	*	*	*	*	*	*	7
6	*	*	*	*	*	*	*	7
7	*	*	*	*	*	*	*	7
8	*	*	*	*	*	*	*	7
9	*	*		*	*	*	*	6
10	*	*	*	*	*	*	*	7
11	*	*		*	*	*	*	7
12	*	*		*	*	*	*	6
13	*	*	*	*	*	*	*	7
14	*	*	*	*	*	*	*	7

14	*	*	*	*	*	*	*	7
15	*	*	*	*	*	*	*	7
16	*	*		*	*	*	*	6
17	*	*	*	*	*	*	*	7
18	*	*		*	*	*	*	6
19	*	*		*	**	*	*	7
20	*	*	*	*	*	*	*	7
21	*	*	*	*	*	*	*	7
22	*	*	*	*	*	*	*	7
23	*	*	*	*	**	*	*	8
24	*	*		*	*	*	*	6
25	*	*		*	*	*	*	6

Quality assessment was checked by Newcastle-Ottawa Scale (NOS) for case-control studies

NOS coding manual for case-control studies:
Selection
1) Was dementia or cognitive impairment screened by well-defined and approved criteria in cases:
a) Yes, with independent validation. (one star)
b) Yes, based on self-report
c) No description
2) Representativeness of the cases:
a) Consecutive or obviously representative. (one star)
b) Potential for selection bias or not stated
3) Selection of controls:
a) Community controls (one star)
b) Hospital controls
c) No description
4) Definition of controls:
a) No history of dementia (one star)
b) No description of source

Comparability
1) Comparability of cases and controls on the bases of the design or analysis controlled for confounders:
a) The study controls for age (one star)
b) The study controls for other factors (one star)
c) Cohorts are not comparable on the basis of the design or analysis controlled or cofounders

Outcome
1) Is triglyceride levels measured clearly (one star)
a) Yes, definitive value was specified
b) No

2) Same method for measurement for cases and controls:
a) Yes (one star)
b) No

Table S2. Characteristics of included studies

Study ID	Author	Year	Country	Journal	Mean age (years)	Sex (% females)	Dementia type	Scale used to measure dementia
study 1	Hui-Feng Guo	2023	China	Brain Behavior	more than 50	36	subtle cognitive decline	(MMSE) and others
study 2	Aashish Reddy Bande	2022	India	JIACM	> 60	31	MCI	MMSE score
study 3	Szu-Han Huang,	2022	Tiwan	Nutrients	63.9 ± 2.8	60.8	Poor Cognitive Function	MMSE
study 4	Arpita Chakraborty	2021	India	Frontiers in Endocrinology	58	35.8	CI	MoCA test
study 5	Mei-Xue Dong	2021	China	Metabolic Brain Disease	over 60	54	parkinsonian dementia	MMSE
study 6	Megan M. Bernath	2020	US, Canada	Neurology	> 65	43.3	MCI, AD	ADAS-Cog 13, ADNI-MEM
study 7	Lu Hua Chen	2020	Hong Kong	Journal of Psychiatric Research	> 65	70.8	AD	NINCDS-ADRDA
study 8	Jingzhu Fu	2020	China	Frontiers in Aging Neuroscience	67.6 (4.89)	55.7	MCI	MMSE
study 9	Hyewon Lee	2020	South Korea	Alzheimer's Research & Therapy	> 65	54.5	AD	(ICD-10) codes
study 10	Seung-Taek Lim	2020	Korea	Brain Sciences	≥65	50.9	CI	KDSQ-C
study 11	Pan Wang	2020	China	Translational Neuroscience	> 56	52.4	AD, frontotemporal dementia	MMSE, MoCA, NPI, ADL
study 12	Xue Wang	2019	China	Frontiers in Endocrinology	69.98 (5.58)	56.5	CI	MMSE
study 13	Marina Felipe Grossi	2018	Brasil	Arquivos de Neuro-Psiquiatria	> 65	50	AD	MMSE
study 14	Yanal A. Shafagoj	2018	Jordan	Neurosciences	≥65	63.2	AD	NINCDS-ADRDA
study 15	Maude Wagner	2018	France	JAMA Psychiatry	> 70	65	AD, VD	DSM-IV
study 16	Qian He	2016	China	Lipids in Health and Disease	> 65	59	MCI	MMSE
study 17	Yue-Bin LV	2016	China	Alzheimer's Research & Therapy	85.8±12.0	46.7	CI	MMSE
study 18	Yan Zou	2014	China	Brain Sciences	> 65	56.6	MCI	MMSE
study 19	Hiroyuki Umegaki	2012	Japan		> 65	57.5	CI	MMSE
study 20	Fahrettin EGE	2011	Turkey	Turkish Journal Of Geriatrics	> 65	37.6	AD	MMSE
study 21	Said Ramdane	2011	Algeria	American Journal of Alzheimer's Disease & Other Dementias	> 60	51.9	AD	NINCDS-ADRDA, DSM-III-TR
study 22	G. Zuliani	2010	Italy	The Journals of Gerontology, Series A®	> 65	60	CI	MMSE
study 23	Chang-Quan Huang	2009	China	Dementia and Geriatric Cognitive Disorders	> 90	67.8	CI	MMSE
study 24	Majon Muller	2007	USA	Lipids in Health and Disease	≥65	67.1	all types of dementia	(DSM)-IV criteria, NINCDS-ADRDA criteria
study 25	George Razay	2007	Australia	Archives of Neurology	> 55	49.6	AD	MMSE

