

6-2014

Saturated and trans fats and dementia: A systematic review

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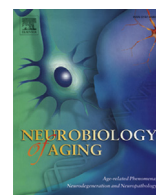
Barnard, N.D., Bunner, A.E., Agarwal, U. (2014). Saturated and trans fats and dementia: A systematic review. *Neurobiology of Aging*.

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Contents lists available at ScienceDirect

Neurobiology of Aging

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ARTICLE INFO

Article history:

Received 24 October 2013

Accepted 27 February 2014

Keywords:

Dementia
Alzheimer's disease
Nutrition
Fatty acids
Saturated fat
Trans fatty acids

ABSTRACT

Cognitive disorders of later life are potentially devastating. To estimate the relationship between saturated and trans fat intake and risk of cognitive disorders. PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for studies reporting saturated or trans fat intake and incident dementia, Alzheimer's disease (AD), or mild cognitive impairment (MCI) or cognitive decline. Only observational studies met the inclusion criteria: 4 for AD or other dementias, 4 for MCI, and 4 for cognitive decline. Saturated fat intake was positively associated with AD risk in 3 of 4 studies, whereas the fourth suggested an inverse relationship. Saturated fat intake was also positively associated with total dementia in 1 of 2 studies, with MCI in 1 of 4 studies, and with cognitive decline in 2 of 4 studies. Relationships between trans fat intake and dementia were examined in 3 reports with mixed results. Several, although not all, prospective studies indicate relationships between saturated and trans fat intake and risk of cognitive disorders.

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1. Introduction

Dementia is a devastating condition, and means of prevention are urgently needed. Its most common form, Alzheimer's disease (AD), affected an estimated 4.7 million Americans aged 65 years and older in 2010, a figure expected to reach 13.8 million by 2050 (Hebert et al., 2013).

Several studies have identified an association between saturated or trans fat intake and risk of dementia, including AD (Laitinen et al., 2006; Luchsinger et al., 2002; Morris et al., 2003). The Chicago Health and Aging Project, which studied a group of 815 individuals aged 65 years and older at baseline, identified positive associations between saturated and trans fat intake and risk of developing AD (Morris et al., 2003). Studies in New York and Finland also showed increased dementia risk with increased saturated fat intake (Laitinen et al., 2006; Luchsinger et al., 2002). However, a report from the Rotterdam Study showing increased dementia risk with increasing saturated fat intake after 2.1 years of follow-up (Kalmijn et al., 1997) was contradicted by a report from the same cohort after 6 years of follow-up (Engelhart et al., 2002a).

Studies have also investigated dietary factors related to risk of mild cognitive impairment (MCI), a condition that has been codified relatively recently (Petersen, 2011; Petersen et al., 1999) and which, for some people, may be preliminary to AD. In a Finnish study, saturated fat intake was associated with increased risk (Eskelinen et al., 2008), whereas studies in Italy (Solfrizzi et al., 2006a), Australia (Cherbuin and Anstey, 2012), and the United States (US) (Roberts et al., 2012) showed no such association.

We therefore undertook a systematic review to identify the strength of associations between saturated or trans fat intake and the risk of AD and other forms of dementia, MCI, and cognitive decline. We hypothesized that evidence from prospective studies would indicate that higher intake of saturated or trans fat is associated with increased risk of dementia, AD, and MCI, and with a greater degree of cognitive decline in later life. This review was registered on PROSPERO (registration number CRD42012003270) on November 12, 2012.

2. Methods

We searched the published scientific literature for prospective cohort studies and randomized controlled trials of adult human subjects reporting saturated fat or trans fat intake and the end-points of incident dementia, AD, or mild cognitive impairment; or decline in cognitive function in later life, using disease incidence or cognitive change in reference populations differing in intake of these fats as the primary comparator.

