

A systematic review on the effects of hypercaloric diet in animal models of Alzheimer's disease

Journal of Alzheimer's Disease

2026, Vol. 112(2) 576–610

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DOI: 10.1177/13872877261448495

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Abstract

Background: According to several published studies, a hypercaloric diet (HD) could be considered a risk factor for neurodegenerative diseases, including Alzheimer's disease (AD). To fully understand the molecular pathways involved, HD has been investigated in several animal models.

Objective: The aim of this systematic review (SR) is to provide an overview of recent published data on the effects of HD on animal models of AD to gain insight into the molecular mechanisms potentially involved and to highlight current knowledge gaps for future studies.

Methods: Structured bibliographic searches were carried out on PubMed, the Cochrane Library, and ISI Web of Knowledge. The SR was conducted following the Cochrane Handbook and the PRISMA statement. Studies enrolling only wild-type models or not using standard diet (SD) as control were excluded, as were non-original publications. Included studies were assessed for risk of bias using SYRCLE's tool.

Results: A total of 77 studies met inclusion criteria. Most reported significant behavioral differences in HD-exposed mice (Morris Water Maze, Open Field, Y-maze), though with considerable variability due to protocol heterogeneity. A significant increase in tau and amyloid deposition was observed after HD exposure, and most studies reported negatively affected learning and memory. However, nearly half found no significant differences between HD and SD groups, likely reflecting heterogeneity in diet duration and type, animal age, and strain susceptibility. Methodological quality varied widely, with many studies omitting randomization, blinding, or sex-stratified analyses.

Conclusions: Despite variability, evidence suggests HD worsens behavioral performance and increases tau and amyloid expression in mouse brain, representing a risk factor for dementia. More rigorous, standardized, and sex-balanced pre-clinical studies are needed, and findings support dietary interventions as early non-pharmacological strategies in AD prevention.

Keywords

Alzheimer's disease, animal models, cognitive decline, hypercaloric diet, neuroinflammation

Received: 23 February 2026; accepted: 8 April 2026

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Introduction

Over the years, the frequency of neurodegenerative diseases has widely increased.¹ Almost 50 million people worldwide have a diagnosis of dementia, with Alzheimer's disease (AD) being one of the most prevalent, involving approximately 17% of the population aged 75 and older.^{1,2} In its early stages, AD is characterized by the accumulation of neurofibrillary tangles, amyloid plaques, and dystrophic neurites. Neurofibrillary tangles and amyloid plaques can lead to neuronal degeneration and cell death, resulting in memory loss, cognitive deterioration, and language impairments.³ Several risk factors have been reported to contribute to the development of AD, including age, genetic factors, head trauma, vascular diseases, infections, and environmental factors.^{4,5} The complexity of these interactions led to consider AD as a multifactorial condition. Interestingly, in people aged 45 and older additional potentially modifiable risk factors become increasingly significant. These include lack of cognitive activity, depression, stress, diabetes, hypertension, obesity, physical inactivity, and cardiovascular diseases.^{6,7} Nutrition has been reported as a potential non-pharmacological strategy for the prevention of AD. Adherence to a "Mediterranean diet" has been reported as associated to a lower incidence of AD,^{8,9} while a high intake of refined carbohydrates, particularly sugars, has been linked to a higher risk of obesity, diabetes and AD.^{10–12} This can induce metabolic alterations that could impair neuronal function and ultimately trigger neuronal apoptosis, leading to cognitive deterioration.¹³ Conversely, other studies reported that HD could improve cognitive function by improving the functioning of the blood-brain barrier and reducing brain atrophy in AD models. However, these diets did not seem to be able to reduce amyloid- β (A β) levels.^{14,15} Therefore, the impact of a HD on the progression of AD remains a topic of debate within the scientific community. Several reviews focusing on diet and neurodegenerative disease have been conducted in recent years. Many of these have concentrated on the supplementation of common dietary components such as ketogenic supplements to evaluate their effects on animal models or non-transgenic mice.^{16,17} To the best of our knowledge, there are currently no systematic reviews investigating the effects of a hypercaloric diet on murine models of AD. Therefore, we sought to address this gap by conducting a systematic review and, where feasible, a meta-analysis of the available preclinical evidence. The aim was to evaluate the effects of HD on cognitive decline, amyloid pathology, and neurodegeneration in animal models of dementia to allow clarify the molecular mechanisms underlying the relationship between diet and dementia, thus highlighting its potential role in the prevention of AD. At the same time, we aimed to assess whether the conditions required to perform a meta-analysis were met and, if not, to critically examine the main

methodological and reporting limitations hindering quantitative synthesis.

Methods

Search strategy and selection criteria

The present SR was carried out following the methodology published in the Cochrane Handbook for systematic reviews¹⁸ (Available from www.training.cochrane.org/handbook and reported following the PRISMA statement for reporting systematic reviews and meta-analyses¹⁹. Structured literature searches were performed in the PubMed, Embase, and Web of Science databases using the following search terms ((diet* OR HFSSD) AND (dementia* OR Alzheimer*) AND (mouse OR mice OR rat OR rats OR transgenic*) AND ("cognitive impairment" OR "behavioural impairment" OR "behaviour impairment" OR "behavior impairment" OR "behavioral impairment" OR "oxidative stress" OR neuroinflammat* OR "mitochondrial dysfunction" OR amyloid* OR "tau hyperphosphorylation" OR gliosis OR "neuronal loss" OR "neuron loss" OR lipid peroxidation)). All literature available up to February 2026 was included, with no restrictions applied regarding publication date, study design, or language. A comprehensive list of all relevant published studies with available results was obtained from all databases, and duplicates were removed. Studies were initially selected based on their relevance and pertinence to the topic of the review.

Study selection

After removing duplicates, the records obtained from the bibliographic searches were selected based on titles and abstracts by using online tool Rayyan (<https://www.rayyan.ai/>). The full texts of selected studies were retrieved and applied the predefined eligibility criteria. Bibliographic references of all included studies were also analyzed to identify further potentially relevant publications. The following eligibility criteria were applied: all studies reporting data on the effect of HD on transgenic mouse models of AD, and studies comparing HD to a control diet were included. Inclusion criteria for HD were strictly defined to ensure consistency across the selected studies. To be included, a dietary intervention had to include a fat content or a combination of high fat and cholesterol like a high fat diet (HFD) or western diet (WD) or a high cholesterol diet (HCD), supplementation with high concentrations of purified carbohydrates, such as sucrose or fructose like high sugar diet (HSD). Diets focused solely on single micronutrient supplementation without an increase in total caloric intake were excluded. Studies enrolling only wild type models or adopting other control conditions (e.g., low-fat diets used as control instead of standard diet, etc.)

were excluded. Letters, commentaries, preprint and grey literature, editorials, conference proceedings, case reports or case series, and non-systematic or narrative reviews were also excluded. Preprints were excluded because they have not yet undergone reviewer assessment and comments, which are essential to define the validity and accuracy required for publication. Exclusion of grey literature was applied due to a potential bias related to the possible lack of replicability. Disagreements in the decision to include studies, when present, were resolved by consensus or by involving an independent reviewer. Systematic reviews, when available, were considered separately to check for references and consistency of results. Literature selection, data extraction, and qualitative assessment were performed by two independent reviewers.

Data extraction and quality assessment

Results were summarized in a narrative form. The qualitative assessment of included studies was carried out using the Syrcle's risk of bias tool specific for animal research.²⁰ Based on this tool, the risk of bias for each study was classified as "high", "moderate" or "unclear".²⁰ This tool contains 10 items addressing 6 domains of potential bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of biases.

The qualitative data were reported as summary of scores for each domain for each included study, as described in previous articles.^{21,22}

Results

Summary of included studies

Bibliographic searches yielded a total of 5552 records, including 1955 records from PubMed, 2005 from Embase, and 1592 from Web of Science. To facilitate the screening and classification of articles after duplicate removal, the lists of records were imported on Rayyan (<https://www.rayyan.ai/>), a web-based tool that had been used by the reviewers for a previously published review.^{23,24} Based on this preliminary screening, 4972 articles were excluded, while 580 articles were retrieved in full-text and were assessed for eligibility based on the predefined eligibility criteria. Of the studies analyzed, 503 were further excluded as they were conference posters, abstracts or reviews. A total of 77 studies met the inclusion criteria. The study selection process is reported in Figure 1. The characteristics of included studies are reported in Table 1. Data was extracted using a standardized form. Collected data included year of publication, characteristics of the animal model, type of diet, and results for all considered outcomes. Supplementary materials were reviewed and included when available. In Table 2, we provide a sum up of the main characteristics and results of the outcomes of

the studies with available data. All studies used mice as animal models, except for four that used rats.^{25–28} 36 studies used transgenic animal models carrying the APP/PS1 double mutation^{12,15,26,27,29–60} and the most represented model was APPswe/PS1^{ΔE9}, though four studies did not describe the type of mutations on the APP and PS1 genes without specific mutation.^{33,34,46,61} In 16 studies, animal model had only one mutation in APP gene, and the most used was APP Swedish mutation.^{43,62–76} Moreover, a total of 13 studies used the 3xTg all expressing mutant PS1M146V, APPswe, and TauP301L.^{68,77–88} Finally, three studies used two experimental models with Aβ injection.^{28,78,89} While one²⁵ used a TG Fischer rat carrying a human Aβ. Overall, 27 studies included both male and female mice,^{12,25–27,29,34,40,43,50,51,57–59,61,62,67,68,77–80,82,83} 10 studies included only female mice,^{14,44,52,54,71,73,74,85,87,88} while the remaining 38 studies included only male mice. The age at the start of diet ranged from 1 to 6 months in most studies except for four studies^{25,62,66,90} that initiated diet in mice aged 8–10 months and three studies that initiated diet in mice younger than one month.^{31,45} The duration of the dietary intervention ranged from 2 to 10 months, except in one study⁸⁸ in which lasted less than one month and in 5 studies^{42,49,51,76,82} in which the diet lasted one month and other 7 studies in which it lasted 10–14 months.^{37–39,47,69,86,91}

HD is defined as any dietary regimen with a caloric density exceeding that of standard laboratory chow. Specifically, we categorized HD into three main types based on their macronutrient composition: HFD, characterized by a fat content ranging from 45% to 60% of total kilocalories; HSD, primarily enriched with sucrose or fructose; and WD, which combine high fat content (approx. 40–45%) with high cholesterol and purified carbohydrates, mimicking typical human WD patterns; HCD, specifically supplemented with 1–2% cholesterol to induce hypercholesterolemia; and high-carbohydrate high-fat diets, designed to mimic a combination of caloric excesses. This classification allows for a better understanding of how different metabolic triggers influence AD pathology.

