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Medium Chain Triglycerides induce mild ketosis and may improve cognition in Alzheimer's disease. A systematic review and meta-analysis of human studies

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ABSTRACT

Introduction/aim: The brain in Alzheimer's disease shows glucose hypometabolism but may utilize ketones for energy production. Ketone levels can potentially be boosted through oral intake of Medium Chain Triglycerides (MCTs). The aim of this meta-analysis is to investigate the effect of MCTs on peripheral ketone levels and cognitive performance in patients with mild cognitive impairment and Alzheimer's disease.

Methods: Medline, Scopus and Web of Science were searched for literature up to March 1, 2019. Meta-analyses were performed by implementing continuous random-effects models and outcomes were reported as weighted Mean Differences (MDs) or Standardized Mean Differences (SMDs).

Results: Twelve records (422 participants) were included. Meta-analysis of RCTs showed that, compared with placebo, MCTs elevated beta-hydroxybutyrate [MD = 0.355; 95 % CI (0.286, 0.424), I^2 = 0 %], showed a trend towards cognitive improvement on ADAS-Cog [MD = −0.539; 95% CI (−1.239, −0.161), I^2 = 0 %], and significantly improved cognition on a combined measure (ADAS-Cog with MMSE) [SMD = −0.289; 95 % CI (−0.551, −0.027), I^2 = 0 %].

Conclusions: In this meta-analysis, we demonstrated that MCTs can induce mild ketosis and may improve cognition in patients with mild cognitive impairment and Alzheimer's disease. However, risk of bias of existing studies necessitates future trials.

1. Introduction

Alzheimer's disease (AD) and its prodrome, mild cognitive impairment (MCI), are characterized by brain glucose hypometabolism in brain regions affected by disease pathology (Kapogiannis and Mattson, 2011; Mullins et al., 2018, 2017; Willette et al., 2015). In contrast, the metabolism of the ketone bodies β-hydroxybutyrate (BHB) and acetoacetate, which are physiological alternative fuels that can be readily utilized by brain cells (Drenick et al., 1972; Owen et al., 1967), does not decline with normal aging (Castellano et al., 2019) and even remains normal in the MCI/AD brain (Castellano et al., 2015; Croteau et al., 2018a). Importantly, brain ketone levels are positively correlated with blood ketone levels (Courchesne-Loyer et al., 2017; Croteau et al., 2018b) providing an easily obtained outcome for interventions aiming to boost brain ketone utilization. Therefore, interventions aimed at increasing blood ketone levels should also increase brain ketone levels and thus increase energy bioavailability, potentially compensating for the glucose under-utilization that occurs in the MCI/AD brain (Croteau et al., 2018b; Cunnane et al., 2011, 2016).

The main approaches taken to date to increase ketones in blood and consequently brain, are through fasting (Mattson et al., 2018), exercising (van Praag et al., 2014v) and nutritional modification (Cunnane et al., 2016). Nutritional ketosis can be achieved by (i) ketogenic (low carbohydrate-high fat or low calorie) diets (Cliff et al., 2018; Meckling et al., 2004), (ii) exogenous administration of ketone esters or salts (Hashim and VanItallie, 2014; Stubbs et al., 2018) and (iii) supplementation with medium chain triglycerides (MCTs) (Cliff et al., 2018; Cunnane et al., 2016). MCTs are fatty acids with the unique property of bypassing the peripheral circulation and entering the liver through the portal vein, where they induce rapid ketone production (Bach and Babayan, 1982). Human breast milk is a natural source of MCTs (Andreas et al., 2015), but, in adult life, the major food-derived sources of MCTs are palm kernel oil and coconut oil (Fernando et al., 2015; Takeuchi et al., 2008). MCT supplements are concentrated palm

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kernel and coconut oils and are generally considered safe (Bach and Babayan, 1982; Traul et al., 2000). The present systematic review and meta-analysis aims to investigate the effects of MCT oil or coconut oil (which contains a high concentration of MCTs) on ketosis induction and cognitive function in patients with MCI or AD, by examining all the available clinical evidence in the literature.

2. Methods

For our systematic review and meta-analysis, we adopted the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009).

2.1. Information sources and literature search

Medline, Scopus and Web of Science were searched for literature up to March 1, 2019. The terms "Medium Chain Triglycerides", "MCTs", "coconut", "ketones", "ketosis", "beta-hydroxybutyrate", "Alzheimer's", "Mild Cognitive Impairment" and "dementia" were combined for the identification of relevant studies.

2.2. Study selection

Two reviewers (Drs. Avgerinos and Kapogiannis) independently searched the Electronic Databases for identification of eligible studies published up until 1, March 2019. Disagreements were solved with the help of a third reviewer (Dr. Egan) until consensus was reached. Retrieved records were imported into a reference manager software (Endnote X8, Thomson Reuters). Any irrelevant titles were excluded and after deduplication, the remaining titles and abstracts were screened based on eligibility criteria. After that, we assessed the remaining studies for eligibility by examining their full texts. After exclusion of several studies for specific reasons, we retained the desired studies for our qualitative and quantitative synthesis. An additional literature search was performed just prior to the article's submission (4/25/2019) to identify any recently published articles that may hadn't been identified in the initial search.

2.3. Eligibility criteria

A study was deemed eligible, if it fulfilled the following inclusion criteria: (1) reported findings in humans (2) was published in any language up to March 1, 2019 (enriched by an additional search on 4/25/2019), (3) included patients with MCI and/or AD, (4) participants were given MCT oil or coconut oil at any dose and for any duration, and they were compared or not to participants taking placebo/nothing, and (5) was designed as randomized control trial (RCT), open label trial, single-arm trial, prospective cohort, case-control, cross-sectional, case series or case report study. A study was excluded if it: (i) reported findings in non-humans, (ii) included patients with diagnoses other than MCI and/or AD, (iii) did not involve supplementation with MCTs/coconut oil in sufficient quantities to induce ketosis [for example studies in which ketosis was produced by modifying the primary nutrient content of the diet ("ketogenic diet", i.e. restricting carbohydrates/increasing fats) rather than by providing MCTs/coconut oil in sufficient quantities to induce or contribute to ketosis]; also, studies involving exclusively fasting or calorie restriction or exercising or administration of ketone esters/salts to induce ketosis), (iv) was a Review or a Conference Abstract, and, (v) did not report cognitive outcomes.