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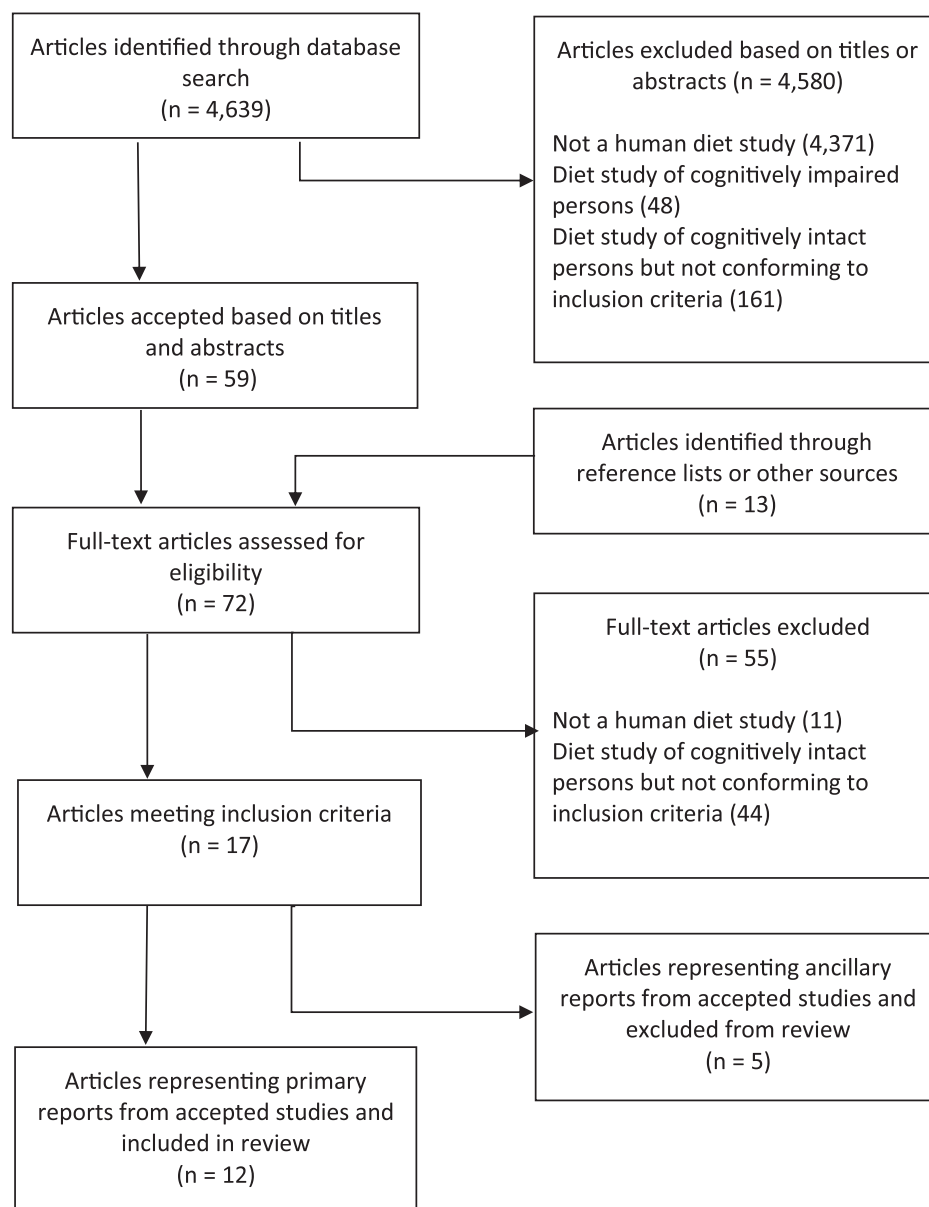


Fig. 1. Study-flow diagram showing the number of studies assessed for eligibility and included in the review.

2.1. Search strategy and article selection

Articles were identified by searches of PubMed (1946 through July 16, 2012), EMBASE (1947 through July 17, 2012), and the Cochrane Central Register of Controlled Trials (1966 through July 19, 2012). For inclusion in the systematic review, articles had to meet the following criteria: exposure to saturated or trans fats was quantified (at any adult age); endpoints included incident dementia, AD, or MCI; or cognitive decline; the outcome was identified in older age (as opposed to early dementia occurring in cases of Down syndrome, e.g.); in prospective studies, an interval of at least 1 year occurred between dietary assessment and determination of cognitive outcome (dementia, AD, MCI) or in studies assessing cognitive decline, between 2 or more assessments of cognitive status. There were no restrictions regarding the gender, race, or ethnicity of participants or on language, sample size, publication status, or publication date. Case reports, case series, case-control studies, and studies limited to individuals with medical

conditions (e.g., dyslipidemia, cardiovascular disease) likely to influence cognitive status and intervention trials including non-dietary methods (e.g., exercise) were excluded because of the potential for bias or confounding in their study designs.

The following syntax was used for the PubMed search: (“fatty acids”[MeSH Term] OR fatty acids[Text Word] OR fat[Text Word] OR saturated fat[Text Word] OR partially hydrogenated[Text Word] OR “trans fatty acids”[MeSH Term] OR trans fat[Text Word]) AND (“alzheimer disease”[MeSH Term] OR Alzheimer’s disease[Text Word] OR dementia[MeSH Term] OR dementia[Text Word] OR cognitive decline[Text Word] OR cognitive change[Text Word] OR cognitive function[Text Word] OR cognitive impairment[Text Word]) AND (“humans”[MeSH Term]). Analogous search terms were used to search EMBASE and the Cochrane Central Register of Controlled Trials.

Two researchers (Neal D. Barnard and Anne E. Bunner) independently reviewed the titles and abstracts of the citations produced by the search. For citations appearing to meet the inclusion

Table 1
Summary of prospective studies on saturated and trans fat intake and incident Alzheimer's disease and other forms of dementia