MCI mild cognitive impairment
CI cognitive impairment
VD vascular dementia
AD Alzheimer Disease
MMSE Mini-Mental State Exam
MoCA Montreal Cognitive Assessment
ADAS-Cog Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADNI-MEM Alzheimer's Disease Neuroimaging Initiative-Memory
NINCDS-ADRDA The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
ICD-10 International Classification of Diseases
KDSQ-C Korean Dementia Screening Questionnaire-Cognition
NPI Neuropsychiatric Inventory Scale
ADL Activities of Daily Living
DMS Diagnostic and Statistical Manual of Mental Disorders

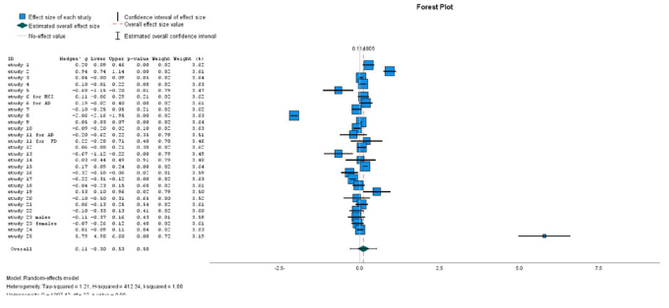

Figure S1: FOREST PLOT OF META-ANALYSIS OF THE INCLUDED STUDIES

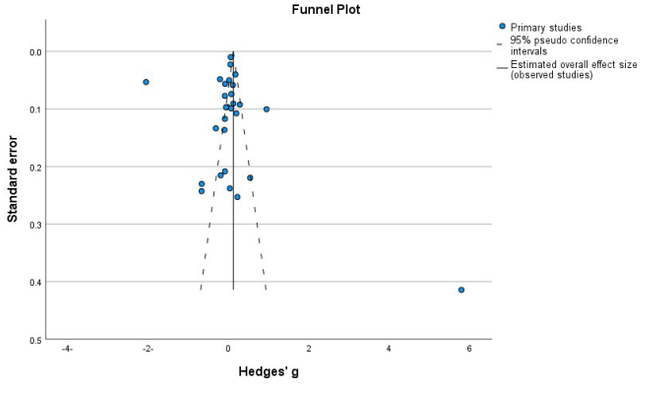

FIGURE S2: FUNNEL PLOT OF META-ANALYSIS OF THE INCLUDED STUDIES

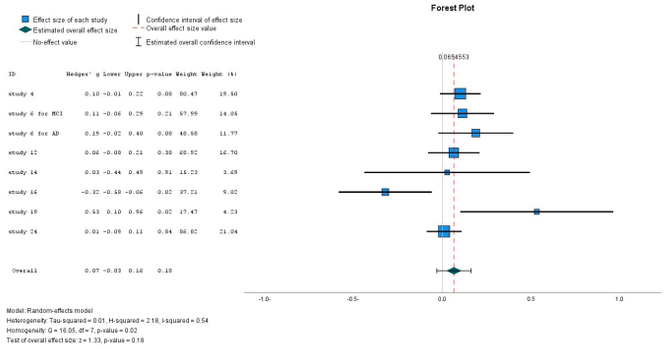

Figure S3: FOREST PLOT OF META-ANALYSIS OF STUDIES SHOWING HIGH TRIGLYCERIDE LEVELS EXCEEDING THE NORMAL LEVEL

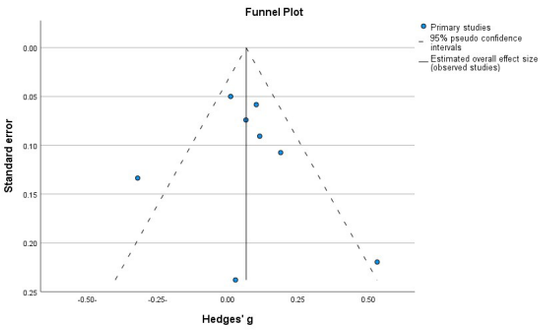

Figure S4: FUNNEL PLOT OF META-ANALYSIS OF STUDIES SHOWING HIGH TRIGLYCERIDE LEVELS EXCEEDING THE NORMAL LEVEL

Discussion

This study aimed to demonstrate triglyceride levels in elderly patients with dementia through twenty-five case-control studies involving 18943 cases and 212144 controls. Eighteen studies (study 1, 2, 3, 5, 7, 8, 9, 10, 11, 13, 15, 17, 18, 20, 21, 22, 23, and 25) showed that the triglyceride levels in both the patients and controls did not exceed the normal range (1.7 mmol/L or 150 mg/dl). Seven studies (study 4, 6, 12, 14, 16, 19, and 24) revealed that triglyceride levels exceeded the normal range, and no significant difference was established between the cases and controls (p-value = 0.18, 95% CI). That goes with findings of trends suggesting that triglyceride levels are decreasing in adults from different categories, including those aged 60 and older, over the years.