2.4. Data collection process and data items

Two reviewers (Drs. Avgerinos and Kapogiannis) collected data independently. Any disagreement was solved with the contribution of a third reviewer (Dr. Egan) until consensus was reached. Extracted data from the eligible studies included the following fields: Title, ID, name of first author and year of study, study design, study duration, number of patients, daily dose and duration of intervention or placebo, levels of beta-hydroxybutyrate (BHB) before and after the treatment/placebo, scores on cognitive scales [Mini Mental State Examination (MMSE), ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale) or other] before and after intervention.

2.5. Quality and Risk of Bias

To our knowledge there is no official tool for the assessment of Risk of Bias (ROB) of single-arm trials (ROBINS-I tool is designed for ROB assessment of non-randomized studies that include a control group) (Sterne et al., 2016). To provide a methodological assessment of included studies without a control group (3 single arm trials, 1 case series and 2 case reports, subsequently referred to as "non-RCT studies" (Farah, 2014; Maynard and Gelblum, 2013; Newport et al., 2015; Ohnuma et al., 2016; Ota et al., 2019; Taylor et al., 2018)), we used the Newcastle Ottawa Scale (NOS), a quality assessment tool for non-randomized trials (Wells, 2019), that was adapted to assess the included non-RCT studies. Notably, the Cochrane Handbook makes a distinction between the assessment of Quality and ROB and favors the latter (see chapter 8.2.2). (Higgins, 2011). It is suggested that a study can be designed according to high standards (good quality) and still be of high ROB in drawing conclusions (Higgins, 2011). To provide a means for assessing results, we wished to provide at least a quality assessment of non-RCT studies to our readers but recommend caution for possible ROB. On the other hand, regarding ROB of RCTs, we used the classical "Cochrane Collaboration's tool for assessing risk of bias in randomized trials" (Higgins et al., 2011). Quality of non-RCTs and ROB of RCTs was assessed by two independent reviewers (Drs. Avgerinos and Kapogiannis). Any disagreement was solved with the contribution of another reviewer (Dr. Egan) until consensus was reached.

The NOS tool originally examines the domains of selection, comparability and outcome for quality and gives ideally four, two and three points respectively for each domain (with maximum score 9/9) (Wells, 2019). For our non-RCT studies which consisted of treatment only group, we didn't take into consideration the "comparability" domain (accounting for 2 points). Also, we didn't take into consideration one of the four parts of the "selection" domain (accounting for 1 point), which also refers to comparison of two groups. Consequently, the ideal scoring of our modified tool would be 6 points (3 for "selection", and 3 for "outcome" domains). A study of good quality would score 2–3 points on each domain. A study of fair quality would score 1 point on one domain but 2 points on the other domain. Finally, a study of poor quality would be a study with 0 point in any of the two domains or 1 point on each of the two domains.

Regarding the ROB tool for RCTs (Higgins et al., 2011), every outcome was evaluated within each study. Possible domains of bias were selection bias, detection bias, attrition bias and reporting bias. If at least one domain of bias was deemed as "high risk", then the whole study was characterized as of high ROB. If at least one domain was of "unclear risk" while the rest domains were "low risk", then the whole study was deemed as unclear ROB. A study was characterized as of low ROB, if all domains were "low risk".

2.6. Synthesis and statistical analysis

For the case series and the case report studies, we provide a qualitative report of the results only. Regarding single arm trials, in addition to qualitative assessment, we performed a weighted pooling of the outcomes of interest in the single group (treatment group). Regarding RCTs, in addition to qualitative assessment, we performed various meta-analyses. The tactic of including any human study relevant to the topic regardless of design, was adopted because we wanted to critically examine the entire existing clinical evidence; thus, in addition to "classical" meta-nalyses of RCTs, we also performed a synthesis of

single-arm trials, as a complementary piece of information, remaining mindful of and cautioning readers to the fact that the synthesis of single arm trials is lower in the level of evidence than that of RCTs.

We performed statistical synthesis for a specific outcome, only if we had relevant data from at least three studies. Our data was continuous, thus we calculated weighted Mean Differences (MDs) or Standardized Mean Differences (SMDs), and implemented the continuous random-effects model (DerSimonian and Laird, 1986). We performed syntheses using results reported for the latest possible timepoint (last outcome assessment) in each study.

Specifically, to assess ketosis induction by MCTs, we calculated and synthesized MDs of peripheral BHB levels. Similarly, for global cognitive assessment, we calculated and synthesized MDs of ADAS-Cog scores. For ADAS-Cog, lower scores are indicative of better cognition; therefore, a negative change in MD would indicate improvement. Furthermore, for additional syntheses of cognitive outcomes that included studies assessing global cognition on a scale different than ADAS-Cog (such as Delayed Recall or MMSE), we converted all cognitive changes to SMDs and combined them for syntheses.

We adopted the < 0.05 two-tailed statistical significance level for all analyses. To assess statistical heterogeneity, we used the resulting I^2 as measurement of the heterogeneity degree (Higgins and Thompson, 2002). Heterogeneity below 75 % was considered acceptable (Higgins and Thompson, 2002). For calculations of MDs/SMDs, statistical syntheses and forest plots' generation we used the OpenMeta[Analyst] statistical software (Wallace et al., 2012).

3. Results

3.1. Literature search results

In the initial literature search (up to 1, March 2019), 1784 titles were identified, after searching in the three databases outlined. Of those, 56 titles were retained for full text assessment and, consequently, 11 articles were included in the systematic review and seven articles in the meta-analysis. In an additional literature search (performed just before the article's submission), we identified one additional eligible article. Collectively, 12 articles were eligible for inclusion into our qualitative synthesis (systematic review). Of those, eight articles were included in the quantitative syntheses (meta-analyses). The full process of study selection and its results are outlined in the flow diagram (Fig. 1).

3.2. Characteristics of included studies

Twelve publication titles (involving 13 studies, which collectively enrolled a total of 422 patients) were deemed eligible for inclusion (Chan et al., 2017; Farah, 2014; Henderson et al., 2009; Maynard and Gelblum, 2013; Fortier, 2019; Newport et al., 2015; Ohnuma et al., 2016; Ota et al., 2019; Rebello et al., 2015; Reger et al., 2004; Taylor et al., 2018; Yang et al., 2015). Of those 13 studies, seven were designed as RCTs, three as single-arm trials and three were case series/case reports. The article by Ota el al reported two separate studies, one RCT and one single-arm trial. Thus, this article contributed both an RCT and a single-arm trial. Table 1 depicts the characteristics of included titles in detail.