Study, N	Baseline age, gender, race, APOE status	Duration, mean (y)	Saturated fat and trans fat intake	Dementia cases	Results and conclusions
Rotterdam study, the Netherlands (Engelhart et al. 2002a), N = 5395	Mean 67.7 y, 59% women, race not reported, APOE not reported. Primary education 35%	6	Mean, 34.4 g/d (SD, 7.2) Mean trans fat: 2.7 g/d (SD, 1.0)	Total: 197 AD: 146 Vascular: 29 Others: 22	Rate ratios per SD increase in intake (95% CI) For total dementia: SFA: 0.91 (0.79–1.05) Trans fat: 0.90 (0.77–1.06) For Alzheimer's disease: SFA: 0.83 (0.70–0.98) Trans fat: 0.80 (0.65–0.97) For vascular dementia: SFA: 1.03 (0.73–1.46) Trans fat: 1.01 (0.71–1.44) HR for AD for SFA quartile 1 versus 4: 1.3 (95% CI, 0.9–1.9); $p = 0.08$ for trend. Association between total fat and AD risk was significant only in those with APOE $\epsilon 4$. This relationship was not reported for SFA.
Washington Heights–Inwood Columbia Aging Project New York, USA (WHICAP) (Luchsinger et al., 2002) N = 980	Mean 75.3 y, 67% women, 25% nonHispanic white, 32% nonHispanic black, 43% Hispanic, 28% APOE $\epsilon 4$. Mean of education 9 y	4	SFA quartiles not reported. Mean total fat intake 38 g/d	AD: 242	Relative risk of AD for Q1 versus Q5 (95% CI in parenthesis): SFA: 2.2 (1.1–4.7) ^a ; $p = 0.09$ for trend. Trans fat: 2.5 (1.0–6.2) ^a ; $p = 0.21$ for trend. APOE status did not influence results.
Chicago Health and Aging Project (CHAP) Chicago, USA (Morris et al., 2003) N = 815	Mean 73.1 y, 61% women, 52% black, 35% APOE $\epsilon 4$. Mean of education 12.6 y	3.9	SFA quintiles, median: Q1: 13 g/d Q5: 26 g/d Trans fat quintiles, median: Q1: 1.8 g/d Q5: 4.8 g/d	AD: 131	For dementia: OR for SFA Q1 versus Q4: 2.74 (0.65–11.56). For AD: OR for SFA Q1 versus Q4: 2.34 (0.51–10.74). SFA intake was associated with increased dementia risk mainly in APOE $\epsilon 4$ carriers.
Cardiovascular risk factors, Aging and Dementia (CAIDE) study, Finland (Laitinen et al., 2006) N = 1449	Mean 50.4 y, 62% women, race not reported, 35% APOE $\epsilon 4$. Mean education 8.6 y	21	Quartiles of SFA from spreads: Q1: ≤ 4.1 g/d Q4: > 15.8 g/d Spreads and milk products contributed approximately half the fat in the diet.	Total: 117 AD: 76	

For studies with comparisons at multiple levels of statistical control, figures listed are for models with the highest levels of control.

Key: AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; OR, odds ratio; Q1, lowest intake quartile or quintile; Q4, highest intake quartile; Q5, highest intake quintile; SD, standard deviation; SFA, saturated fat.

^a Data from Model 2, multivariable analysis.

criteria, the same researchers independently reviewed full-text articles to identify eligible studies. Disagreements were resolved by consensus. From the reference lists of reviewed articles and through contacts with research experts, additional articles were identified and reviewed for eligibility, and, when possible, authors of the identified articles were contacted for additional information.

2.2. Data extraction

Two investigators (Neal D. Barnard and Anne E. Bunner) independently extracted data from the selected studies, using a data-extraction table, which was piloted using 10 references and revised accordingly. The extracted data included study location, participant numbers, demographics, APOE status, study dates and duration, diet assessment method, baseline diet characteristics, cognitive outcomes and assessment methods, and relative risk of cognitive outcomes or degree of cognitive change related to dietary exposure. Differences were settled by consensus.

2.3. Outcome measures

The principal outcomes of interest were incident dementia, AD, or MCI or cognitive decline, using comparison population groups that differed in intake of saturated or trans fats or, for controlled trials, untreated control groups, if available.

2.4. Quality measures

Study reports were examined for means of dietary assessment, diagnosis and cognitive assessment, sample size, baseline dietary variability, attrition, and statistical measures.

3. Results of search

The PubMed search yielded 1772 citations, the EMBASE search yielded 3794 citations, and the Cochrane Central Register of Controlled Trials search yielded 47 citations. After removal of duplicates, 4639 citations remained. An additional 13 articles were identified from reference lists and research experts. The disposition of these articles is described in Fig. 1.

The articles meeting the inclusion criteria represented the following: AD and other forms of dementia were the subjects of 4 prospective studies, which took place in Finland, the Netherlands, and the US, of which one produced reports at 2 time points (Engelhart et al., 2002a; Kalmijn et al., 1997; Laitinen et al., 2006; Luchsinger et al., 2002; Morris et al., 2003). MCI was the subject of 4 prospective studies taking place in Australia, Finland, Italy, and the US (Cherbuin and Anstey, 2012; Eskelinen et al., 2008; Roberts et al., 2012; Solfrizzi et al., 2006a). Cognitive decline was the subject of 4 prospective studies, which took place in Italy and the US (Morris et al., 2004; Naqvi et al., 2011; Okereke et al.,

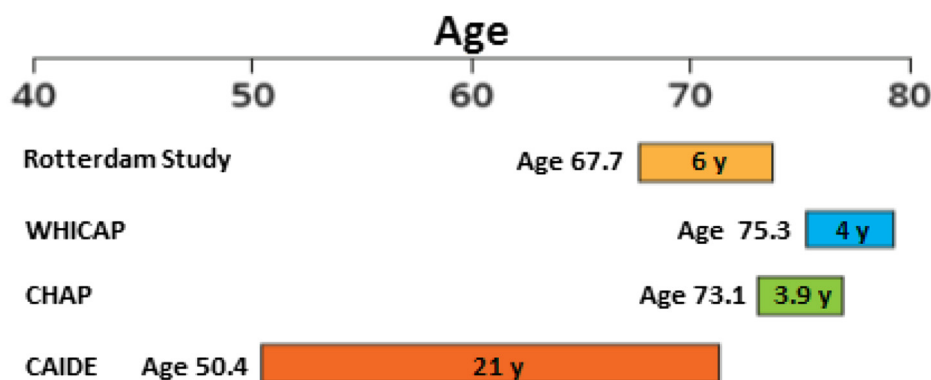


Fig. 2. Baseline age of participants and duration of prospective studies of diet and incident Alzheimer's disease.