Qualitative assessment

Results of the qualitative assessment for each domain in all included studies are reported in Figure 2. Overall, the methodological quality of the included articles was widely variable. Only a minority of studies had a relatively low risk of bias across domains, with more than 60% of the items rated as "Yes".^{26,27,98} These studies reported an adequate baseline comparability between groups, had an appropriate management of missing data, and clearly defined outcome measures. Most studies had insufficient methodological transparency. The most common methodological limitations included the absence of reported methods for random allocation, lack of blinding of caregivers and

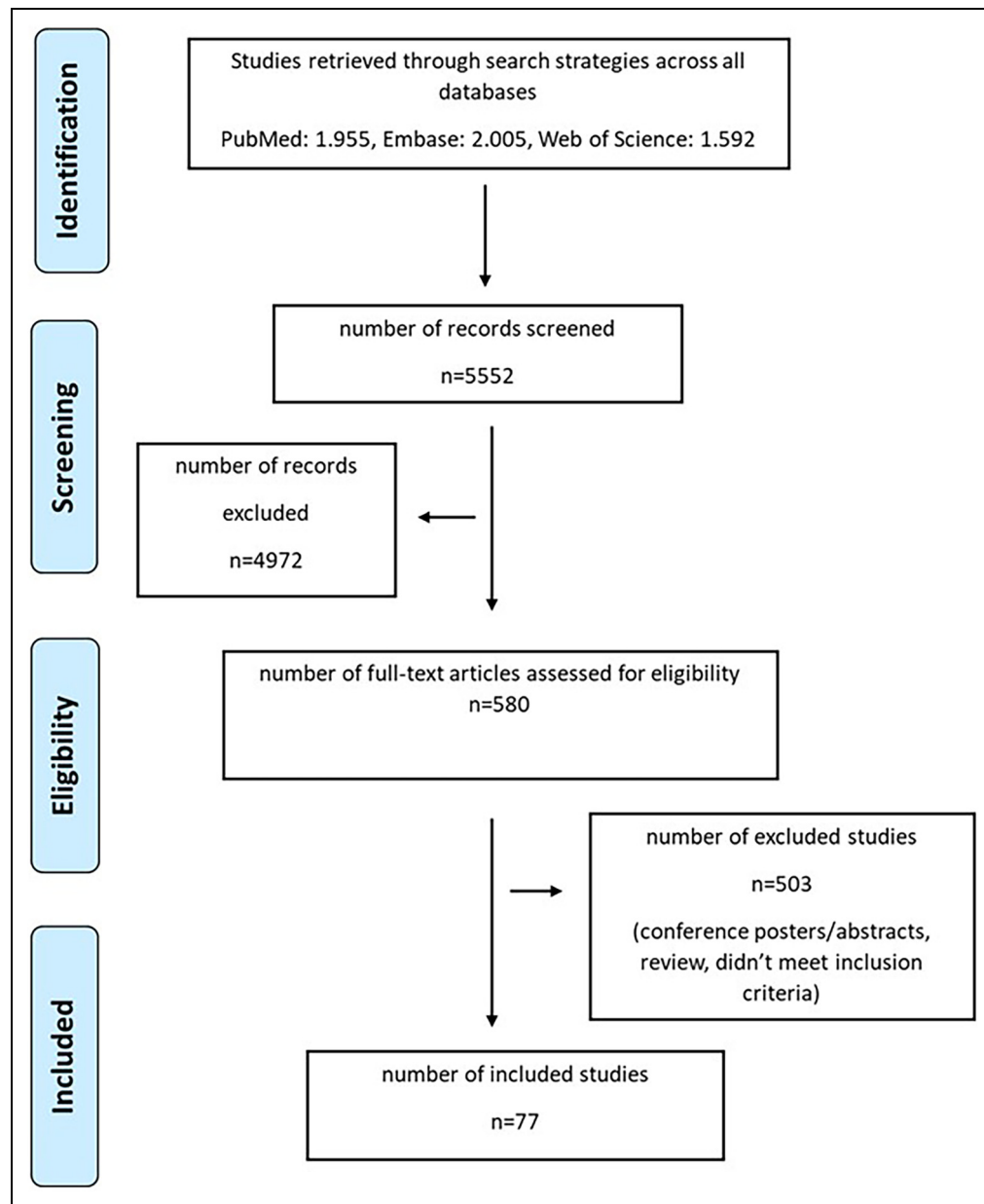


Figure 1. Modified PRISMA flow diagram for clinical trial selection.

outcome assessors, and unclear or inappropriate management of missing outcome data. Moreover, most of the included studies had a limited sample size, and no information was provided whether animals who dropped out of the initial experimental samples or control group were replaced with other animals to maintain the sample size. Specifically, 13 studies were rated as having an overall low risk of bias,^{27,36–38,41,44,47,49,54,57,70,83,98} 36 studies were rated as having a moderate risk of bias since most domains were scored as unclear,^{14,15,25,26,28,30,33,35,40,42,45,46,48,50,55,60–63,69,71,73,75,77,79,81,82,84,85,88–90,94,96,100} and 28 studies were rated as at high risk of bias, since most domains were scored as high risk.^{29,31,32,34,39,51–53,56,58,59,64,66,67,}

^{72,74,76,78,80,86,87,93,95,97,100,101} Among the objectives of this systematic review, we initially planned to perform a meta-analysis on the identified outcomes to estimate the effect of a hypercaloric diet on murine models of AD. However, this was not feasible, primarily because the majority of the included studies reported their results only in graphical form, without providing numerical data such as means or medians with corresponding standard deviations or standard errors and also because during the evaluation of the studies, it was not possible to assess the effect measures, as in many studies these were not reported or had not been evaluated.

Table 1. Characteristics of included studies.

Reference	Species	Animal model (strain)	Sex	Age (weeks, months)	Diet	Diet duration (months)	Sample size
29	Mouse	APPswe/PS1 ^{ΔE9} APPswe/PS1 ^{ΔE9} (B6)	M&F	4m	HFDSD	4m	NR
30	Mouse	APPswe/PS1 ^{ΔE9} (C57bl/6)	M	4m	HFD 45%SD	4m	HFD:4-8SD:4-8
32	Mouse	APPswe/PS1 ^{ΔE9}	F	6m	HFD 45% + palmitic acidSD	4m	NR
31	Mouse	APPswe/PS1 ^{ΔE9} (C57BL/6)	M	3w	HFD: (Cat# D08061110)SD	2m	HFD:10SD:10
62	Mouse	APP23—Swedish and Indiana mutation (C57bl/6)	M&F	8–10m	HCDSD	4m	HCD:16SD:16
33	Mouse	APPswe/PS1 ^{ΔE9} —Shanghai Model Organisms Co., Ltd, Production license number SCXK 2014-004 (C57BL/6j)	M	NR	HFD: 63.6% basic feed, 15% lard, 20% sucrose, 1.2% cholesterol, and 0.2% cholateSD	NR	NR
34	Mouse	APPswe/PS1 ^{ΔE9} C57BL/6Smoc-Tgtn (APP-PSEN1(P)) ISmoc	M&F	2.5m	HFD: (D12492, research diets)SD	4m	HFD:13SD:15
92	Mouse	APPswe/PS1 ^{ΔE9} (C57BL/6j)	M	1m	HFD: 60% high fat dietSFA 105.38 g/Kg MUFA 112.30 g/Kg PUFA 52.51 g/KgSD MO: (Cat: 5001) LFD: (Cat: D12450)HFD: (Cat: D12492) SD: (LabDiet, St Louis)	6.5m	HFD:10SD:10
36	Mouse	AβPP/PS1—Mo/HuAPP695swe / PS1 ^{ΔE9} (C57BL/6j)	M	2–3m	TWDS	8m	HFD:12LFD:11
37	Mouse	APPswe/PS1 ^{ΔE9} (C3HeJ × C57BL/6j)	M	6m	TWDS	12m	TWD:9SD:8
38	Mouse	APPswe/PS1 ^{ΔE9} (C3HeJ × C57BL/6j)	M	2m	TWDS	6 or 13m	8 months: TVD:13SD:11 15 months: TVD:9STD:10 WD:11SD:11
25	Rat	APP21—APPswe and Indiana mutation	M&F	8.5–9.5m	WD: (D12079B) SD: (Prolab RMH 3000 5P00).	3m	HFD:12SD:12
63	Mouse	APPsweDI	M	2m	HFD: 15P, 43C, 42F; (TD.120084)SD	6m	NR
39	Mouse	APP-Tg—APPswe, PS ^{ΔE9} -85Dboj	NR	NR	HFDSD	2.5m or 12m	NR
40	Mouse	APPswe/PS1 ^{ΔE9}	M&F	NR	HCHF SD	3 or 6m	NR
64	Mouse	APP _{SL} —Swedish and London mutation	NR	3m	HFD: (D12451 mod.)SD: (Sniff, Soest, Germany)	4m	HFD:5-8SD:5-8
41	Mouse	APPswe/PS1 ^{ΔE9} (C57BL/6j)	M	1m	HFD: (D12492)SD: (D18091704)	3.5m	HFD:30SD:6
93	Mouse	APP Tg swe—K670N/ M671L and Indiana -V717F- mutations (J20)	M&F	2–3m	HFD: (Research Diet, Inc., Canada)SD: (Oriental Yeast Co., Ltd, Tokyo, Japan)	5m	HFD:10SD:9
65	Mouse	APP Tg swe—K670N/ M671L- and Indiana—V717F—mutations (J20)	F	2–3m	HFD: (Research Diet, Inc., Canada)SD: (Oriental Yeast Co., Ltd, Tokyo, Japan)	5m	HFD:5SD:5
66	Mouse	APP Tg J20 swe—K670N/M671L and Indiana—V717F—mutations	NR	7–8m	HFD: (Research Diet, Inc., Canada)SD: (Oriental Yeast Co., Ltd, Tokyo, Japan)	5m	HFD:3SD:3
67	Mouse	APP Tg J20 swe—K670N/M671L— and Indiana—V717F—mutations	M&F	2–3m	HFD: (Research Diet, Inc., Canada)SD: (Oriental Yeast Co., Ltd, Tokyo, Japan)	5m	HFD:10SD:9

(continued)

Table 1. Continued.

Reference	Species	Animal model (strain)	Sex	Age (weeks, months)	Diet	Diet duration (months)	Sample size
42	Mouse	APP Swedish mutation—K595N/M596L and PS1 ^{ΔE9}	NR	1.5m	HFDSD	1m 4m 8m	1 monthHFD: 5HFD: 8SD: 58 monthsHFD: 10 SD: 5
43	Mouse	APPswe/PS1 ^{ΔE9}	M&F	3.5m	HFD: (D12079B Diet, Research Diets)SD: (Prolab Isopro RMH 3000, Lab Diet Isopro RMH 3000)	3m	HFD:6-7SD:6-7
94	Mouse	APP23—Swedish and Indiana mutation (C57Bl6)	NR	12m	HFDSD	3m	NR
95	Mouse	APPswe/PS1 ^{ΔE9} , Tau P301L	F	7m	WD: 21% fat, 0.15% C, 35% sucroseSD: 5% fat	6m	46
44	Mouse	APPswe/PS1 ^{ΔE9}	NR	3m	HFDSD	6m	NR
45	Mouse	APPswe/PS1 ^{ΔE9} (C57BL/6)	M	3w	HFD: (Cat# D08061110 Research Diets Inc, New Brunswick, USA)SD	6m	HFD:10SD:10
46	Mouse	APPswe/PS1 ^{ΔE9}	M	1.5m	CHOLSD	4.5m	CHOL:42SD:40
61	Mouse	APPswe/PS1 ^{ΔE9} mice (B6.Cg-Tg(Thy1-APPswe, Thy1 PSEN1* ^{L166P})2JcKcr)	M&F	2.1m	WD: (E15721-347, ssniff, Soest, Germany) ND: (V1534-000, ssniff, Soest, Germany)	6m	WD:12SD:9
47	Mouse	2APPswe/PS1 ^{ΔE9} (line 4462)	M	2.1m	HFDSD	14m	HFD:10SD:10
48	Mouse	APPswe/PS1 ^{ΔE9} (C57BL/6)	M	1m	HFD: 60% Kcal from fat, (OpenSource, New Brunswick, NJ, USA)SD	6m	NR
49	Mouse	PSAPP: APPK670N; M671L—line Tg2576 and mice expressing the human familial mutant PS1M146 V	M	1.1m	HCD: (Purina Test Diet No. 5801C)SD: (Purina Test Diet No. 5755C).	1.5m	HCD:9SD:7
81	Mouse	3xTg-AD APPswe, tauP301L, and Psen1tm1Mpm (C57BL/6;129X1/SvJ;129S1/Sv)	M&F	3m	HFD: 60% fat, 5.24 kcal/g: (D12492, Research Diets, New Brunswick, NJ)SD: 10% fat: (D12450B, Research Diets)	3m	HFD:18-25SD:18-25
73	Mouse	APPswe (SJL/J)	F	2m	HFHCSD	7-10m	HFHC:5SD:5
74	Mouse	APPswe (SJL/J)	F	2m	HFHCSD	10m	NR
75	Mouse	APPswe—K670N/M671L (C57BL/6)	NR	6m	WD: (#88137)SD: (Harlan Teklad #98224)	6m	WD:5SD:5
50	Mouse	APPswe/PS1—mPrP-APP ^{ΔE9} swe/PS1 ^{ΔE9}	M&F	1.5m	HFDSD	6m	NR
51	Mouse	APPswe/PS1 ^{ΔE9} -ΔNL and P264L	M&F	1m	WD: (Diet #D12079B)SD: (Diet #98052602)	1m	HFD:8 m, 6fSD: 8 m, 6f
52	Mouse	APPswe/PS1 ^{ΔE9} mice IGF2	F	5m	WDSD	4m	NR
15	Mouse	APPswe/PS1 ^{ΔE9} (C57BL/6j)	M	3 young, asymptomatic; 12 aged, symptomatic m	WDSD	4m	WD:8-10SD:8-10

(continued)

Table 1. Continued.