3.3. Quality and Risk of Bias

All non-RCTs, were of good quality (4/6 - 6/6); for most studies there was a loss of a point due to inadequate description of the outcome assessment procedures that had been followed (Table 2). Despite being of good quality, there was a high risk of bias in drawing conclusions from the synthesis of those studies, since they did not include comparison groups, a fact that categorizes them as low in the pyramid of evidence level. Regarding RCTs, three studies were deemed of high ROB because they had at least one domain of high ROB. Three studies were of unknown risk due to multiple domains with unclear ROB, while one study was of low ROB (Table 3).

3.4. Ketosis induction and cognitive outcomes

3.4.1. Non-RCTs

Of the non-RCTs, the case series study (Maynard and Gelblum, 2013) and the two case reports (Farah, 2014; Newport et al., 2015) did not assess blood ketone levels after the administration of MCTs. Regarding the case series study, there was an improvement in mean MMSE scores in a 18.8 month-period, but it did not reach statistical significance (Maynard and Gelblum, 2013). However, mean scores were derived only from 23 of all 55 patients due to absence of MMSE score records for 32 participants (Maynard and Gelblum, 2013). Results from caregivers surveys' showed that for most participants, the ability to recall numbers, names and finding objects remained stable during the MCTs administration period (Maynard and Gelblum, 2013). In the two case reports, there were substantial improvements in neuropsychological testing scores (ADAS-Cog, MMSE, Montreal Cognitive Assessment) (Farah, 2014; Newport et al., 2015). For example, *Newport et al* reported an 8 points increase in MMSE after a 2.5 months period (Newport et al., 2015), while *Farah et al* reported a 5 points increase in MMSE after a 3 month period of treatment with MCTs (Farah, 2014).

The three single-arm trials assessed the change of plasma BHB levels in response to MCTs administration. Of those, two studies reported fasting BHB levels at baseline and at various timepoints during treatment (Ota et al., 2019; Taylor et al., 2018), but one study did no clarify if the measurements were fasting or not (Ohnuma et al., 2016). After pooling the mean differences of plasma BHB, we found a significant increase of BHB [MD = 0.108; 95 % CI (0.053, 0.163), I^2 = 62.49 %] in response to MCTs, suggesting that ketosis was induced by the treatment (Fig. 2). However, a combined cognitive measure (ADAS-Cog and Delayed Logical Memory), showed a trend only for improvement in cognitive performance (note that negative values denote improved performance) [SMD = −0.365; 95 % CI (−0.880, 0.149), I^2 = 36.842 %] (Fig. 3).

3.4.2. RCTs

BHB levels of individual RCTs were reported for fasting (before MCTs' administration) and following MCTs' administration on the same day, for the baseline and subsequent visits. In two studies, there was no measurement of BHB levels (Chan et al., 2017; Hu Yang et al., 2015). The rest of the RCTs were combined in a meta-analysis of acute change in BHB levels (levels after minus levels before treatment at the same day). This synthesis showed that, compared with placebo, MCTs increased plasma BHB levels acutely [MD = 0.355; 95 % CI (0.286, 0.424), I^2 = 0 %], suggesting the induction of ketosis (Fig. 4).

Regarding cognitive function, when compared with placebo, MCTs showed a trend towards decreased ADAS-Cog scores (indicating improvement) [MD = −0.539; 95 % CI (−1.239, 0.161), I^2 = 0 %] (Fig. 5A). To pursue this trend further, we conducted an additional meta-analysis, which included an additional study that assessed cognitive performance with the Spanish version of MMSE (Yang et al., 2015). The cognitive performance on this combined measure was expressed as SMD and negative results indicated improvement in cognitive performance. Compared with placebo, MCTs improved cognitive performance on this combined scale [SMD = −0.289; 95 % CI (−0.551, −0.027), I^2 = 0 %] (Fig. 5B). It is important to mention that two studies reported no difference in general cognitive function (measured with MMSE) between the two groups, but the raw MMSE scores were not available and thus those studies were not included in any of the statistical synthesis of cognitive function (Chan et al., 2017; Fortier, 2019). Of note, all performed meta-analyses of RCTs, were highly homogeneous and this was reflected with a statistical measurement of heterogeneity (I^2) equal to 0.