2012; Solfrizzi et al., 2006b). These studies are described in the following and in Tables 1–3. We identified no clinical trials that met the inclusion criteria.

3.1. AD and other forms of dementia

The Rotterdam Study included 5395 residents of the Netherlands aged ≥ 55 years (mean baseline age 67.7 years). Prevalence of the APOE $\epsilon 4$ allele was not reported. In an initial report after a 2.1-year follow-up period, 58 cases of dementia were identified, including 37 cases of AD with no vascular component, 12 cases of vascular dementia, and 9 cases of dementia of other types (Kalmijn et al., 1997). Total dementia, vascular dementia, and AD were each positively related to saturated fat intake, but the trend reached statistical significance only for vascular dementia. A second Rotterdam Study report after 6 years of observation identified 197 cases of dementia, including 146 with AD, 29 with vascular dementia, and 22 with other types (Engelhart et al., 2002a). In contrast to the earlier report, total dementia risk and vascular dementia risk were not related to saturated or trans fat intake, although AD risk was negatively associated with saturated and trans fat intake (Table 1, Fig. 2).

The Washington Heights–Inwood Columbia Aging Project (WHICAP) included 980 New Yorkers aged ≥ 65 years, of whom 28% carried the APOE $\epsilon 4$ allele (Luchsinger et al., 2002). After 4 years of follow-up, 242 cases of AD were identified. Alzheimer's risk was positively, but nonsignificantly, associated with saturated fat intake. A subanalysis based on genetic type showed the relationships between energy intake or total fat intake and Alzheimer's risk were primarily found in those with the APOE $\epsilon 4$ allele. This subanalysis was not done for saturated fat intake.

The Chicago Health and Aging Project (CHAP) reported on a stratified sample of 815 individuals in Chicago, IL, aged 65–94 years (mean 73.1 years), of whom 35% carried the APOE $\epsilon 4$ allele (Morris et al., 2003). After 3.9 years of observation, 131 Alzheimer's cases were identified. Intake levels of both saturated and trans fat were positively and significantly associated with Alzheimer's risk.

The Cardiovascular risk factors, Aging and Dementia (CAIDE) study included 1449 individuals in Finland with a mean baseline age of 50.4 years, of whom 35% carried the APOE $\epsilon 4$ allele (Laitinen et al., 2006). After a follow-up of 21 years, 117 cases of dementia were identified, including 76 with AD. Moderate saturated fat intake was positively and significantly associated with both total dementia and AD, but the association did not reach statistical significance for the highest saturated fat intake group. In a subanalysis based on APOE status, elevated risk of AD or dementia related to saturated fat intake appears to have been

mainly evident in APOE $\epsilon 4$ carriers; among carriers with moderate (second quartile) saturated fat intake, the odds ratio for incident dementia was 3.16 (95% confidence interval [CI], 1.12–8.91).

3.2. Mild cognitive impairment

The CAIDE study, in its 2008 report, reported findings from 1341 participants with a mean baseline age of 50.2 years (standard deviation, 6.0) (Eskelinen et al., 2008). After a mean follow-up of 21 years, 82 cases of MCI, defined by the Mayo Clinic Alzheimer's Disease Research Center criteria (Smith et al., 1996), were identified. Saturated fat intake was positively and significantly associated with MCI risk, particularly among women. A subanalysis showed that the association between saturated fat intake and MCI was limited to participants with the APOE $\epsilon 4$ allele (odds ratio = 5.06, 95% CI, 1.35–18.94).

The Italian Longitudinal Study on Aging (ILSA) included 278 participants with a mean baseline age of 73 years (Solfrizzi et al., 2006a). After a mean follow-up of 2.6 years, and using an MCI definition slightly modified from Petersen et al. (1999) in which subjective memory impairment was not required and noncognitive disabilities and comorbid illnesses were allowed, 18 cases of MCI were identified. Saturated fat intake was not associated with MCI risk and APOE status was not reported.

The Personality and Total Health (PATH) Through Life Study included 1528 residents of Australia with a mean baseline age of 62.5 years (Cherbuin and Anstey, 2012). After a 4-year follow-up, 10 cases of MCI, diagnosed using the criteria of Jack et al. (1999) were identified. Saturated fat intake was not associated with MCI risk. APOE $\epsilon 4$ status was controlled for in analyses, but data for APOE $\epsilon 4$ carriers were not reported separately.

The Rochester Epidemiology Project included 937 Minnesota residents with a median baseline age of 79.5 years (Roberts et al., 2012). After a median follow-up of 3.7 years, 200 cases of incident MCI based on criteria from Petersen (2004) or dementia (192 MCI, 8 dementia) were identified. Higher saturated fat intake was associated with reduced risk of MCI, which was no longer significant after further adjustment for potential confounders, including APOE status (Table 2). Higher trans fat intake was associated with nonsignificantly reduced MCI risk.