Reference	Species	Animal model (strain)	Sex	Age (weeks, months)	Diet	Diet duration (months)	Sample size
53	Mouse	APP ^{swE} /PS1 ^{ΔE9} (C57BL/6xC3H and C57BLKS/J)	NR	3w	HFDSD	6m	HFD:6/8/5SD:12
77	Mouse	A7-Tg—APP695 harboring KM670/671NL and T714I (C57BL/6J)	M	3m	HFD (HFD32, CLEA Japan Inc.)SD	6m	HFD:11SD:12
96	Mouse	APP ^{swE} /PS1 ^{ΔE9} (C57BL/6J)	M&F	2m	HFD: (Research Diets: #D12492)SD: (Purina 5001)	9.5 and 12m	HFD:15-29 SD:15-29
97	Mouse	3xTg: human APP KM670/671NL—Swedish—MAPT P301L, and PSEN1 M146 V (C7BL/6;129X1/SvJ;129S1/Sv)	M&F	3m	HFD: 1,25% cholesterolSD	9m	HFD:14SD:14
68	Mouse	APPKINL-G-F/NL-G-F Swedish (NL), Arctic (G), and Beyreuther/Iberian (F) mutations	M	1m	HFD: (Research Diets, Inc.) SD: (CE-2; CLEA Japan Inc)	9m	HFD:5SD:5
69	Mouse	APP ^{swE} mice Tg line #1349; B6; SJL-Tg—APP ^{swE} —2576Kha	M	3m	HFDSD	17m	HFD:5SD:6
54	Mouse	APP ^{swE} /PS1 ^{ΔE9}	F	3.5m	HFDSD	3.5m	HFD:7SD:7
60	Mouse	APP ^{NL-G-F} Arctic, Swedish, and Beyreuther/Iberian mutations	M	2m	HFD: D12492 60% fat, 20% protein, and 20% carbohydrate. ND:MF diet from ORIENTAL YEAST ad libitum, containing 12.4% fat, 26.1% protein, and 61.5% carbohydratesSD	2.1m 4.1m 7.2m	NR
78	Mouse	Tg2567 Swedish mutations (KM670/671 NL)	M	1m	HFDSD	3m	HFD:10SD:10
55	Mouse	APP ^{swE} /PS1 ^{ΔE9} B6.Cg-Tg—APP ^{swE} /PS1 ^{ΔE9} —85Dbo/Mmjax	M	5m	HSD: 67.3%, fat at 4.3%, and sucrose at 35% by weight (D12450B, Research Diet, USA) SD: 50.0%, fat at 5.0%, and sucrose at 1.16% by weight (5010, Lab Diet, USA)	2.5m	NR
26	Rat	TgF344-AD—APP ^{swE} /PS1 ^{ΔE9}	M&F	9m	HCHFSD	3m	HCHF:13SD:14
56	Mouse	Tg6799—APP ^{swE} /PS1 ^{ΔE9}	M	1, 3, 6m	HFD: (Research Diets Inc.)SD: (Research Diets Inc.)	5m	9-11/group
27	Rat	TgFischer344	M&F	6-8m	WDSD	2m	HFD:7-8SD:7-8
82	Mouse	3XTg-AD—APP ^{swE} , PS1M146 V, tauP301L	M&F	3m	HFDSD	4m	HFD:10SD:8
83	Mouse	3xTg-AD—APP ^{swE} , PS1M146 V, tauP301L (C57BL/6J129SvJ)	M&F	6m	HFD: 60%SD	9m	HFD:7-12SD:7-12
14	Mouse	Tg601—tau overexpression (C57BL/6 J)	F	10m	HFD: 35%SD	5m	HFD:27 SD:27
84	Mouse	3xTg AD, APP ^{swE} , PS1 M146 V, TAU P301L	M&F	6m	HFD: 60%SD	7m	HFD:11-19 SD:11-19
70	Mouse	Tg2576—APP ^{swE} (C57BL/6J)	M	2m	HFD: (TD.06414)SD	10.5m	NR

(continued)

Table 1. Continued.

Reference	Species	Animal model (strain)	Sex	Age (weeks, months)	Diet	Diet duration (months)	Sample size
58	Mouse	B6.Cg-Tg—APP ^{swe} , PS1 ^{ΔE9} —85DboI/Mmjax (C57BL/6J)	M&F	2m	WD: (TestDiet 5W80)SD	10m	NR
57	Mouse	Tg AD—APP ^{swe} /PS1 ^{ΔE9} (C57B6)	M&F	/	WD: (TD 88137, Harlan Teklad)SD	4m	HFD:4-7SD:4-7
59	Mouse	B6C3-Tg—AβPP ^{swe} /PS1 ^{ΔE9} —85DboI	M&F	4m	HFDSD	2m	HFD:3SD:3
71	Mouse	Tg2576 (overexpress APP)	F	3–4m	HFDSD	6–5m	HFD:5-7SD:5-7
85	Mouse	3xTg-AD mice APP ^{swe} , PS1 M146 V, TAU P301L	NR	4m	low amount of linolenic acid and a low n-3:n6 PUFA ratio-high-fat westernized diet similarly low n-3:n-6 PUFA ratioSD	9m	NR
98	Mouse	B6:129-Tg (APP ^{swe} , tauP301L) IL1fa Psen1 ^{em1Mpm} /Mmjax (3xTg-AD)	F	4m	HFD: (Inotiv TD.06414; energy density of 5.1 kcal/g; 18.4% calories from protein, 21.3% from carbohydrates [90 g/kg sucrose, 160 g/kg maltodextrin], and 60.3% from fat [37% saturated, 47% monounsaturated, 16% polyunsaturated]) SD: (Inotiv TD.8640; energy density of 3.0 kcal/g; 29% calories from protein, 54% from carbohydrates [no sweetener added], and 17% from fat [0.9% saturated, 1.2% monounsaturated, 2.7% polyunsaturated])	2w	NR
99	Mouse	Tg-SwDI	M&F	3m	HFD (60% fat from lard, 20% protein, 20% carbohydrate, 5.24 kcal/g; D12492, Research Diets, New Brunswick, NJ)SD: (10% fat from lard, 20% protein, 70% carbohydrate, 3.82 kcal/g; D12450), Research Diets)	6m	HFD: 25SD:25
86	Mouse	3xTgAD, APP ^{swe} , PS1 ^{M146V} , and TauP301L transgenes (C57BL/6)	M&F	3–4m	HFD: (Research Diets, D14022601)SD	1m	HFD:8-9SD:8-9
87	Mouse	3xTgAD mice, expressing mutant PS1M146 V, APP ^{swe} and TauP301L (C57BL/6)	M&F	2m	HFD: (58G9, Test Diets)SD: (BK001, Special Diets Services, UK)	2 or 12m	2m: HFD:9-12 SD:9-12 12m: HFD:8-11 SD:8-11
72	Mouse	TgAPP mice—Tg APP, line 2576	M&F	4.5m	HFDSD	4.5m	56
80	Mouse	TgCRND8 mice	NR	1m	HFDSD	3.5m	57
88	Mouse	3xTg model, PS1M146 V, APP ^{swe} , and tauP301L	M&F	2m	HFD: 60.3% kcal from fatSD: ingredient-equivalent low-fat control diet (10.5% kcal from fat)	6m	HFD: 10SD:10

(continued)

Table 1. Continued.

Reference	Species	Animal model (strain)	Sex	Age (weeks, months)	Diet	Diet duration (months)	Sample size
89	Mouse	3xTg-AD—APPSwe,tauP301L—ILfa Psen1tm1Mpm/Mmjax (C57BL/6)	F	1m	HFD: 60% fatSD: 10% fat	4m	HFD: 10SD: 10
90	Mouse	3xTg-AD B6;129 Psen1tm1MpmTg—APPSwe, tauP301L	M	2m	HFD: 58% kcals from fatSD: 11% kcals from fat.	6 and 12m	HFD: 22SD: 22
76	Mouse	Tg2576 mice APPOSK-Tg mice—APP ^{O₃aka E693Δ} mutation	M	5m	HCD: 2% cholesterol and 4% fatSD	1m	HCD: 8SD: 8
91	Mouse	3xTg-AD, APPSwe, PSI ^(M146V) , tau ^(P301L) (C57BL/6J29SvJ)	F	6m	HFD: 60% kcal fatSD	9m	NR
100	Mouse	KM mice injected with Aβ1–42	M	3m	HFDSD	2m	HFD: 8SD: 8
101	Mouse	ICV Aβ (C57BL/6J)	M	3m	HFDSD	3m	HFD: 6SD: 6
28	Rats	ICV Aβ1–42 (Wistar)	NR	NR	HFD: standard feed; lard (fat), 45.1%; protein, 20.1%; carbohydrate, 34.7%SD	5m	HFD: 5SD: 5

SD: standard diet; HCHF: High carbohydrates and high fat diet; HFD: high fat diet; HCD: High-cholesterol diet; WD: western diet; SFA: saturated fatty acid; MUFA: multiple unsaturated fatty acids; PUFA: polyunsaturated fatty acids; LFD: low fat diet; CHOL: Cholesterol-enriched diet; APPSwe: APP Swedish; KM: Kunming; NR: not reported.