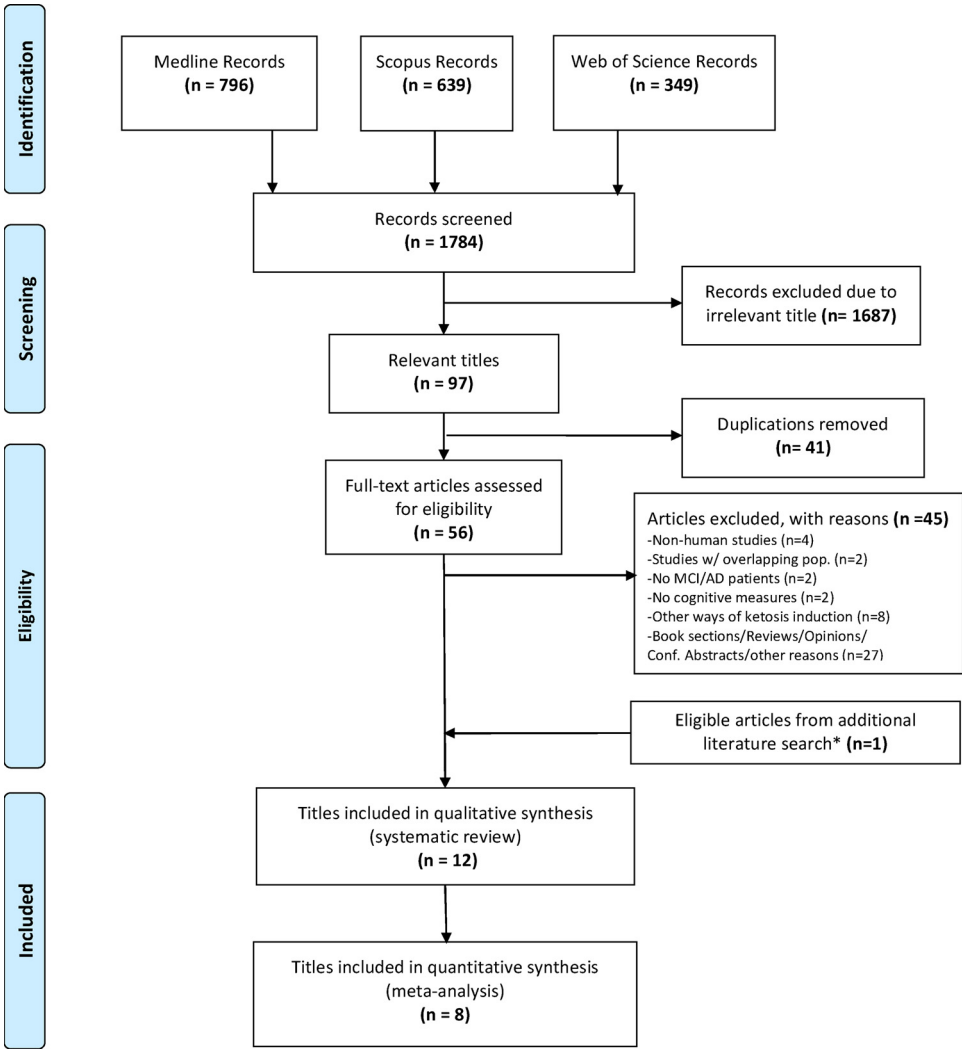

Fig. 1. Flow diagram showing the selection process of eligible studies. One of the included titles (Ota et al) consisted of two studies of different design (one RCT and one single-arm trial). The two studies were handled separately in the meta-analysis (Ota part A and Ota part B). Consequently, we included 13 studies (12 titles) for systematic review and 9 studies (8 titles) for meta-analysis. *The additional literature search was performed on 4/25/19 to incorporate any newly published title after the initial literature search (performed on 3/1/19).

4. Discussion

In the present systematic review and meta-analysis, we investigated the effects of MCTs on peripheral BHB levels and cognitive performance in patients with MCI and AD, by examining all available evidence from human studies. Results from a highly homogeneous meta-analysis of RCTs, indicated that MCTs induced elevation of plasma BHB acutely and thus resulted in a state of ketosis in MCI/AD. In addition, a homogeneous meta-analysis of RCTs based on a combined cognitive measure indicated that MCTs may be able to improve cognitive performance in MCI/AD. On the other hand, pooling of single-arm trials demonstrated an elevation of BHB but failed to show any cognitive improvement. However, single arm trials offer lower level of evidence compared to RCTs; therefore, we base our conclusions and discussion on the former.

Ketones are recognized as being neuroprotective (Maalouf et al., 2009) and their positive effects may extend to various neurological conditions characterized by glutamate receptor-mediated excitotoxicity including AD. In animal studies, dietary ketone supplementation has been shown to increase brain BHB (Pawlosky et al., 2017), increase mitochondrial biogenesis (Srivastava et al., 2012), and improve cognitive-behavioral outcomes and decrease beta-amyloid and tau pathologies in a mouse model of Alzheimer's disease (Kashiwaya et al., 2013). Given the profound abnormalities in glucose metabolism characterizing the AD brain and its preserved ability to utilize ketones, interventions aiming to shift brain metabolism to a state of ketosis have gained attention.

Strict ketogenic diets are effective in inducing ketosis (Hashim and VanItallie, 2014; Meckling et al., 2004), are widely implemented efficacious treatments for epilepsy (D'Andrea Meira et al., 2019; Lutas and Yellen, 2013; Neal et al., 2008; Sariego-Jamardo et al., 2015) and may result in improved cognitive outcomes (Nordli et al., 2001; Pulsifer et al., 2001) in patients with intractable epilepsy, although it is unclear if this effect is due to seizure frequency reduction or due to ketosis per se. On these grounds, ketogenic diets have also been tried in AD. In a clinical study enrolling MCI patients, dietary ketosis was associated with improved verbal memory performance (Krikorian et al., 2012). However, ketogenic diets can be difficult to follow, and there is a concern of causing malnutrition especially for AD patients (Wlodarek, 2019). Other known ways to induce ketosis, such as fasting and exercise, are practical for MCI patients, but may be problematic for AD patients (Suttanon et al., 2013). A novel concept to induce ketosis with administration of a sodium glucose transporter 2 inhibitor (ClinicalTrials.gov Identifier: NCT03852901) is currently being studied by us in healthy elderly individuals, but its effectiveness in AD is as yet unknown.

Table 1
Characteristics of Included studies.