[6] Additionally, a recent cohort study that included 18294 participants with a median age of 75 years revealed that higher triglyceride levels were associated with a decrease decline in cognition.[5] Moreover, the findings of a large cohort study of 254,575 women and 214,891 men in the UK Biobank assessed that high triglyceride levels were associated with higher dementia risk aged <60 years, but the inverse was observed for those aged ≥60 years.[4] On the other hand, some studies2, 3 support the classical concept that says higher triglyceride levels are associated with dementia.

This study has multiple limitations concerning heterogeneity in the numbers of cases and controls, as the total number of cases in the included studies ranges from 23 to 10732 and the total number of controls ranges from 33 to 167854. Additionally, the percentage of cases compared to controls varied between studies. In some studies, the number was closed, and in others, the number of controls was extremely high in comparison to the number of cases. Furthermore, mean triglyceride levels widely vary. For the dementia group, it ranges from 0.79 to 1.88 with standard deviations ranging from 0.02 to 1.86, and for the control group, it ranges from 1.04 to 1.83 with standard deviations ranging from 0.03 to 1.05. The strength of this study comes from including high-quality and well-designed case-control studies according to the quality assessment by Newcastle-Ottawa for case-control studies and strict application of the defined inclusion criteria.

More studies are needed to better understand the risk factors associated with dementia.

Conclusion

Triglyceride levels may not be a serious factor that should be considered in dementia, which is different in other areas of medicine such as cardiovascular diseases.

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