Table 2. Summary of the main characteristics and results of the outcome of included studies with available data.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
29	NR	↑ Gliosis in Cx and Hip at 11 and 21 m	↑ A β 40 monomers at 11 and 21 m ↑ A β 40 insoluble fractions ↑ amyloid plaque in Cx at 21 m and in Hip at 11 and 21 m = A β 42	Y-maze HFD = SD Object recognition HFD = SD	NR
30	NR	↑ 4-HNE HFD vs. SD	↑ A β 42, and A β 42/A β 40 ↓ A β 40 in hippocampus and Cx HFD vs. SD ↑ A β aggregates by relative area in Cx	OPF, NOL and NOR ↑ cognitive impairment HFD vs. SD	NR
32	NR	HFD ↑ neuroinflammation in APP mice	HFD ↑ A β plaques in Cx of APP mice	MWM and NOR test ↑ cognitive decline HFD vs. SD	NR
31	HFD significantly ↓ PGC-1 α protein level	Microglia: Glial activation between dietary groups = . Accumulation of GFAP and Iba1-positive activated cells around amyloid deposits/aggregates in both groups=	Amyloid deposition: ↑ mRNA expression and protein levels of APP in HFD vs. SD ↑ accumulation of cortical A β and fibrillar plaques HFD vs. SD. ↑ in the levels of brain A β 1-40 soluble and insoluble and A β 1-42 insoluble peptides HFD vs. SD Tau expression: tau phosphorylation = HFD vs. SD	NOR HFD = SD = lipid peroxidation, protein oxidation, and antioxidant enzymes.	
62	NR	NR	↑ amyloid Cx and Hip plaques, Cx soluble and insoluble A β 40 and A β 42 HFD vs. SD Amyloid deposition: levels of A β 42 = HFD vs. SD	MWM, swimming speed, time spent in, latency ↓ HFD vs. SD MWM HFD = SD	NR
33	NR	Neuroinflammation: the mRNA expression of different, IL-1b, IL-6, TNF- α , MCP-1, IL-12A, IL-12B, and IFN- γ , were ↓ HFD vs. SD TNF- α and IL-1b ↓ HFD vs. SD			NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
34	NR	Dendritic morphology—Golgi Staining: neurite arborization and dendritic length CA1 ↓ HFD vs. SD In hippocampus Synapsin-I, Synaptophysin and PSD93 ↓ HFD vs. SD ↑ serum TNF- α level HFD vs. SD	A β deposition ↑ HFD vs. SD Soluble and insoluble A β : ↑ HFD vs. SD Tau expression HFD = SD	NOR HFD ↓ vs. SD BM HFD ↑ latency and primary errors vs. SD	NR
92	NR		Hippocampal senile plaques number ↓ cortical soluble A β 1-40 and A β 1-42 ↑ HFD vs. SD ↑ APP expression HFD vs. SD HFD = SD	MWM ↑ latency of escape in HFD vs. SD MWM after 27 weeks Latency to reach to the platform ↑ HFD to locate the hidden escape platform during the first training block of Day 2 vs. Day 1 Cumulative distance HFD mice travelled further from the hidden escape platform on the first training block of Day 2 compared to their Day 1 performance.	NR
36	NR	NR			NR
37	NR	NR	↑ A β plaque load in the Dentate Gyrus vs. to all other hippocampal and cortical regions TWD vs. SD = A β in the hippocampus and PL area. TWD vs. SD In 8-month-old mice no diet effects could be observed on vascular or parenchymal A β . In 15-month-old mice no diet effects could be observed on parenchymal A β in cingulate gyrus TWD vs. SD	NR	NR
38	NR	NR		Open field, MWM, reverse MWM TWD = SD	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Anyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
25	NR	Microglia activation: ↑ microgliosis in all white matter regions WD vs. SD ↑ Iba-1 immunolabelled microglial cells in corpus callosum WD vs. SD Astroglia (GFAP-immunopositive astroglia): ↑ in astrocyte number in the corpus callosum and fimbria in WD vs. SD Inflammation levels = in the dorsal hippocampus between the four groups of animals in both genotypes.	No detectable human amyloid aggregation and deposition in the brain tissue	MWM = HFD vs. SD	NR
63	NR	Inflammation levels = in the dorsal hippocampus between the four groups of animals in both genotypes.	= in A β HFD vs. SD	Open field test. zero maze test HFD = SD social recognition test ↓ HFD vs. SD	NR
39	NR	CD4+, CD8+, B220+, and F4/80+ ↑ cells in the livers HFD vs. SD TNF- α , IL-6 and IL-17 ↑ HFD vs. SD TLR 1, 2, and 6 in the brains ↑ HFD vs. SD Iba, microglia activation ↑ HFD vs. SD Microglia activation in the PFC ↓ HCHF vs. SD	Cx A β plaque 2 and 5 months ↑ HFD vs. SD Plaque sizes ↑ HFD vs. SD Overall plaque load for 1 year in cortex and hippocampus ↓ HFD vs. SD pTau staining in the hippocampus and cortex ↑ HFD vs. SD A β plaques ↑ the Cx = Hip of ϕ HCHF at 3 months Tau density ↑ in the at 3 months HCHF vs. SD the PFC ↑ after 6 months HCHF vs. SD Phosphorylated tau: Cx ↑ after 3 months ϕ HCFC vs. SD	NR	NR
40	NR			BM ↑ spatial learning at 3 months HCHF vs. SD ↑ executive function in female at 6 months HCHF vs. SD	NR
64	NR	NR	↑ Cortical insoluble A β ₁₋₄₀ and A β ₁₋₄₂ levels HFD vs. SD, =Cortical levels soluble A β ₁₋₃₈ , A β ₁₋₄₀ , A β ₁₋₄₂ , ↑ A β plaque in Cx and Hip HFD vs. SD ↑ CAA in Cx and Hip HFD vs. SD	NR	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
41	NR	serum TNF- α levels $\uparrow$ HFD vs. SD $\uparrow$ iNOS, $\downarrow$ TNF- α , COX2 and IL-6 cortical mRNA levels HFD vs. SD	$\uparrow$ soluble A β_{1-40} and A β_{1-42} in the cortex. $\downarrow$ aggregated A β_{1-40} and A β_{1-42} in the cortex HFD vs. SD A β plaque = HFD vs. SD A β deposition: cerebral A β deposition $\uparrow$ HFD vs. STD A β oligomer $\uparrow$ HFD vs. STD APP processing through detecting APP C-terminal fragment: $\uparrow$ HFD vs. SD A β plaque = HFD vs. SD	NR Escape latency in the acquisition phase: $\uparrow$ time to the platform HFD vs. SD Swimming length in the acquisition phase: $\uparrow$ HFD vs. SD The time to the target quadrant in the probe trial phase: $\uparrow$ platform quadrant HFD vs. SD	NR
67	NR	NR			NR
65	NR	NR	A β deposition hippocampal A β deposition $\uparrow$ HFD vs. SD A β oligomer in formic acid fraction: $\uparrow$ A β 40, A β 42, A β oligomer in TBS-fraction HFD mice vs. SD Filter trap assay $\uparrow$ A β oligomers HFD vs. SD $\uparrow$ relative band intensity of APP CTF β /APP full length HFD vs. SD	MWM (probe trial phase) $\uparrow$ time to goal position HFD vs. SD $\downarrow$ time in goal quadrant HFD vs. SD	NR
66	NR	NR	$\uparrow$ BACE1/clathrin complex and BACE1/AP2 interaction HFD vs. SD	NR	NR
93	NR	NR	$\uparrow$ A β plaques, A β oligomers HFD mice vs. SD	MWM (probe trial phase) $\uparrow$ time to the platform quadrant HFD vs. SD: $\downarrow$ cross times HFD vs. SD	NR
42	NR	Neuroinflammation: microgliosis $\uparrow$ -reactive astrocytes $\uparrow$ HFD vs. SD	Amyloid: A β plaque $\uparrow$ (10 m) Total TAU = Tau phosphorylation $\uparrow$ (6 m) HFD vs. SD	NR	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
43	NR	NR	↑ A β deposition- anti-A β HFD vs. SD	NR	NR
94	↓ genes which regulate apoptosis and inflammation HFD vs. SD	NR	↑ amyloid deposition HFD vs. SD	MWM ↓ HFD vs. SD	NR
95	NR	NR	= total β -amyloid load, β -amyloid peptide ratios and plaque diameter TWD vs. SD ↑ number of plaque-associated dystrophic neurites TWD vs. SD	MWM = swimming speed TWD vs. SD = escape latencies TWD vs. SD ↑ memory impairment TWD vs. SD	NR
44	NR	NR	NR	Open Field test = HFD vs. SD γ -maze ↓ HFD vs. SD	NR
45	Transcriptional co-regulator of mitochondrial biogenesis PGC-1 α . ↓ HFD vs. SD	NR	numbers of senile plaques in the brain = HFD vs. SD Insoluble A β 1-42 ↑ HFD vs. SD pSer404-Tau in hippocampus ↑ HFD vs. SD	NOR test HFD ↓ on memory function vs. SD	NR
46	NR	NR	NR	NR	↑ hepatic elevation in Ho-1 and Nox-2 mRNA CHOL vs. SD ↓ mRNA expression of Sod-1, Sod-2 and Nox-4 CHOL vs. SD
47	NR	NR	A β 42 and A β 40 peptide levels ↑ HFD vs. SD	MWM = HFD vs. SD	NR
48	NR	Microglia: ↑ activation HFD vs. SD. ↑ in microglia burden in HFD vs. SD Microglia size ↑ HFD vs. SD	Tau expression = tau phosphorylation HFD vs. SD Senile plaques burden ↑ HFD ↑ in number of new plaques HFD vs. SD Cortical soluble A β 40 and A β 42 levels ↑ HFD vs. SD	MWM: HFD = SD	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
49	NR	NR	↑ total Aβ for HCD deposit number and size insoluble Aβ40, Aβ42, Aβ38, Aβ34 ↑ HCD = APP holoprotein ↑ APP CTFβ accumulation HCD vs. SD ↓ APP CTFα accumulation HCD vs. SD	NR	NR
81	NR	IL-10 and IL-12 (p40) ↑ HFD vs. SD MIP-1α and MIP-1β ↑ HFD vs. SD inflammation in the periphery ↑ HFD vs. SD Hypothalamic expression of Iba1, GFAP and pro-inflammatory cytokines (TNF-α and IL-1β) ↑ HFD vs. SD	NR	Open Field test HFD = SD	NR
73	NR	↑ microglial activation after 10-month HFHC vs. SD	↑ Hippocampal Aβ deposition after 7, 10-month HFHC vs. SD = Hippocampal insoluble Aβ40, Aβ42 levels after 10 month HFHC vs. SD ↑ Plasmatic apoE and apoB levels correlated with Aβ deposit HFHC vs. SD ↑ Hippocampal intraneural Aβ deposit HFHC vs. ND Aβ levels ↑ HFD vs. SD Total APP HFD = SD	NR	NR
74	NR	NR		NR	NR
75	NR	NR		NR	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
50	NR	Microgliosis ↑IBA1 in Hippocampus ♀/♂, Cortex ♀/♂, Ventromedial Hypothalamus ♀/♂; Arcuate Nucleus ♀ HFD vs. SD	↑Aβ1–42 deposits in Hippocampus ♀/♂, Cortex ♀/♂ HFD vs. SD ↑Aβ17–24 deposits in Hippocampus ♀/♂, Cortex ♀/♂..HFD vs. SD	Open field test ↑Total distance ♀/♂ mice, ↑Average Velocity ♀, ↑Anxiety-like behavior ♀. HFD vs. SD Porsolt forced swimming test: ↑Time spent immobile ♀ HFD vs. SD Y-maze test: ↓spontaneous alternation percentage ♀/♂ HFD vs. SD BM: ↑Latency to Escape ♀/♂, Time in the Target Quadrant Zone ♀/♂ HFD vs. SD	NR
51	NR	NR	= level of Aβ in the brain WD vs. SD	NR	↑ protein carbonyls (antidinitrophenylhydrazine) and protein nitrosylation levels ↑ lipid hydroperoxides levels in the brain of mice on WD vs. SD NR
52	NR	= protein levels of GFAP HFD vs. STD mice. In the temporal cortex related ↓independently of the genotype in the mRNA, but not in the protein levels of TNFα HFD vs. SD	↑ 3R and 4R-tau mRNA levels HFD vs. SD ↑ 4R-tau/3R-tau mRNA and protein levels ratio HFD vs. SD	NR	
15	NR	MMP-2/9 basal enzymatic activities ↓ WD vs. SD ↓ in MMP-2/9 WD vs. SD = mRNA levels of MMP-9 WD vs. SD ↓BDNF RNA, protein, expression WD vs. SD	= Aβ plaques size and number in cortex WD vs. SD Hippocampus = Aβ plaques size and number Brain soluble Aβ = Aβ 1–42 or Aβ 1–40 WD vs. SD In isolated cerebral microvessels of 16 months old WD-fed ↑vs. ND-fed	T-water maze = WD vs. STD NOR: = during learning phase WD vs. SD NOR-index: ↓ on recognition index during retention phase in 7 WD vs. SD NOR-index: ↓ 7 months old and 16 months old ↓ cognitive in all groups of mice reported in the T-water maze paradigm and NOR WD vs. SD	MDA levels, in cerebral microvessels as marker of oxidative stress, significantly ↑ in both 7 and 16 months old WD-fed animals = protein expression level of claudin-5, two tight junction proteins, WD-fed animals, in vs. to SD-fed littermates.