Study	Country	Study Design	Number and type of patients	Diagnostic criteria for inclusion	Study groups	Intervention dose	Duration of intervention	Plasma beta-hydroxybutyrate measurement method	Cognitive measures
Fortier et al. (2019)	Canada	RCT	52 with MCI	Subjective memory complaint, MoCA, MMSE	MCTs (C8:C10 ≈ 3:2) vs Placebo	30gr/d	6 months	colorimetric assay using an automated clinical chemistry analyzer (Dimension XPand Plus, Dade Behring Inc., Newark, DE)	MMSE, MoCA, 16 item free and cued word learning and recall, Trail Making Test, Stroop Test, Verbal Fluency, Digit Symbol Substitution, Boston Naming Test
Ota et al. *part A* (2019)	Japan	RCT	20 with mild/ moderate AD	NINCDS-ADRDA	MCTs (C8:C10 ≈ 3:1) vs Placebo	20gr/d	2 days	enzymatic method at SRL Corp. (Tokyo)	WAIS III, WMS-R, Stroop test, Trail Making Test
Chan et al. (2017)	Malaysia	RCT	41 with mild/ moderate/ severe AD	MMSE	Coconut oil (C8:C10 NR) vs Placebo	60 ml/d*	6 months	NA	MMSE, Clock drawing test
Rebello et al. (2015)	USA	RCT	6 with MCI	National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.	MCTS (C8:C10 ≈ 5:4) vs Placebo	56gr/day	6 months	NR	ADAS-Cog, Trail Making Test Digit Symbol Test
Yang et al. (2015)	Spain	RCT	44 with AD	Institutionalized AD patients (unclear diagnostic criteria)	Coconut oil (C8:C10 ≈ 5:1) vs placebo	40 ml/d	3 weeks	NA	MMSE (Spanish version)
Henderson et al. (2009)	USA	RCT	152 with mild/ moderate AD	NINCDS-ADRDA and DSM-IV criterial	MCTs (C8) vs Placebo	20 gr/d	3 months	method Allied Research International (formerly SFBC) of Miami, FL using the BHB Liquicolordiagnostic kit supplied by Stanbio Laboratories (Boenre, TX)]	MMSE, ADAS-Cog
Reger et al. (2004)	USA	RCT	20 with probable AD or amnestic MCI	NINCDS-ADRDA criteria	MCTs vs (C8) Placebo	40 ml	2 days	enzymatically, using procedure 310-UV (Sigma Diagnostics, Inc.)	MMSE, ADAS-cog, Stroop Test, Paragraph recall
Ota et al. part B* (2019)	Japan	1 arm trial	19 with mild/ moderate AD	NINCDS-ADRDA criteria	MCTs (C8:C10 ≈ 3:1)	20gr/d	3 months	enzymatic method at SRL Corp. (Tokyo)	WAIS III, WMS-R, Stroop test, Trail Making Test
Taylor et al. (2018)	USA	1 arm trial	10 with very mild/ mild/ moderate AD	National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.	MCTs + low carb/high fat diet (C8:C10 ≈ 5:3)	22.5–45 ml/d	3 months	NR	MMSE ADAS-Cog
Ohnuma et al. (2016)	Japan	1 arm trial	20 with moderate/ severe AD	NINCDS-ADRDA	MCTs (C8 = 50 %; C10 % NR)	20gr/d	3 months	ELISA using buffer solution and reaction reagent for total ketone bodies (Kainos Laboratories Inc, Tokyo, Japan). The procedure was performed according to the manufacturer's protocol using the BioMajesty™ system (JCA-BM8000; JEOL, Tokyo, Japan) at SRL Inc (Tokyo, Japan)	MMSE, ADAS-Cog
Maynard and Gelblum (2013)	USA	Case series	55 with probable mild/ moderate AD	MMSE	MCTs (C8)	20 gr/d	18.8 ± 9.2 months	NA	MMSE
Newport et al. (2015)	USA	Case report	Young-onset sporadic AD	Clinical diagnosis, MMSE scores, MRI, Apoe4 carriage	MCTs + coconut oil (4:3 ratio); C8:C9 NR	165 ml/d	2.5 months	Precision Xtra Glucose and Ketone Monitoring System® (Abbott)	MMSE, ADAS-Cog
Farah (2014)	USA	Case report	Probable AD	MMSE, MoCA, FDG PET	MCTs (C8)	20 gr/dl	~ 3 months	NA	MMSE, MoCA

MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MCTs, Medium Chain Triglycerides; WAIS, Wechsler Adult Intelligence Scale; WMS-R, Wechsler Memory Scale-Revised; MMSE, Mini Mental State Examination; ADAS-Cog, Alzheimer's Dis. Assessment Scale-cognitive subscale; MoCA, Montreal Cognitive Assessment Scale. NINCDS-ADRDA, National Institute of Neurological and Communicative Disease and Stroke and the Alzheimer's Disease and Related Disorder Association; NA, Not Applicable; NR, Not Reported; FDG PET, fluorodeoxyglucose (18 F) positron emission tomography; C8, caprylic acid; C10, capric acid.

Table 2
Quality of non-randomized studies.

Study	SELECTION			COMPARABILITY	OUTCOME			
	Representativeness cohort	Exposure ascertainment	Demonstration that outcome wasn't present at start of study	Comparability of cohorts	Outcome assessment	Adequate follow up for outcomes to occur	Adequate cohort follow up	Overall score (judgment)
Ota et al. part B (2019)	1	1	1	N/A	0	1	1	5/6 (Good)
Ohnuma et al. (2016)	1	1	1	N/A	0	1	1	5/6 (Good)
Taylor et al. (2018)	1	1	1	N/A	0	1	1	5/6 (Good)
Maynard and Gelblum (2013)	1	1	1	N/A	1	1	1	6/6 (Good)
Newport et al. (2015)	0	1	1	N/A	0	1	1	4/6 (Good)
Farah (2014)	1	1	1	N/A	0	1	1	5/6 (Good)

N/A, Not applicable; Quality was assessed with Newcastle-Ottawa Quality Assessment Scale.

Table 3
Risk of Bias Assessment of RCTs.

Study	Random sequence generation (Selection Bias)	Allocation concealment (Selection Bias)	Blinding of participants-personnel Bias	Blinding of outcome assessment Bias	Incomplete outcome data (Attrition Bias)	Selective reporting Bias	Other bias	Overall Risk of Bias
Fortier et al. (2019)	Low	?	?	?	High	Low	Low	High
Ota et al. part A, (2019)	?	?	?	?	?	Low	Low	?
Chan et al. (2017)	Low	Low	High	?	High	Low	Low	High
Yang et al. (2015)	?	?	?	?	?	Low	Low	?
Rebello et al. (2015)	Low	Low	Low	Low	Low	Low	Low	Low
Henderson et al. (2009)	High	High	Low	?	High	Low	?	High
Reger et al. (2004)	?	?	?	?	?	Low	Low	?

Low, Low Risk of Bias;?, Unknown Risk of Bias; High, High Risk of Bias; Risk of Bias was assessed with the Cochrane Tool for Risk of Bias.