3.3. Cognitive decline

The CHAP study, in its 2004 report, included findings from 2560 individuals with a mean baseline age of 74 years (Morris et al., 2004). Cognitive function was described with a composite of 4 cognitive tests. Over a 6-year period, a high saturated fat intake

Table 2
Summary of prospective studies on saturated and trans fat intake and incident mild cognitive impairment

Study, N	Baseline age, gender, race, APOE status	Duration (y)	Saturated fat intake	MCI cases	Results and conclusions
Cardiovascular risk factors, Aging and Dementia (CAIDE) study, Finland (Eskelinen et al., 2008) N = 1341	Mean 50.2 y, 62% women, race not reported, APOE not reported. Mean education of 8.7 y	Mean, 21	SFA from milk products and spreads. Low: <21.6 g/d High: >21.6 g/d	82	OR for MCI (95% CI) All participants High SFA: 2.36 (1.17–4.74) Among women High SFA: 3.20 (1.13–9.06) Among people with APOE ε4 allele. High SFA: 5.06 (1.35–18.94) HR (95% CI) for MCI for Q1 versus Q4: 0.86 (0.21–3.49); p = 0.85 for trend.
Italian Longitudinal Study on Aging Italy (Solfrizzi et al., 2006a), N = 278	Mean 73.0 y, 45% women, race not reported, APOE not reported. Mean education 4 y	Median, 2.6	Median SFA: 19.24 g/d SFA quartiles: Q1: ≤15.5 g/d Q4: ≥24.3 g/d	18	
PATH Through Life Study, Australia (Cherbuin and Anstey, 2012), N = 1528	Mean 62.5 y, 51% women, 97.5% white, race not reported, APOE not reported. Mean education of 14.1 y	4	Baseline dietary intake not specified.	10	OR (95% CI) for MCI per SD of SFA intake: 1.15 (0.45–2.94); p = 0.772. APOE status was controlled for in analyses.
Rochester Epidemiology Project, Minnesota, USA (Roberts et al., 2012), N = 937	Median 79.5 y, 49% women, race not reported, 21.5% APOE ε4. Mean education of 14.1 y	Median, 3.7	Mean SFA, 10.5 en% SFA quartiles: Q1: <8.4 g/d Q4: >12 g/d Trans fat quartiles: Q1: <0.23 g/d Q4: >0.57 g/d	192 ^a	HR (95% CI) for MCI for SFA Q1 versus Q4: 0.64 (0.39–1.05); p = 0.25 for trend. HR (95% CI) for MCI, for trans fat Q1 versus Q4: 0.82 (0.52–1.30); p = 0.84 for trend. Adjusted for APOE in statistical models.

For studies with comparisons at multiple levels of statistical control, figures listed are for models with the highest levels of control.

Key: 95% CI, 95% confidence interval; en%, percent of total energy intake; HR, hazard ratio; MCI, mild cognitive impairment; OR, odds ratio; Q1, lowest intake quartile; Q4, highest intake quartile; SFA, saturated fat.

^a In addition to 192 incident MCI cases, dementia was identified in 8 participants; these participants were included in the remaining analyses.

compared with a low intake was associated with a greater reduction in cognitive function. APOE status was not measured and thus not available for analyses (Table 3).

The Cognitive Change in Women study included 482 participants with a mean baseline age of 71 years who were tested for memory, vision, executive function, language, and attention (Naqvi et al., 2011). Over a 3-year interval, saturated fat intake and trans fat intake were not associated with cognitive decline. APOE status was included in the statistical analysis, but did not show an effect on the relationship between saturated fat intake and cognitive change.

The Italian Longitudinal Study on Aging (ILSA study), in its 2006 report on diet and cognitive decline included 278 individuals with a mean baseline age of 73 years (Solfrizzi et al., 2006b). Cognitive function was evaluated using the Mini-Mental Status Examination. After an interval of 8.5 years, saturated fat intake was not associated with cognitive change and APOE status was not reported.

The Women's Health Study included 6183 participants with an average baseline age of 72 years (Okereke et al., 2012). Cognitive function was assessed in telephone interviews testing general cognition, verbal memory, and semantic fluency. Over a 4-year period, higher saturated fat intake was associated with worse trajectory in global cognitive function and verbal memory. However, APOE status was not reported.

In summary, saturated fat intake was positively associated with AD risk in 3 of 4 cohort studies (Laitinen et al., 2006; Luchsinger et al., 2002; Morris et al., 2003), whereas the fourth suggested an inverse relationship (Engelhart et al., 2002a). Saturated fat intake was also positively associated with total dementia in 1 (Laitinen et al., 2006) of 2 studies, with MCI in 1 (Eskelinen et al., 2008) of 4 studies, and with cognitive decline in 2 (Morris et al., 2004; Okereke et al., 2012) of 4 studies. Relationships between trans fat intake and AD were examined in only 2 reports with mixed results (Engelhart et al., 2002a; Morris et al., 2003), and the relationship between trans fat intake and total dementia was described in only one study with a nonsignificantly negative finding (Engelhart et al., 2002a).