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
53	NR	NR	=Aβ40 and Aβ42 levels in the cortex HFD vs. SD. CAA deposition was $\uparrow$ in >25 and $\leq$50 μm vessels in HFD vs. SD $\uparrow$ amyloid plaque burden by 28 weeks of age HFD vs. SD $\uparrow$ the number of new amyloid plaques increased in when compared with the rest of the groups in the long term HFD vs. SD	NR	$\uparrow$ oxidative stress associated with amyloid plaques was significantly higher in AD/WD mice $\uparrow$ MMP (metalloproteinases) activity in AD/WD = oxidative stress or MMP activity were analyzed in association with CAA in mice fed WD. 8-OHdG was increased in AD colony used to study the effect of prediabetes
77	NR	NR	At 9 months of age, i.e., prior to plaque deposition: $\uparrow$ Insoluble Aβ40 $\uparrow$ soluble and insoluble Aβ42 cerebral Cx HFD vs. SD $\uparrow$ levels of Aβ42 hippocampus HFD vs. SD At 15 months of age: $\uparrow$ the levels of insoluble Aβ42 in neocortices HFD vs. SD $\uparrow$ amyloid deposition in Cx and Hippocampus HFD vs. SD At 18 months of age: $\uparrow$ amyloid deposition in Cx of HFD vs. SD	NR	NR
96	NR	Neuroinflammation $\uparrow$ GFAP expression HFD vs. SD $\uparrow$ TNF-α expression HFD vs. SD	= tau phosphorylation HFD vs. SD $\uparrow$ insoluble Aβ1-40 HFD vs. SD. $\uparrow$ soluble Aβ1-42 HFD vs. SD = insoluble Aβ1-42 HFD vs. SD = ratio of total Aβ1-42/1-40 HFD vs. SD $\uparrow$ RAGE in hippocampus HFD vs. SD $\uparrow$ Aβ deposits in HFD vs. SD $\uparrow$ p-Tau in HFD vs. SD $\uparrow$ Parenchymal CAA burden	Locomotor activity $\downarrow$ exploration in HFD males vs. SD $\downarrow$ activity in HFD vs. SD Two trial Y-maze $\downarrow$ percent time spent in the novel arm in HFD vs. SD $\downarrow$ memory retention at 12 months HFD vs. SD Contextual fear conditioning test $\downarrow$ freezing time in HFD vs. SD	NR
97	NR	Neuroinflammation $\uparrow$ cerebral blood vessel permeability in the cortex of HFD vs. SD $\uparrow$ GFAP in the pyramidal layer and subiculum of HFD vs. SD			- $\uparrow$ ROS and $\downarrow$ GSH in the brain tissues of HFD vs. SD - $\uparrow$ endostatin in brain tissues HFD vs. SD

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
68	NR	NR	= levels of A β 40 and A β 42 in the T-PER fractions of the hippocampus in APPKINL-G-F/NL-G-F HFD vs. SD	Open field, passive avoidance test, the water T maze test, and elevated plus maze = hippocampus-related behaviors HFD vs. SD	NR
69	NR	↑ GFAP (astrogliosis) in the hippocampal brain region HFD vs. SD ↑ Iba1 signals HFD vs. SD ↓ CD68 levels HFD vs. SD	↑ hippocampal full length APP and APP-CTFS levels in 4-month-old HFD vs. SD hippocampal accelerated formation of Aβ plaques in 8-month-old 16-month-old HFD vs. SD	NR	NR
54	NR	↓ Presynaptic proteins (synaptotagmin, synaptophysin, and synapsin-1) in HFD vs. SD ↑ pro-inflammatory proteins, including COX2 and iNOS, in the hippocampus of HFD vs. SD	↑ Aβ plaque in HFD vs. SD ↑ soluble Aβ1–40 level in HFD vs. SD ↑ soluble Aβ1–42 level in HFD vs. SD	BM ↓ Spatial learning and memory in HFD-fed mice compared to SD	NR
60	NR	Iba1, thioflavin and BAN50+ ↑ HFD vs. SD	A β in somatosensory cortex and hippocampus immunofluorescence staining targeting A β 1–16: ↑ HFD vs. SD	NR	NR
78	NR	NR	↑ Aβ immunoreactive sp-like structures and neurons only in temporal cortex and superior cortex HFD vs. SD	NR	= SOD, glutathione peroxidase (GpX) and Ceruloplasmin HFD vs. SD
55	NR	Peripheral inflammation status and central neuroinflammation ↑ in HSD vs. SD	↑ HSD cortical levels of soluble and insoluble Aβ1–40 and Aβ1–42 HSD vs. SD	attenuation of locomotion HSD vs. SD altered food-entrainable HSD vs. SD circadian rhythms during NF ↑ noncognitive impairment in HSD vs. SD	↑ IL-6 and interleukin 1b present in HSD vs. SD

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
26	NR	NR	↑ Aβ plaques in the somatosensory cortex of HCHF vs. SD cerebral amyloid angiopathy↑ HCHF vs. SD plaque-associated tau inclusions ↑ SsCx HCHF vs. SD	NR	NR
56	NR	NR	Aβ plaques ↓(%Aβ area, Cx, Hip whole brain, if diet starts at 1 m,3 m) ↑ (whole brain if diet starts at 6 m) HFD vs. SD	NOR training day = HFD vs. SD Object recognition = HFD vs. SD Response to Novelty↑ HFD vs. SD	NR
27	NR	Dysregulation of microglial population, endothelial cells, inhibitor neurons and excitatory neurons and oligodendrocytes HFD vs. SD	Soluble Aβ1-42 = in dorsal hippocampus HFD vs. SD	Fear conditioning ↑ HFD vs. SD Spatial working memory ↓ HFD vs. SD Arms entries = HFD vs. SD	NR
82	NR	NR	↑ Aβ hippocampal HFD vs. SD = Female Tau phosphorylation HFD vs. SD NR	↓ Y-maze task (SAB) HFD vs. SD NOR: ↓ HFD vs. SD NR	NR
83	OXPHOS expression = HFD vs. SD	NR	↑ hippocampal human and mouse tau phosphorylation at Ser214 and Ser396/Ser404 HFD vs. SD ↑ tau oligomerization. (tau species (100, 140 and 250 kDa were detected by PS396 tau) HFD vs. SD ↑ sarkosyl-insoluble transgenic and endogenous tau in HFD vs. SD	MWM, Y-maze spontaneous alteration task and elevated plus maze test: ↓ hippocampal function in HFD vs. SD	NR
14	NR	NR	↑ female soluble Aβ40 HFD vs. SD = Tau expression and phosphorylation HFD vs. SD	NOR =HFD vs. SD	NR
84	NR	NR			

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
70	NR	NR	=Soluble and insoluble A β 40 HFD vs. SD	MWM and anxiety $\uparrow$ HFD vs. SD	NR
58	NR	Microglia activation: number of IBA1 + and CD68 + cells around plaques in hippocampus $\uparrow$ WD vs. STD. (with strong correlation between the number of IBA1 + cells and amyloid- β plaque number in the hippocampus) $\uparrow$ microglia/monocytes in the entorhinal cortex surrounding plaque WD vs. SD	Amyloid deposition in the hippocampus $\uparrow$ in plaque number in WD vs. SD. A β 42 levels $\uparrow$ WD vs. SD	NR	NR
57	NR	NR	= A β levels (insoluble A β 1-40; A β 1-42; A β 42/40) in the cortex TWD vs. STD mice = tau expression and tau hyperphosphorylation TWD vs SD = APP holoprotein and CTF TWD vs. SD	= ambulatory distance (gross horizontal locomotion) and escape latency to reach the hidden platform MWM:= STD vs. TWD	NR
59	NR	$\uparrow$ microglia activation	NR	HFD $\uparrow$ cognitive impairments	NR
71	NR	NR	$\uparrow$ Insoluble A β 1-40 and A β 1-42 peptide and = APPHoloprotein content in the hippocampal formation of 9-month-old HFD vs. SD $\uparrow$ in cerebral cortical amyloid plaque burden HFD vs. SD $\uparrow$ cerebral cortical amyloid plaque volume HFD vs. SD	MWM: 9-month $\downarrow$ spatial learning and $\uparrow$ latencies throughout testing HFD vs. SD	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
85	NR	NR	A β 40 $\uparrow$ parietotemporal cortex HFD vs. SD A β 42 $\uparrow$ parietotemporal cortex HFD vs. SD = App, α and β -APP carboxy terminal fragment, oligomers Cortical detergent-insoluble A β 42/40 ratio = HFD vs. SD Total tau protein $\uparrow$ HFD vs. SD Phosphorylated tau protein = HFD vs. SD	NR	NR
98	NR	Neuroinflammation: gene expression IL-6, IL-10, IL-14, IL-1RN, TNF- α and IL-1 β : $\uparrow$ HFD vs. SD	APP and phospho-tau (Thr231) levels: = HFD vs. SD	Y-maze: =HFD vs. SDFear conditioning: Contextual fear: $\downarrow$ HFD vs. SD Post-tone freezing: $\downarrow$ HFD vs. SD SDMWM: time in quadrant: = HFD vs. SD SDplatform crosses: =HFD vs. SD Locomotor activity $\uparrow$ HFD vs. SD Y-maze test $\uparrow$ HFD vs. SD NOR test = HFD vs. SD	NR
86	Mitochondrial dysfunction with high-resolution respirometry (HRR): HFD vs. SD=	NR	NR		

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
87	Number of mitochondria: in any of the group's number of mitochondria in the capillary endothelium of the hippocampus and cortex = Mitochondria abnormalities: ↑hippocampal mitochondrial abnormalities and empty spaces HFD vs. SD	Synaptic density = HFD vs. SD	NR	Odor recognition test = HFD vs. SD Y-maze = HFD vs. SD	NR
61	NR	Neuroinflammation: TSPO-PET tracer [18F]GE-180 ↑ WD vs. SD	NR	NR	NR
72	NR	↑ expression of inflammatory/ phagocytosis-related genes in male mice (IL-6) HFD vs. SD ↑ IL-6, IL-12β, TNFα, CD36, IRAK4, PYRY6 Female HFD vs. SD	NR	motor activity HFD = SD motor activity and ↑ time in the periphery in the open field ↓ HFD vs. SD	NR
80	NR	NR	↑ male and female solubilizable Aβ42 levels HFD vs. SD = male and female solubilizable Aβ40 levels HFD vs. SD Aβ40 and Aβ42 ↑ in females than males HFD vs. SD = between diet and sex for either solubilizable Aβ40 or solubilizable Aβ42 HFD vs. SD = plaque density HFD vs. SD	NR	NR
88	NR	NR	NR	NOR ↓ HFD vs. SD ↑ impaired performance HFD vs. SD. MWM = HFD vs. SD. Time spent floating = HFD vs. SD	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
89	NR	NR	A β and p-Tau pathology = HFD vs. SD	MWM test ↑ training days HFD vs. SD ↑ memory impairment HFD vs. SD Y-maze test: ↓ spontaneous alternation percentage HFD vs. SD NOR: = male and female HFD vs. SD Barnes Maze: = male and female HFD vs. SD Open field: male HFD = SD, time in the corner and time in the center ↑ female HFD vs. SD Distance traveled: male and female ↓ HFD vs. SD Y-Maze Test At 14 months ↓ of total arm entries, total distance, speed and zone transition in HFD vs. SD	↓ antioxidant defense system (p-Nrf2, p-AKT, HO-1, MnSOD) HFD vs. SD
99	NR	Glia activation: CA1 so: ↑ female HFD vs. SD Neuroinflammation: IL-1 α and TNF- α : ↑ female HFD vs. SD, IL-17 ↑ male and female HFD vs. SD, MCP-1, RANTES and MP-1b ↑ female HFD vs. SD, Eotaxin ↑ male and female HFD vs. SD	A β : = HFD vs. SD		NR
90	NR	At 8 months ↑ leptin and resistin in HFD vs. SD At 14 months ↑ leptin, TNF-alpha and resistin levels in HFD vs. SD	NR		NR
76	NR	↓ in synaptophysin levels in the hippocampus WD vs. SD	immunohistochemical staining for A β peptides and A β oligomers ↑ in neurons in the cortex and in the hippocampal CA3 region WD vs. SD. hypercholesterolemia accelerated accumulation of intraneuronal A β oligomers The levels of soluble A β 1-40 and A β 1-42 ↑ WD vs. STD ↑ of phosphorylated tau in hippocampal Mossy fibers at 6 months of age WD vs. SD.	MWM (6 months) ↓ in performance with longer escape latencies in the memory acquisition HFD vs. SD ↓ time occupancy in the target quadrant in the probe HFD vs. SD	NR

(continued)

Table 2. Continued.