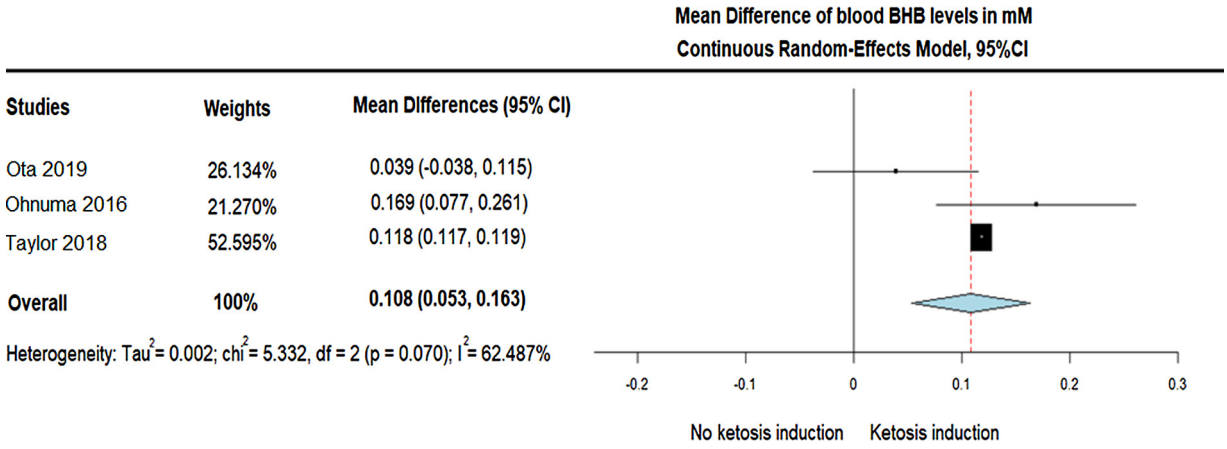

Fig. 2. Forest plot showing ketosis induction (depicted as positive Mean Difference of beta-hydroxybutyrate (BHB) levels in plasma), in response to the administration of Medium Chain Triglycerides (MCTs). Results from pooling of 3 single arm trials (treatment group only) using Continuous Random-Effects Model.

The limitations inherent in the means for endogenous ketone induction has prompted researchers to consider administration of exogenous ketones as a way to exert positive effects in AD. The oral administration of a ketone ester is particularly promising (Kashiwaya et al., 2013; Newport et al., 2015), but its long-term safety and efficacy has not been studied systematically in AD. By far, the most studied exogenous administration approach is supplementation with oral MCTs (Cliff et al., 2018; Cunnane et al., 2016; van Praag et al., 2014v). MCTs' administration is considered safe in general populations (Traul et al., 2000). This was confirmed by the few included (in our meta-analysis) studies that reported side effects (Henderson et al., 2009; Maynard and Gelblum, 2013; Ohnuma et al., 2016; Taylor et al., 2018). Most of the reported treatment-related side effects were of gastrointestinal (GI) nature, such as diarrhea, flatulence and abdominal pain; those occurred in a relatively small proportion of participants, in frequencies that varied from study to study (13.5%–50%) (Henderson et al., 2009; Maynard and Gelblum, 2013; Ohnuma et al., 2016; Taylor et al., 2018). Strategies such as splitting of the total dose into multiple doses might help in controlling the GI side effects. The degree of ketosis induced by MCTs is not as large as with exogenous ketone ester intake (Cliff et al., 2018; Stubbs et al., 2018), but it is comparable to that of ketogenic diets (Cliff et al., 2018; Huttenlocher, 1976) and is greater than ketosis occurring after a 12 -h fasting period (Boden et al., 2005; Cliff et al., 2018).

Our results (both from the pooling of single arm trials and the meta-analyses of RCTs), confirmed that MCTs can induce acute BHB elevation and thus result in a state of peripheral ketosis (Figs. 2 and 4). In the synthesis of single-arm trials, one included study (Taylor et al., 2018) implemented low carbohydrate/high fat (ketogenic) diet in addition to the administration of MCTs; the study was included because MCTs administration covered 24–32 % of energy intake and likely contributed substantially to ketosis. Nevertheless, the combination of studies implementing different interventions is a limitation for this synthesis. Despite using a slightly different intervention, the level of ketosis achieved in this study was very mild (BHB ~ 0.1 mM) and similar to that of the rest of the included studies (see Fig. 2)). Interestingly, RCTs' synthesis (which provide a higher level of evidence) showed a greater level of ketosis induction in comparison to single arm pooling. However, the meta-analysis on BHB, did not include the studies by Chan et al. and Yang et al., because there was no report on this outcome. Specifically, RCTs' meta-analysis showed an absolute 0.36 mM greater increase in BHB blood levels following MCT consumption, compared with placebo. It has been reported that after fasting for 12 – 24 h (corresponding to plasma ketone body concentration of 0.3-0.5 mM), the brain derives 3–5 % of its total energy from ketones (Hashim and VanItallie, 2014). Thus, for the 0.36 mM of BHB elevation that was attributed to the MCTs in our meta-analysis, the brain may receive at least 3–5 % additional energy from ketones (Courchesne-Loyer et al., 2017; Cunnane et al., 2016). This proportion may be even higher in the AD brain given its state of chronic starvation from glucose underutilization (Courchesne-Loyer et al., 2017; Cunnane et al., 2016; Mamelak, 2012) and this additional energy may counterbalance the

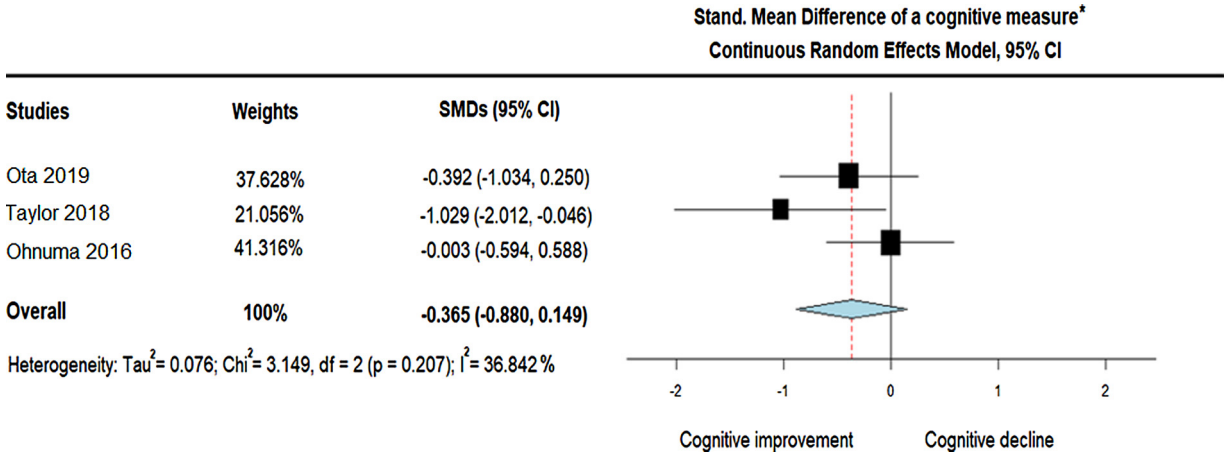

Fig. 3. Forest plot showing performance on a combined cognitive measure (measured as Standardized Mean Difference on (i) Delayed Logical Memory in Ota et al study and (ii) ADAS-Cog in the rest studies), after the administration of Medium Chain Triglycerides (MCTs). Results from pooling cognitive outcomes of 3 single arm trials (treatment group only) by using Continuous Random-Effects Model. Note that negative results indicate cognitive improvement (similarly to ADAS-Cog scores).