3.4. Study quality

Studies of AD and other dementia types varied in size and duration of follow-up. Cohort sizes ranged from 815 to 5395, and follow-up periods varied from 2.1 to 21 years. All studies assessed dietary intake by food frequency questionnaires, except for the CAIDE study, which used a 20-item dietary questionnaire limited to questions about dairy products and spreads (Laitinen et al., 2006). Diagnosis of dementia was made based on individual examinations; the Rotterdam study also used medical records when participants were unavailable or deceased. For diagnosis of AD, all studies used the same established criteria (McKhann et al., 1984).

In studies of MCI, cohort sizes ranged in size from 278 to 1528. All studies assessed dietary intake using food frequency questionnaires, except for the CAIDE study, which as noted previously, used a 20-item dietary questionnaire limited to questions about dairy products and spreads (Laitinen et al., 2006). In all studies, MCI diagnosis was done by clinical examination, using criteria developed by Petersen (2004) or modifications of them (Smith et al., 1996).

Studies of cognitive decline were less uniform. Study sizes ranged from 278 to 6183, with observation periods ranging from 3 to 8.5 years. Methods for assessing of cognition varied from study to study.

Because the means for reporting the relationships between dietary intake and cognitive endpoints varied substantially between studies, a meta-analysis was not possible.

4. Discussion

Several studies report relationships between saturated and trans fat intake and cognitive disorders. However, the divergence in findings between the various studies merits examination. All 4 cohort studies investigating relationships between diet and

Table 3
Summary of prospective studies on saturated and trans fat intake and cognitive decline

Study, N	Baseline age, gender, race, APOE status	Duration (y)	Saturated fat and trans fat intake	Cognitive tests	Results
Chicago Health and Aging Project (CHAP), USA (Morris et al., 2004), N = 2560	Mean 74.0 y, 63.9% women, 58% black, APOE status was not included in this report. Mean education of 12.4 y	Median, 5.6	Mean SFA: 18.1 g/d SFA quintiles: Q1: <12.2 g/d Q5: >24.3 g/d Trans fat quintiles: Q1: <2.1 g/d Q5: >4.9 g/d	Composite of 4 tests: East Boston Tests of Immediate and Delayed Recall MMSE Symbol Digit Modalities Test	SFA: SFA Q1 versus Q5 associated with a difference in rate of cognitive change of -0.023 SU/y; $p = 0.06$ for difference; $p = 0.04$ for trend. Trans fats: Q1 versus Q5: -0.020 ; $p = 0.07$ for difference; $p = 0.07$ for trend. Change in cognitive function score by intake quartiles. SFA: Q1: -0.20 (SE, 0.05) Q4: -0.13 (SE, 0.04) $p = 0.69$ Trans fats: Q1: -0.17 (SE, 0.04) Q4: -0.17 (SE, 0.04) $p = 0.54$ APOE status did not influence the relationship between saturated fat intake and cognitive change.
Cognitive Change in Women, USA Naqvi et al. (2011) N = 482	Mean 70.9 y, 100% women, 87% white, APOE details not reported. Education (%): Less than or equal to high school, 20% Some college, 24% Greater than or equal to college degree, 56%	Mean, 2.9	SFA median, 11.1 en% SFA quartiles: Q1: ≤ 9.12 g/d Q4: ≥ 13.01 g/d Trans fat quartiles: Q1: ≤ 1.45 g/d Q4: ≥ 2.65 g/d	Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list learning, constructions, and word fluency tests; Wechsler Memory Scale-Revised Logical Memory, Visual Reproduction, and Digit Span tests; Boston Naming Test; F-A-S Word Fluency and Judgment of Line Orientation tests; Visual Target Cancellation Test; Trail Making Test Part A and B; Visual-Verbal test Baseline scores were standardized to zero mean and unit SD (Z-scores). Mini-Mental Status Examination	Estimated change in cognitive function (β and 95% CI) per SD intake per 4 y increment: -0.001 (-0.003 to 0.001) (lower scores indicate better function) SFA Q5 versus Q1 had a mean 4 y difference in global cognitive change of -0.12 (-0.20 to -0.03) and in verbal memory of -0.13 (-0.23 to -0.03). OR (95%CI) of worst (lowest 10%) cognitive change over 4 y. SFA Q5 versus Q1: Global: 1.64 (1.04 – 2.58); $p = 0.02$ for trend. Verbal: 1.65 (1.04 – 2.61); $p = 0.02$ for trend. Trans fat Q5 versus Q1 had a mean 4 y difference in global cognitive change of 0.02 (-0.05 to 0.09) and in verbal memory of 0.04 (-0.05 to 0.12). OR (95%CI) of worst (lowest 10%) cognitive change over 4 y. Trans fat Q5 versus Q1: Global: 0.76 (0.52 – 1.11); $p = 0.49$ for trend Verbal: 0.72 (0.49 – 1.06); $p = 0.32$ for trend
Italian Longitudinal Study on Aging, Italy (Solfrizzi et al., 2006b), N = 278	Mean 73.0 y, 45% women, race not reported, APOE not reported. Mean education of 4 y	Median, 8.5	Mean, 20.8 g/d (SD, 7.8)		
Women's Health Study, USA Okereke et al. (2012), N = 6183	Mean of 71.9 y, 100% women, 94%–97% white, APOE not reported. Education: 34% college degree	4	SFA: median, 9.8 en% SFA quintiles: Q1: median, 7.0 en% Q5: median, 13.1 en% Trans fat: median, 1.04 en% Trans fat quintiles: Q1: median, 0.55 en% Q5: median, 1.84 en%	(1) Telephone Interview for Cognitive Status (TICS); (2) immediate trials of the East Boston Memory Test (EBMT); (3) delayed recall trials of the EBMT; (4) delayed recall trial of the TICS 10-word list; and (5) category fluency Testing done by telephone.	