Reference	Mitochondrial dysfunction	Synaptic/Neuroinflammation	Amyloid/Tau expression	Behavioral/ cognitive impairment	Oxidative stress
91	NR	NR	9-month ↑ soluble Aβ40 and Aβ42, soluble/insoluble Aβ42 ratio in Cx HFD vs. SD 9-month = amyloid plaques load, APP holoprotein and soluble α-APP HFD vs. SD	NOR Recognition Index: ↓ HFD vs. SD BM time to find the exit zone ↑ HFD vs. SD in voluntary locomotor activity = HFD vs. SD anxiety-like behavior = HFD vs. SD NR HFD = SD MWM HFD = SD NR HFD < SD Elevated plus maze (anxiety evaluation) HFD > SD MWM ↑ escape latency, ↓ target platform traversals and ↓ exploration time within the target quadrant HFD vs. SD	NR
100	NR	NR	NR	NR	NR
101	NR	IBA1 and GFAP HFD > SD TPSO HFD > SD	NR	NR	NR
28	NR	NR	NR	NR	NR

SD: standard diet, HCHF: high carbohydrates and high fat diet, HFD: high fat diet, HCD: high-cholesterol diet, WD: western diet, SFA: saturated fatty acid; MUFAs: multiple unsaturated fatty acids; PUFAs: polyunsaturated fatty acids, LFD: low fat diet, NOR: Novel object recognition; MWM: Morris Water Maze; NOL: novel object localization; OF: open field test; BM: Barnes maze test; TSPO: translocator protein; NR: not reported; CA Iso: cornu ammonis I; DGpo: polymorphic layer of the dentate gyrus.

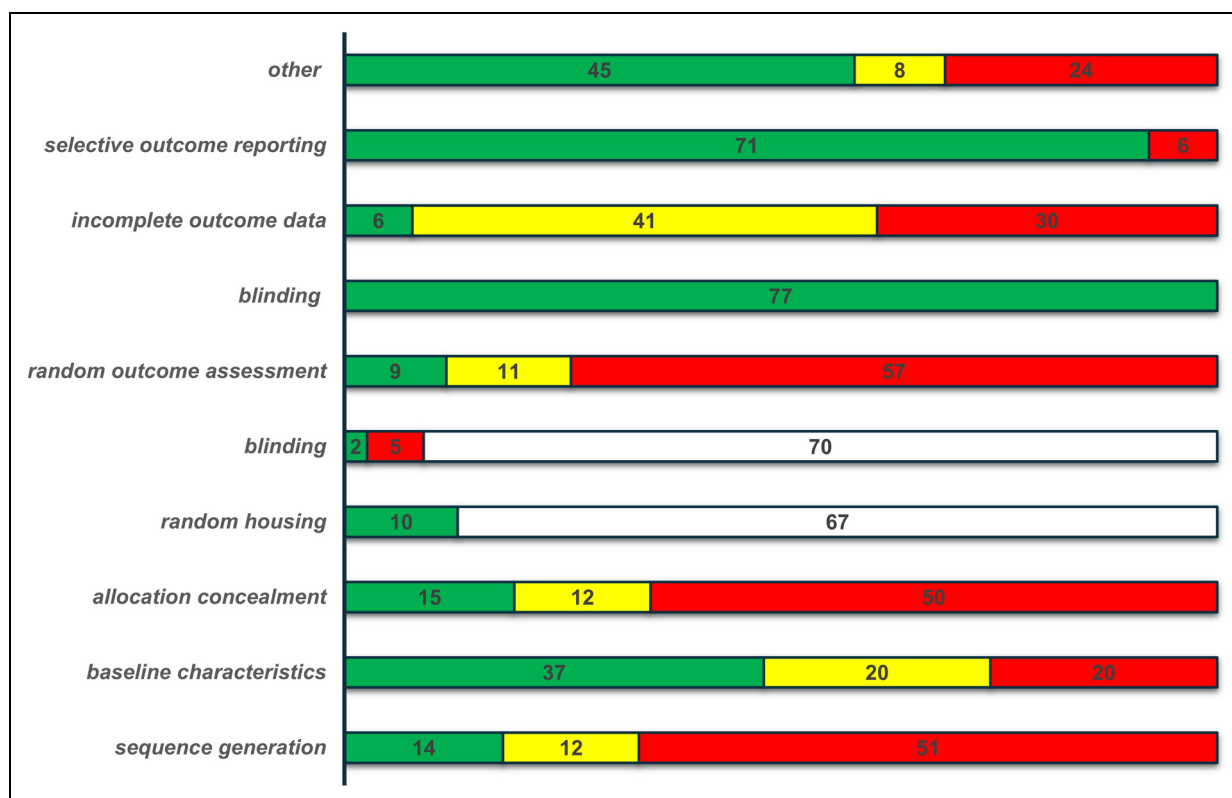


Figure 2. Risk of bias included studies (n = 72). Summary of scores for each domain for each included study. Green indicates a low risk of bias, yellow indicates an unclear risk of bias, red indicates a high risk of bias, while white indicates that the item was not applicable.

Effects of hypercaloric diet

Behavioral and cognitive impairment. To evaluate the impact of HD on cognitive functions in AD animal models, most included studies employed standardized behavioral tests such as the Morris Water Maze (MWM), Y-maze, Barnes Maze, and Novel Object Recognition (NOR), which assess spatial learning, memory, and exploratory behavior. Regarding cognitive functions, our semi-quantitative synthesis shows that approximately 50% of the studies employing the MWM reported significant learning and memory impairments in HD-fed animals compared to those on SD. Conversely, the remaining 50% of the studies included failed to detect significant differences between groups, highlighting a high degree of heterogeneity in behavioral responses. Approximately half of the studies using the MWM reported significant impairments in HD-fed animals compared to those on a SD, including longer escape latencies, reduced time spent in the target quadrant, and greater distances traveled, indicating deficits in spatial learning and memory.^{14,28,32,35,36,47,62,70,71,76,89,98,101} Similar trends were observed in Y-maze tests, where HD-fed animals exhibited lower spontaneous alternation rates and less time in the novel arm, suggesting compromised working memory and only one study⁸³ did not perform this behavioral test. The NOR test was performed in about 18% of the studies. Five

studies reported poorer object recognition in HD-fed animals,^{15,30,34,45,84} while four^{32,56,82,96} found no significant differences. Barnes Maze results were consistent with these findings: animals on HD generally required more time to locate the escape zone, confirming spatial memory deficits except for⁸⁷ and⁹⁶ found no differences between groups in locomotor activity while⁹⁶ showed a worsening in anxiety-like behavior. Despite these observations, nearly 50% of the studies did not detect significant differences between HD and SD groups. This variability may reflect differences in diet composition, duration of exposure, age at intervention onset, strain susceptibility, and the frequent lack of sex-stratified analyses. Notably, a few studies even reported improvements in specific cognitive domains, suggesting that the effects of HD are context dependent. Animal models demonstrated varying degrees of vulnerability to dietary triggers. APP/PS1 and 3xTg-AD models proved most sensitive, with 61.1% and 69.2% of studies respectively reporting significant pathological exacerbation. In contrast, models with a single mutation (e.g., APP Swedish) showed lower reactivity (37.5%), often requiring more extreme dietary protocols or longer durations to manifest comparable AD-like hallmarks. Indeed, this differential sensitivity is further modulated by dietary composition; specifically, our findings indicate that WD, which combines high fat with purified carbohydrates, act as more potent drivers of cognitive and pathological

decline compared to pure HFD, triggering deficits in 65% versus 48% of relevant studies, respectively.

Amyloid and tau burden

The impact of hypercaloric diets on A β or tau pathology was a primary focus in 75.3% of the included studies. Within this group, an increase in the insoluble fraction of the A β _{1–40} fragment was documented in 59.1% of the studies reporting this specific outcome. In contrast, the effects on tau pathology were less consistent, with only 33.3% of the relevant studies reporting a significant increase in tau phosphorylation. Overall, 58 studies investigated A β or tau pathology in mouse models^{14,15,25–27,29–43,45,47–49,51–58,60–65,68–71,73,75,76,78,80,81,85,87,88,90,91,93,95,97,98,100,101} and 3 studies investigated them in rat models.^{25,26} Out of these, 23 studies provided results on possible variations of A β _{1–40} peptide levels in its soluble fraction^{29,31,34,35,41,48,51,53–55,62,64,76,80,81,87,91,95,97,98,100,101} and 22 studies provided results on its insoluble fraction^{29,31,34,41,47–49,51,53,55,57,62,64,65,71,73,76,81,87,91,97}. Overall, 12 studies reported a significant increase in soluble A β _{1–40},^{29,31,34,35,41,48,54,55,62,76,80,87} while 11 studies reported no variations^{51,53,61,64,67,81,91,95,97,98,100} and 1 study reported a significant reduction in soluble A β _{1–40}.³⁰ Thirteen studies reported a significant increase in the concentration of the insoluble form of the A β _{1–40} fragment,^{29,31,34,49,55,62,64,65,67,71,81,91,97} one study reported a reduction in its concentration,⁴¹ and 8 studies reported no variations.^{47,48,51,53,57,73,76,87} A comprehensive analysis of brain A β _{1–42} peptide expression in relation to HD exposure was performed in 34 studies.^{15,27,29–31,33,35,36,41,45,47–49,51,53–55,57,58,62,64,65,67,70,71,73,76,81,87,91,95,97,98,100} Of these, 25 reported data on the presence of the peptide in its soluble fraction^{15,27,29,30,32,33,35,41,48,51,53–55,62,64,67,70,76,81,87,91,95,97,98,100} and 25 reported data on its insoluble fraction^{15,27,29–31,33,35,41,48,51,53,55,62,64,67,70,76,81,87,91,95,97,98,100}. Twelve studies observed an increase in soluble A β _{1–42},^{30,35,41,48,54,55,62,76,87,91,95,97} while 13 observed no significant changes in time.^{15,27,29,31,33,51,53,64,67,70,81,98,100} When considering the insoluble fraction, 12 studies reported an increase in A β _{1–42} levels,^{31,45,47,49,55,58,62,64,65,71,81,97} one study reported a decrease in A β _{1–42} levels,⁴¹ and 13 studies reported no variation in time.^{29,36,48,51,53,57,67,70,73,76,87,91} Only one study observed an increase in the A β _{42/40} ratio because after exposure to HD,³⁰ while four studies reported no significant changes over time.^{57,87,91,98} One study that investigated the effects of WD reported a significant increase in A β _{1–34} and A β _{1–38} protein levels over time.⁴⁹ However, previous findings reported no changes in A β _{1–38} concentrations over time.⁶⁴ Conversely, one study reported that mice exposed to a high-fat diet showed significantly lower concentration of total A β .⁵⁶ Overall, 41 studies reported results from morphometric analyses of amyloid accumulation in brain