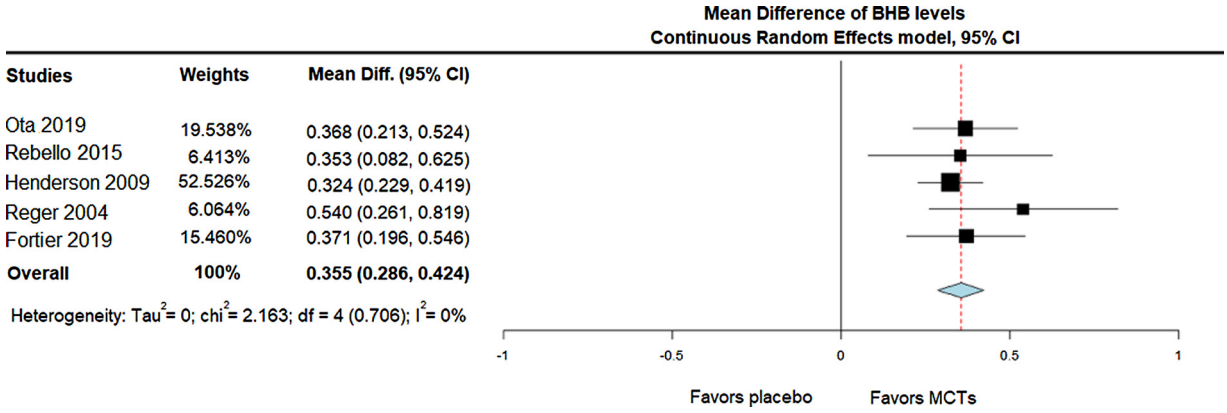

Fig. 4. Forest plot showing ketosis induction (measured as Mean Difference of beta-hydroxybutyrate (BHB) levels in plasma), after administration of Medium Chain Triglycerides (MCTs) or placebo. Results from meta-analysis of 5 Randomized Controlled Trials, using Continuous Random Effects Model.

energy deficit seen in AD due to glucose hypometabolism. Considering that most of the studies included in our meta-analysis implemented a daily MCT dose of 20 g, there may be physiologic room for administration of higher MCT doses, and thus higher levels of peripheral ketosis induction and brain ketone utilization. For example, several human studies have reported MCT administration of 50 g or more resulting in higher peripheral BHB levels (Freemantle et al., 2009; Seaton et al., 1986). Theoretically, a daily dose of 40 – 50 g MCTs could be divided in