For studies with comparisons at multiple levels of statistical control, figures listed are for models with the highest levels of control.

Key: 95% CI, 95% confidence interval; en%, percent of total energy intake; OR, odds ratio; Q1, lowest intake quartile or quintile; Q4, highest intake quartile; Q5, highest intake quintile; SD, standard deviation; SE, standard error; SFA, saturated fat; SU, standard unit.

Alzheimer's risk used similar study designs and the same diagnostic criteria. The following factors may have been contributors to the observed heterogeneity.

Age and duration of observation: at the end of the observation period, the Rotterdam Study participants were younger (mean age 73.7 years) compared with 79.3 years for WHICAP and 77.0 years for CHAP. CAIDE participants were also relatively young (71.3 years). However, the CAIDE study included a long (21 years) observation period, which would have been expected to capture a larger number of cases.

Race: the racial composition of the cohorts varied; 32% of WHICAP participants and 52% of CHAP participants were black. Race was not described in either the Rotterdam Study or CAIDE, but presumably these northern European cohorts were largely white. In CHAP, the association between saturated fat intake and AD risk was found primarily in black participants (Morris et al., 2003). If the association between saturated fat intake and AD risk is less robust in white participants, this could help explain the lower case-finding in the Rotterdam Study and CAIDE.

APOE status: in the WHICAP and CAIDE studies, the Alzheimer's risk related to saturated fat intake was largely confined to individuals with the APOE ϵ 4 allele (Laitinen et al., 2006; Luchsinger et al., 2002). In CHAP, APOE ϵ 4 status had no significant effect on this relationship (Morris et al., 2003). APOE status was not reported in the Rotterdam Study. If the relationship between saturated fat intake and AD risk is influenced by APOE status, it might be obscured in studies that do not account for genetic variability.

Diet: baseline saturated fat intake appears to have been higher in the Rotterdam Study than in CHAP or CAIDE. Reported mean absolute saturated fat intake in the Rotterdam study was 34.4 g/d. In CHAP, median reported saturated fat intake was 18.5 g/d in the middle quintile. In CAIDE, the range of reported saturated fat intake in the second and third quartiles was from 4.2 to 15.8 g/d; given that this was limited to fat from spreads, total saturated fat intake would likely have been about twice this magnitude. The WHICAP study did not report baseline saturated fat intake. As a percentage of total energy intake, however, the mean level of saturated fat intake in the Rotterdam Study may not have been unusual (Engelhart et al., 2002a).

The variability in saturated fat intake in the Rotterdam Study appears to have been limited, judging by the similarity between the lowest and highest tertiles (Table 1). These observations suggest that the high and rather uniform saturated fat intake in the Rotterdam Study cohort would be likely to blunt any observable effect of saturated fat intake.

Rotterdam participants also reportedly had an unusually high vitamin E intake (13.9 mg/d, compared with 9.0 mg/d in CHAP) (Engelhart et al., 2002a; Morris et al., 2003). High vitamin E intake was associated with reduced Alzheimer's risk in the Rotterdam Study (Engelhart et al., 2002b) and other prospective studies (Devore et al., 2010; Morris et al., 2005).

Similar considerations may apply to studies of MCI. The one study (CAIDE) that identified an association between saturated fat intake and MCI risk assessed diet at a mean age of 50 years, with an ensuing 21 years follow-up (Eskelinen et al., 2008). The PATH Through Life Study observed individuals only until a mean age of 66.5 years, identifying only 10 MCI cases, <1% of participants in this comparatively young cohort (Cherbuin and Anstey, 2012). On the other hand, the Rochester Epidemiology Project began observation with individuals whose median age was 79.5 years, ending observation 3.7 years later (Roberts et al., 2012). The more advanced age of this cohort may account both for the higher case finding and, if a degree of cognitive impairment eventually manifests in many elderly people, the lack of apparent effect of saturated fat intake. The remaining cohort study, ILSA, was much

smaller and may have had little statistical power (Solfrizzi et al., 2006a).

For studies of cognitive function, the 2 studies that identified associations between saturated fat intake and cognitive decline over time (Morris et al., 2004; Okereke et al., 2012) were much larger than the 2 that did not find associations. One of the negative studies (Solfrizzi et al., 2006b) had the advantage of a long observation period (8.5 years), but had a high dropout rate, a hazard of lengthy studies in elderly people.

4.1. Mechanisms

Several possible mechanisms link saturated or trans fat intake to dementia risk. Both types of fat tend to elevate plasma total and low-density lipoprotein cholesterol concentrations which, in turn, may be associated with AD risk. In a study of 9844 Kaiser Permanente patients, serum cholesterol levels drawn in midlife (mean age 42 years) were associated with AD risk nearly 3 decades later (mean age 69 years) (Solomon et al., 2009).