tissue,^{15,25,26,29–32,34–43,45,48,53,54,56,58,60,62–65,67,69,71,73,76,78,87,88,90,93,97,98,101} specifically in the cortex^{15,26,29–32,34,35,37,39–43,45,48,53,56,58,62,64,71,87,97,98}, hippocampus,^{15,29,34–37,40–42,45,48,54,56,58,62–65,67,71,78,97,98,101} striatum,²⁶ or more generally in either composite areas (cortex plus hippocampus),^{60,90} or in the whole brain.^{25,37,73,88,95} The overall presence of amyloid plaques in the cortex of animals fed a HD was measured in terms of amyloid burden, number of plaques, plaque density, percentage of cortex area covered, percentage of cortex volume. Sixteen studies reported a statistically significant increase in the area of immunoreactivity and plaque size,^{26,29–32,34,39,40,42,43,48,53,62,64,71,97} 8 studies reported no change in the same outcomes,^{15,35,37,41,45,58,87,98} and one study reported a statistically significant decrease in the same outcomes.⁵⁶ Dietary duration emerges as a critical factor for proteinopathy development: long-term exposure, exceeding 6 months, was required to observe a significant increase in insoluble A β _{1–40} in 59.1% of the studies. This confirms that advanced amyloid accumulation is a chronic process strictly dependent on the length of exposure. Thirteen studies reported an increase in amyloid burden or plaques within the hippocampus in animals fed a HD,^{29,34,37,54,58,62,64,66,67,71,78,97,101} while 11 studies reported no significant changes in time.^{15,35,36,40–42,45,48,56,63,98} However, one study among the latter group reported results from two different transgenic models that showed an increase in hippocampal amyloid load after a HD.⁹⁸ One study reported a gender-specific response, with an higher presence of both diffuse and fibrillar amyloid plaques in the cortex and hippocampus exclusively in female mice.⁹⁰ Another study analyzed the striatum in rats and found no significant diet-induced changes in amyloid deposition.²⁶ A similar result was observed in three studies that analyzed the whole brain.^{25,38,95} In contrast, one study showed an increase in amyloid deposition in whole brain slices.⁴⁹ Similarly, another study reported an 5-months earlier onset of A β plaques in animals fed a HD diet compared to controls.⁶⁹ Another study showed that intraneuronal A β oligomers accumulation started about two months earlier in both the hippocampus and cortex of two different transgenic models.⁷⁶ An increase in A β among the total number of immunoreactive neurons was observed in the cortex⁹³ and in the hippocampus⁷³ of animals fed with HFD. Since amyloid peptides are derived from the secretory processing of the APP holoprotein, several authors have analyzed APP expression profiles in brain tissue following high-fat diet administration. Specifically, four studies showed an increase in APP expression,^{31,35,69,71} whereas six studies found no significant differences.^{49,57,75,81,87,90} The analysis of APP transcripts largely confirmed previous observations, with one study reporting an increase in one article³¹ and another reporting no changes.³² Some studies further investigated into the molecular mechanism underlying APP processing, with four reporting an accumulation of APP CTF β ^{49,65,69,81,87,101} whereas no significant differences in

expression levels were observed in others.^{81,87} The expression of APP CTF α was reported as increased in,⁶⁷ while in⁴⁹ was decreased or unchanged in.⁸¹ One study analyzed the expression of soluble α -APP and found no variations associated with HD administration.⁸¹ The relationship between HD and tau pathology has been extensively investigated by several researchers. Results from five studies showed no alterations in tau protein expression levels.^{31,42,57,80,88} However, one study observed an increase in both the soluble and insoluble fractions of this protein. Included studies predominantly focused on tau phosphorylation.⁸¹ Five studies reported an increase in tau phosphorylation^{14,40,42,76,100} while ten studies reported no significant variations.^{31,34,45,48,57,78,80,81,85,91} The most investigated phospho-epitopes were Ser202, Thr205 (detected using antibodies AT8, CP13, 44738G), with one study reporting an increase in phosphorylation⁴² and six studies reporting no changes in animals fed HD.^{31,48,57,80,81,94} Similarly, for Ser396 and Ser404 (detected using antibodies PHF1,44752G, 44748G), three studies reported an increase in their expression levels,^{14,40,76} and four studies reported no changes.^{31,45,80,81} A single study that quantified the tau isoforms associated with the number of tubulin-binding repeats reported a significant increase in mRNA and protein levels of 3R-tau, 4R-tau and 3R-tau/4R-tau ratio.⁵²

Neuroinflammation and synaptic plasticity state.

Neuroinflammation is well-known to play a critical role in the pathogenesis of AD, a process that might be exacerbated by HD. Neuroinflammation is typically mediated by the activation of glial cells, such as microglia and astrocytes, with subsequent production of pro-inflammatory cytokines, chemokines, ultimately contributing to synaptic dysfunction and neuronal loss.^{102–104} Neuroinflammation was explicitly investigated in 50.6% of the systematic review's corpus. Among these, 51.3% provided clear evidence of microgliosis and/or astrogliosis in regions such as the cortex and hippocampus, while 15.4% reported no significant neuroinflammatory changes associated with the diet. Among the 76 studies included in this systematic review, 39 specifically investigated the effects of HD on neuroinflammation in AD mouse models, while the remaining 33 primarily focused on amyloid/tau expression and behavioral testing, as previously described.^{14,35,37,38,44,45,47,49,51,53,56,64–67,70,71,74,75,79,80,82,84–87,90,93–95,97,100,101}

Specifically, 20 studies reported evidence of microgliosis (Iba1+) and/or astrogliosis (GFAP+, OX-6+) in several brain regions, including the cortex and hippocampus.^{25,27,32,36,39,42,48,50,55,58–60,69,73,74,77,81,91,94,100}

Interestingly, two studies^{69,94} observed higher levels of neuroinflammation, but lower levels of CD68 levels, a marker of microglia phagocytic activity, in the hippocampus of mice fed a HD compared to mice on a standard diet. These findings suggest that HD might impair the ability of microglia to phagocytose A β deposits.⁶⁹

Furthermore, one study⁷⁷ observed gender differences in hypothalamic gliosis, with higher astrogliosis observed only in female mice fed an HD.⁷⁷ Conversely, four studies reported a lower gliosis in AD mice after HD administration, suggesting that this type of diet might reduce inflammation in some AD mouse models.^{26,40,90,98} Metabolic and inflammatory shifts appear to occur early in the disease progression. Indeed, short-term interventions, less than 8 weeks, primarily induced neuroinflammation in 51.3% of relevant studies, often preceding over amyloid deposition. Several studies also assessed the release of one or more pro-inflammatory cytokines, such as TNF α and interleukins in brain tissue. Eight studies reported higher levels of these cytokines in the cortex and hippocampus of mice fed HD compared to those on a standard diet^{39,46,54,60,62,88,91,96} while five studies reported lower levels of the same cytokines in animals on HD compared to controls.^{26,33,41,52,80} Notably, one study observed an increase in IL-6 specifically in male mice and a decrease in IL-6 and TNF α mRNA levels in females mice on HD compared to those on a standard diet.⁷² One study found a significant decrease in cortical TNF-alpha, COX2, and IL-6 mRNA expression but an increase in iNOS (a pro-inflammatory protein) mRNA expression in mice on HD compared to standard diet.⁴¹ Six studies reported no significant changes in neuroinflammation between the two groups, both in terms of gliosis and in the levels of pro-inflammatory cytokines.^{29–31,46,57,63} However, one study reported an isolated increase in TNF α , with no corresponding changes in IL-6, IL-1 β , and TGF α levels.⁴⁶ To explore potential associations between this selective increase and other neuroinflammatory factors, the study also assessed transcript levels of astrocyte, macrophages, and adhesion cell markers, but found no significant differences between groups.⁴⁶ To further investigate the molecular mechanism underlying the worsening of cognitive decline observed in AD mice on HD, six studies investigated synaptic plasticity, by focusing on synapse-associated proteins and synaptic density. Five of these studies reported a significant decrease in presynaptic proteins (Synapsin-1, Synaptophysin, etc.) in mice fed HD,^{15,34,54,81} while one study reported no significant alterations in synaptic density in both the cortex and hippocampus of AD mice, suggesting that the effects of HD on synaptic integrity may be model- or context-dependent.⁸³

Mitochondrial dysfunction. Mitochondria are known to be the powerhouse of the cell, as they can produce large quantities of ATP, which has the role of transporting and providing cells with the energy necessary for their functioning.¹⁰⁴ Mitochondrial dysfunction and bioenergetic crisis have been suggested to play a crucial role in the pathophysiology of neurodegenerative disease, including AD.¹⁰⁵ Overall, only 5 studies explicitly focused on the potential interrelation between mitochondria status, HD diet, and dementia. One study investigated the potential relationship

between neuropathological A β plaque formation in the hippocampus and obesity at an early presymptomatic disease stage in APP/PS1 mice.³¹ The authors reported an almost 50% decrease in the levels of peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1 α), a member of a family of transcription coactivators that plays a central role in the regulation of cellular energy metabolism, in the hippocampus of APP/PS1 mice fed with HD, suggesting a possible involvement of this protein in both mitochondrial biogenesis alterations and metabolic function. However, the study observed no alterations in downstream effectors of PGC-1 α , such as nuclear respiratory factors 1 (NRF1) and 2 (NRF2). Another study investigated the potential effects of HD on the OXPHOS enzymatic system, mRNAs, and protein levels of molecules associated with mitochondrial energy status and biogenesis in APP/PS1 transgenic mice.⁴⁵ The authors reported a significant decrease in mitochondrial OXPHOS metabolism in the hippocampus of animals on HD. Moreover, when considering the APP/PS1 mice group, small but statistically significant differences were observed in the mRNA expression of NRF1 and NRF2 between mice on HD compared to mice on standard diet. Two studies investigated the potential effects of HD in 3xTgAD mice. One study assessed the potential effects of HD on mitochondrial respiration in intact hippocampal slices from 3xTgAD mice.⁸² The study reported a small impact of the AD genotype on overall oxygen consumption rates (OCR), but a 25% increase in basal OCR in the 3xTgAD mice on standard diet. However, a significant decrease in basal and maximal OCR levels was observed to be 3xTgAD mice on HD, showing a significant impact of HD on tissue OCR. These results suggested that an 8-week HD could significantly compromise mitochondrial function in the hippocampus. One study investigated endothelial and neuronal mitochondria number and morphology along with synaptic density using transmission electron microscopy in the subiculum area of the hippocampal formation and in the cortex of 8-months-old mice, thus at a stage before amyloid plaque pathology is observable.⁸² Results showed no changes in the number of mitochondria in the hippocampus and cortex in 3xTgAD mice regardless of the type of diet. However, 3xTgAD mice on HD showed a higher percentage of elongated mitochondria (~38%, $p < 0.05$ versus SD) in the hippocampus but not in the cortex. Moreover, data also showed severe morphological alterations in the mitochondria in the hippocampus of 3xTgAD mice on HD, including enlarged, swollen, and/or absent cristae, and less dense or empty matrix. Another study investigated the effects of a 3-month HD diet on APP23 transgenic mice in terms of amyloid deposition and cognitive functions.⁹⁰ Since the phospholipid composition of cellular membranes is extremely important for cell signaling, including apoptosis and phagocytosis the study carried out a specific analysis of the brain lipidomic

profile. In this context, the most significant changes observed in response to HD were associated with cardiolipin (CL) a major phospholipid of the inner mitochondrial membrane. A wide imbalance between CL and other phospholipids, such as phosphatidylinositol biphosphate and phosphatidyl triphosphate, was observed in the brain lipids of APP23 mice on HD. This imbalance was closely related to mitochondrial dysfunction,¹⁰⁶ characterized by a different and significant modulation of several genes associated with mitochondria components.