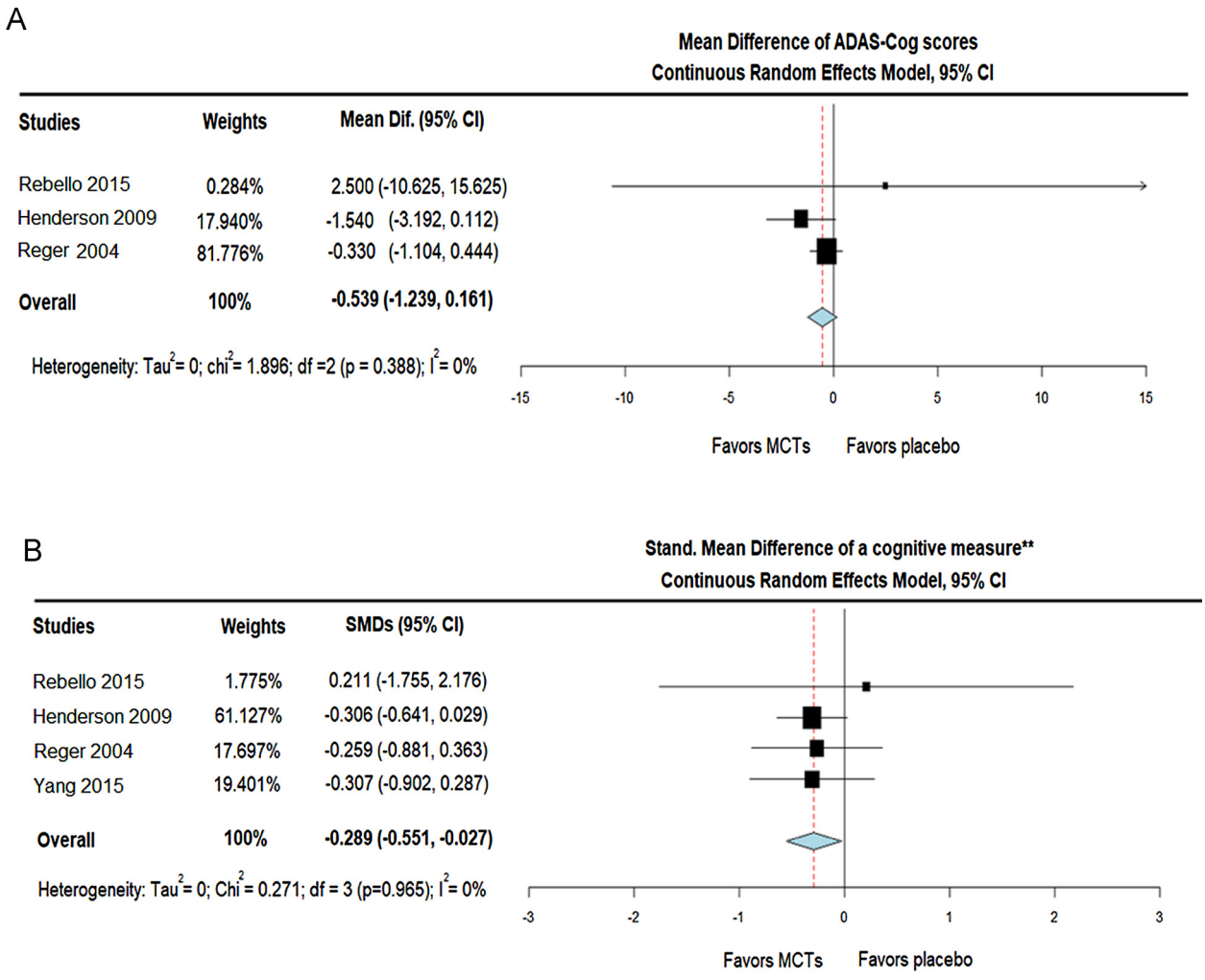

Fig. 5. A. Forest plot showing cognitive performance change (measured as Mean Difference on ADAS-Cog scale) after administration of Medium Chain Triglycerides (MCTs) or placebo. Results from meta-analysis of 3 Randomized Controlled Trials that had originally used the same assessment scale (ADAS-Cog). We used Continuous Random Effects Model. Note that on ADAS-Cog scale, negative changes indicate cognitive improvement. **B.** Forest plot showing cognitive performance (measured with Standardized Mean Difference derived from changes on (i) the Spanish version of MMSE in Yang et al study and (ii) ADAS-Cog for the rest studies). Results from meta-analysis of 4 Randomized Controlled Trials, using Continuous Random-Effects Model. Note that as with ADAS-Cog scale, negative changes here also indicate cognitive improvement.

two or three doses starting in the morning with the highest dose (for example 20 − 25 g of MCTs), so that the resulting BHB increase from MCTs would be additive to the already existing mild ketosis from the overnight fasting. MCTs increase satiety (Bach et al., 1996; Kinsella et al., 2017) and thus individuals could potentially fast for several hours again after their breakfast. Additional doses (for example 10 − 15 g each) of MCTs could be given later in the day adding to the already existing mild ketosis from the short-term fasting.

Regarding cognition, our meta-analysis of RCTs based on the combined cognitive score (combined SMDs from ADAS-Cog and MMSE changes) showed that cognitive performance of MCI/AD patients was significantly increased after MCTs administration, compared with placebo. It is important to notice that three RCTs did not provide data on general cognitive measures, so they couldn't be combined in this meta-analysis. Of those three, Chan et al. and Fortier et al. described no changes in MMSE, despite not providing raw scores or score changes. The negative results of these two studies might be discouraging, but we cannot drive any safe conclusions on what could have been their effects on the combined result. Also, Ota et al. study did not assess general cognition. On the other hand, even though results from pooling single-arm trials showed no significant improvement, single-arm trials do not include a control group, thus the result from pooling them is of lower quality compared to the meta-analysis of RCTs. Therefore, we consider the cognitive results of the meta-analysis of RCTs as the safest basis to drive conclusions. However, one study (Taylor et al., 2018), which involved a ketogenic diet supplemented with administration of MCTs and which was included in the single-arm trials' pooling, showed greater cognitive benefit than the rest of the included studies, which exclusively relied on MCTs supplementation (Fig. 3). Since this study resulted in a similar to other included studies low level of ketosis (Fig. 2), it could be hypothesized that the combination of MCTs with a ketogenic diet by means of restricting carbohydrates/increasing fats could have some additional cognitive benefits, compared to exclusive MCTs' administration. However, as described previously, the use of different interventions when performing quantitative syntheses is a limitation that adds to the uncertainty of drawing conclusions from single-arm trials syntheses.

The mechanisms of action responsible for cognitive improvement are likely to be protean. Evidence from animal studies suggests that in addition to providing an extra source of energy to the brain, ketones are associated with a variety of possible beneficial effects to the neurons, including protection from excitotoxicity (Kashiwaya et al., 2000; Maalouf et al., 2009), improved mitochondrial function (Kashiwaya et al., 2000; Maalouf et al., 2009), increased autophagy (Finn and Dice, 2005), stimulation of brain-derived neurotrophic factor production (Marosi et al., 2016) and activation of pathways associated with decreased inflammation and longevity (Elamin et al., 2017).

Meta-analyses of RCTs with low degree of heterogeneity (I^2) (as in the present meta-analysis) are considered to provide the highest quality of clinical evidence. To our knowledge this study represents the first attempt to systematically investigate the effects of MCTs on ketosis induction and cognitive performance in MCI/AD based on all available RCTs. For sake of comprehensiveness, we wished to examine and present all existing evidence from human studies. Thus, we performed additional pooling of single-arm trials and qualitative presentation of observational studies and case series/case reports. Another strength was that the included studies were conducted in multiple countries (see Table 1), allowing for relative generalizability of our results in terms of race and ethnicity. It is also important that regarding two RCTs included in our syntheses, the duration of MCT treatment was short (1 day for each group) (Ota et al., 2019; Reger et al., 2004) and thus potential chronic benefits of MCTs may not have been shown. Considering the short duration of treatment in some of the included studies we consider the overall results as encouraging. Sensitivity analyses based on the duration of the intervention (acute or chronic MCTs' administration) would be desirable, but this was not possible due to the small number of available studies that were combined in the meta-analyses. As more studies get published, we hope that it may become possible to assess potential effects of C8:C10 composition through a meta-regression. Despite the encouraging results, there were several limitations in our study. First, the number of included studies in each synthesis was relatively small. Second, there were only seven RCTs among all included studies. Of those, three were deemed as unclear for ROB, and three were high for ROB. Furthermore, several studies provided only descriptive report of the outcomes without report of raw scores of measures of general cognition and/or peripheral levels of BHB; thus, they were not included in the statistical synthesis and forests plots. Finally, available data did not allow us to examine whether there is a change-change correlation between BHB levels and cognitive scores, which would have provided further support to the hypothesis.

5. Conclusions

In this systematic review and meta-analysis, we investigated the effects of oral MCTs administration in patients with MCI/AD. Highly homogeneous meta-analyses of RCTs found that MCTs result in mildly elevated peripheral BHB levels and improved cognitive performance in a combined cognitive measure. This action may have been mediated by the increased availability of ketone bodies to the hypometabolic brain of MCI/AD that is unable to utilize glucose. MCTs can be easily administered without the need for following onerous instructions, such as with ketogenic diets, fasting or exercise. Despite the encouraging results, the relatively small sample size of our synthesis and the potential bias of several included studies necessitate a relatively cautious interpretation of the results. Future high-quality RCTs of increased duration of treatment could add to the existing evidence on MCTs as a promising intervention for MCI/AD.

Declaration of Competing Interest

None.

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