Cholesterol may play a key role in β -amyloid production and deposition (Puglielli et al., 2001). Although it may be intracellular cholesterol distribution, not circulating cholesterol concentrations, that regulates β -amyloid generation, the boundaries between the roles of cholesterol in the plasma and in the brain are not clear. In a postmortem study of 64 individuals with AD, serum total and LDL cholesterol concentrations were associated with the quantity of β -amyloid N-42, but not with the less pathogenic β -amyloid N-40, in the cerebral cortex. These associations were independent of APOE genotype (Kuo et al., 1998).

Supporting the role of cholesterol in dementia risk is the fact that cholesterol-lowering statin drugs have been associated with reduced Alzheimer's risk in some, although not all, studies. In the Rotterdam study, after 9 years of follow-up, statin use was associated with a roughly 50% reduction in AD risk (Haag et al., 2009). Similarly, in a study of 1789 Latinos living in the Sacramento area, statin use was associated with a similar reduction of dementia or cognitive impairment during a 5-year follow-up period, after adjustment for education, smoking status, the presence of the APOE ϵ 4 allele, and history of diabetes or stroke (Cramer et al., 2008). The Prospective Study of Pravastatin in the Elderly (PROSPER) (Shepherd et al., 2002) and the Medical Research Council/British Heart Foundation Heart Prevention Study (Collins et al., 2002) did not support a preventive effect of statin use on dementia, perhaps because of design differences. In a recent meta-analysis, statin users were at significantly reduced risk of AD (relative risk [RR], 0.70; 95% CI, 0.60–0.83) and of dementia overall (RR, 0.82; 95% CI, 0.69–0.97) (Wong et al., 2013).

Although a modification in cholesterol concentrations or activity is an attractive explanation for the apparent protective effect of statins and of low-saturated fat diets in relation to AD, the Rotterdam study presented a complication. In this cohort, a reduction in AD risk was found for statin users but not for users of cholesterol-lowering drugs of other classes (Haag et al., 2009), raising the possibility that the reduction in AD risk observed with statin use may occur by a mechanism other than their effect on cholesterol or that passage into the central nervous system, which varies among lipid-lowering medication classes, may be at issue.

Some studies have suggested that the effect of saturated fat intake on Alzheimer's risk may be most evident in (or even limited to) carriers of the APOE ϵ 4 allele. The ApoE protein produced by the APOE gene is a major plasma apolipoprotein and the primary cholesterol carrier in the brain (Puglielli et al., 2003). As a group, APOE ϵ 4 carriers have higher plasma total and LDL concentrations compared with APOE ϵ 3 homozygotes (Bennett et al., 2007). Moreover, APOE status may influence the relationship between

dietary intake and plasma lipid concentrations; a greater effect of dietary saturated fat on LDL cholesterol concentrations has been observed among APOE $\epsilon 4$ carriers (Rubin and Berglund, 2002). In a substudy of the European Prospective Investigation of Cancer and Nutrition (EPIC), saturated fat intake correlated significantly with serum LDL cholesterol concentrations only in individuals carrying the $\epsilon 4$ allele (Loktionov et al., 2000).

It should be noted that the current widespread use of statins complicates efforts to isolate the effects of diet on cognitive function. If saturated or trans fats influence cognition because of their effect on cholesterol metabolism, the use of cholesterol-lowering drugs would be expected to mask that effect.

Apart from their effect on cholesterol concentrations, dietary saturated fats also contribute to insulin resistance and diabetes, presumably by the accumulation of intracellular or cell membrane lipid in skeletal muscle, liver, and pancreatic tissues (Haag and Dippenaar, 2005; Samuel et al., 2010). Individuals with type 2 diabetes are at greatly increased risk of developing AD (Ohara et al., 2011). Possible mechanisms (which are not mutually exclusive) include diabetes' contribution to cerebrovascular disease, glucose toxicity in the form of glycation of brain proteins or microvascular changes, a contribution of hyperinsulinemia to vasculature damage, increased β -amyloid secretion, or reduced β -amyloid elimination (Biessels, 2006). It may be that cardiovascular risk factors, including hypercholesterolemia and diabetes, increase the risk of cerebral white matter lesions, resulting in mental decline (Breteler et al., 1994).

4.2. Limitations

This review has important limitations. The limited number of available observational studies and the absence of intervention trials reflect the challenges of conducting such studies and suggest that caution is needed in drawing conclusions. Attrition is a challenge in studies of elderly people, and individuals with cognitive problems may be most likely to be lost to follow-up. The variation in means of reporting dietary intake and its relationship to cognitive problems presents a barrier to combining the results of studies. The limitations of the included studies are carried forward in the meta-analysis.

5. Conclusion

Several, although not all, prospective studies indicate relationships between saturated and trans fat intake and risk of cognitive problems.

Disclosure statement

Dr Barnard writes books and articles and gives lectures related to nutrition and health and has received royalties and honoraria from these sources. The authors are affiliated with the Physicians Committee for Responsible Medicine, which promotes the use of low-fat, plant-based diets and discourages the use of animal-derived, fatty, and sugary foods.

Acknowledgements

The authors wish to thank Richard Holubkov, PhD of the University of Utah Health Sciences, for consultation regarding statistical analyses; Paul Levett of the Himmelfarb Health Sciences Library, The George Washington University School of Medicine and Health Sciences, and Meghan Wallace and Jonathan Hartman of Dahlgren Memorial Library, Georgetown University School of Medicine for their assistance in planning and executing database searches.

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