Oxidative stress. Oxidative stress (OS) is also reported as having a relevant role in the pathogenesis of neurodegenerative diseases of the central nervous system (CNS), AD, and Parkinson's disease.⁹² An increasing number of studies suggested that diets rich in saturated fats and/or refined sugars might activate pro-inflammatory pathways that can result in the production of reactive oxygen species (ROS), and initiate a process of neurodegeneration.^{92,107} However, the potential role of HD in modulating OS in neurodegenerative disorders remains unclear. To attempt to clarify whether a direct correlation exists between HD and OS, we included in this systematic review studies that specifically investigated the effects of HD on this specific outcome. Only 11.7% of the studies analyzed OS. Only nine of the included studies analyzed the impact of different HD on OS. Of these, eight studies used APP/PS1 mice models of AD, while one study used 3xTgAD mice.⁸⁵ Results from all studies consistently reported an association, regardless of the type of mouse model used, between HD and OS and antioxidant defense mechanisms. One study reported higher levels of ROS and endostatin expression in the brain of mice fed with HD, along with a significant decrease in glutathione (GSH).¹⁰⁰ Similarly, two other studies reported a decreased expression of several proteins involved in antioxidant response mechanisms (Nrf2, MnSOD, HO-1) and a burst of ROS.^{46,85} One study investigated the mRNA hepatic expression of antioxidant defense enzymes in APP/PS1 mice fed with high cholesterol diet.⁴⁶ The study reported a decrease in SOD1, SOD2 and NOX4 mRNA levels along with an overexpression of the HO-1 and NOX2 genes. These results were not consistent with results from another study, likely due to differences in the dietary composition and the specific animal model selected.⁸⁵ Only one study reported that HD induced prediabetes in AD mice, along with an increase in OS, higher metalloproteinase activity, and amyloid plaques deposition.⁵³ In addition, the study evaluated the deposition of A β plaques around arterioles, a condition known as cerebral amyloid angiopathy.⁵³ Results showed a significantly higher frequency of cerebral amyloid angiopathy in mice on HD, suggesting a disruption of antioxidant defense pathways in the AD brain. Two studies investigated the impact of HD on lipid peroxidation and protein oxidation in APP mouse models. While one of the studies observed no

significant differences between HD and standard diet,³¹ the other study reported higher levels of lipid hydroperoxides and protein nitrosylation in animals on HD compared to standard diet.⁵¹ These findings are consistent with other studies on mice models suggesting that HD might induce the accumulation of potentially toxic products that may promote neuronal stress.¹⁰⁸ The complex mechanistic pathways linking hypercaloric dietary triggers to metabolic stress, neuroinflammation, and the subsequent exacerbation of AD pathological hallmarks are visually summarized in the Infographic.

Discussion

Results from the studies included suggested that the exposure to HDs in transgenic animal models of AD is frequently associated with a decline in cognitive functions and an increase in the misfolding of A β and tau proteins, along with neuroinflammation, mitochondrial dysfunction, and OS. Our findings align with human epidemiological data linking WD to AD risk, although structural differences in rodent metabolism and the use of familial mutations limit direct translation. Nevertheless, the early onset of diet-induced neuroinflammation suggests that managing metabolic health represents a key non-pharmacological “window of opportunity” for human AD prevention. However, these findings should be interpreted taking into due consideration the substantial heterogeneity across studies in terms of experimental design, dietary composition, type of animal model, and methodological quality. A quantitative analysis of data through meta-analyses should be useful but was not feasible mainly due to this heterogeneity and lack of quantitative data of the outcome considered. Most studies investigating behavioral outcomes reported that mice on HDs had worse performances in learning and memory tasks, especially in spatial navigation tasks such as MWM and Y-maze. However, nearly half of the studies included found no significant differences between animals on HD and SD. This discrepancy may be due to the heterogeneity observed in the duration of dietary intervention, the age at the beginning of the intervention, and the strain susceptibility. Notably, studies using diets with higher saturated fat content and longer duration of the intervention were more likely to report a negative effect of the diet on cognitive functions, indicating that both the dose and the length of exposure may play a relevant role. The observed heterogeneity in AD-like hallmarks is strictly modulated by experimental variables: specifically, APP/PS1 (61.1%) and 3xTg-AD (69.2%) models demonstrate significantly higher sensitivity to dietary manipulation than single transgenic strains (37.5%). Furthermore, while WD induce cognitive decline more consistently (65%) than pure HFD (48%), the progression of proteinopathy remains duration-dependent, with chronic exposure (>6 months) being a fundamental requirement for the

accumulation of insoluble A β_{1-40} in 59.1% of studies. However, some studies present conflicting evidence, reporting even an improvement at the behavioral level. The causes for these discrepancies are likely diverse, including the duration of the diet, the specific animal model employed, the sex of the animals, and other factors such as genetic background and the precise nutritional composition of the diet as indicated in a recent study.¹⁰⁹ A key question emerging from our synthesis is whether diet-induced obesity and the resulting metabolic phenotype are mandatory prerequisites for the exacerbation of AD. Our analysis suggests that while severe cognitive impairment and amyloid deposition are often strongly correlated with significant weight gain and insulin resistance, obesity is not an absolute requirement for neurodegeneration. In several included studies, even short-term exposure to HD triggered neuroinflammatory markers and mitochondrial dysfunction prior to the onset of a full metabolic syndrome or overt obesity. This indicates that the nutritional composition of the diet may exert direct neurotoxic effects, likely through increased blood-brain barrier permeability and OS, independent of the systemic accumulation of adipose tissue. Therefore, while a metabolic phenotype characterized by obesity and insulin resistance acts as a potent accelerator of AD, the diet itself can initiate early pathological shifts regardless of the animal's final body weight. The divergence in cognitive outcomes (approximately 50% of studies reporting no significant impairment) is closely linked to diet composition. Our subgroup analysis reveals that WD, which combines fats and sugars, are more effective in triggering deficits (65% of cases) compared to pure HFD (48%). This suggests that the synergistic effect of saturated fats and purified carbohydrates is a more potent driver of synaptic dysfunction than lipid intake alone. When considering neuropathological markers, a significant number of studies reported higher levels of both soluble and insoluble A β_{1-40} and of A β_{1-42} in animals on HD, particularly in the cortex and hippocampus, which are involved in memory and cognitive processing. Similarly, higher tau phosphorylation at multiple phospho-epitopes (Ser202, Thr205, Ser396, Ser404) was observed in a subset of studies. However, several studies reported conflicting results, including no change in amyloid burden or even a lower amyloid burden, emphasizing how complex and context-dependent relationship can be between diet and neuropathology. Gender, genetic background, and gut microbiota composition could also be involved in modulating the response to dietary interventions. Neuroinflammation was also reported as a relevant mediator of brain pathology after HD. Several studies reported increased gliosis (microgliosis and astrogliosis) and higher levels of pro-inflammatory cytokines such as TNF- α and IL-6 in mice on HD. Interestingly, some studies showed the opposite effect or gender-specific patterns, with females showing higher vulnerability in some

instances. These findings suggest that the inflammatory response to HD may vary not only in relation to gender, but also in relation to brain region and may also change over time. Moreover, reductions in microglial phagocytic activity suggest a detrimental shift toward a dysfunctional immune phenotype that may impair A β clearance. Mitochondrial dysfunction was also frequently reported in animals after being fed with HD. HD was reported as being associated with impaired oxidative phosphorylation, lower expression of key regulatory factors such as PGC-1 α and TFAM, and the onset of structural abnormalities in hippocampal mitochondria. These alterations, particularly the loss of mitochondrial cristae integrity and the disruption of lipid composition such as cardiolipin imbalance, can indicate energy failure and a higher vulnerability to neurodegeneration. Some studies also reported a reduction in presynaptic markers such as synaptophysin, thus supporting the hypothesis that HD might contribute to synaptopathy even before the evident deposition of plaques.¹¹⁰ OS is consistently reported as having a relevant role in the neurodegenerative processes. Results from included studies confirmed that HD can increase ROS production, while impairing antioxidant defenses, including lower levels of Nrf2, MnSOD, and HO-1. Considering the central role of redox imbalance in triggering inflammatory and apoptotic cascades, future studies should systematically incorporate OS markers. A significant limitation of included studies was the underrepresentation of female animals, which may prevent the identification of potential gender-specific responses to diet.¹¹¹ Despite the consistently reported higher prevalence of AD in women, most studies relied exclusively on male mice or did not stratify data according to gender. This is a significant limitation considering the well-documented modulatory effects of estrogens on amyloid metabolism, tau phosphorylation, and mitochondrial function.¹⁰⁸ While a small number of studies highlighted gender-specific effects of HD, these were the exception rather than the norm. Future research should specifically consider gender as a biological variable and explore its interactions with hormonal status and *APOE* genotype. One critical issue raised by the data of this systematic review concerns the role of sex as a contributor to the observed heterogeneity and as a potential source of bias. The pronounced underrepresentation of female animals within the analyzed body of literature represents a significant methodological gap, hindering the identification of sex-specific responses to hypercaloric challenges. Given that sex acts as a pivotal biological modifier influencing amyloid metabolism, tau phosphorylation, and mitochondrial integrity, the predominance of male-only models (49.4%) and the lack of sex-stratified reporting limit the generalizability of the current evidence; thus, future research must systematically incorporate both sexes to accurately reflect the differential vulnerability observed in human AD pathology. The marked predominance of

male-only murine models, together with the frequent lack of sex-stratified analyses, limits the generalizability of the findings. As a result, the overall worsening of behavioral and pathological outcomes associated with hypercaloric diet exposure should be interpreted with caution, as it predominantly reflects evidence derived from male models. Importantly, the limited number of studies that included female animals and reported sex-specific outcomes suggests that the effects of a hypercaloric diet are not uniform across sexes. Both exacerbating and divergent effects were observed in female models, indicating that sex may act as a biological modifier rather than a simple confounder. These findings highlight the need for systematic inclusion of both sexes and for sex-disaggregated data reporting in future preclinical studies.

A significant result from our review was the low methodological quality of many of the included studies. Key aspects such as randomization, blinding, and transparency in the reporting of exclusions were inconsistently applied. Only 4.28% of the included studies explicitly reported having implemented a form of randomization,^{65,93,100} and even fewer studies provided details on the randomization procedures used. Moreover, blinding of outcome assessors was reported by only 20% of the studies, implying a substantial risk of bias that may affect the reliability of the reported results.^{15,25,26,29,30,36,44,47,70,77,80,83,94,100} A very small number of studies included clearly stated the number of animals excluded from the analyses, thus limiting the transparency and reproducibility. This lack of transparency affects the internal validity and the reproducibility of results, which is a critical issue often reported in preclinical research. However, some critical issues should be observed in relation to the checklist used in this systematic review to assess the quality of included studies, as some criteria cannot be uniformly applied or equally weighted across all experimental contexts. While the SYRCLE's RoB Tool is widely adopted for assessing internal validity in animal studies, some of its items may not be fully appropriate for all experimental designs, particularly in studies involving AD models fed specific types of diets.¹¹² Several domains, such as random housing and blinding of caregivers or investigators, are difficult to be consistently applied across preclinical studies where group allocation may not be feasible or clearly reported. Similarly, the domain assessing selective outcome reporting often requires accessing pre-registered protocols, which are uncommon in animal research. This limitation has been reported in literature, with recent studies¹¹² underlining that some SYRCLE items lack empirical validation within the context of animal research and may result in a high number of "Unclear" ratings due to poor reporting rather than actual methodological flaws. For this reason, our assessment adopted a conservative approach: we maintained all SYRCLE items to ensure comparability with previous reviews, but we explicitly marked domains such as

random housing and caregiver blinding as “Not applicable” when they were impossible to be applied due to the specific study design. This adjustment was aimed at preserving the interpretability of quality scores, while acknowledging the structural limitations of applying a clinical-oriented RoB framework to studies on animal models.¹¹³ In conclusion, while most studies focused on more common endpoints such as the accumulation of A β and tau, emerging areas such as the modulation of the gut-brain axis, neurovascular integrity, and brain connectivity remain largely unexplored in studies exploring the potential relation between HDs and AD. Moreover, few studies adopted a longitudinal design capable of distinguishing between the short- and long-term effects of the exposure to HD. The integration of multi-omics approaches, such as transcriptomic, lipidomic, metabolomic could provide a more comprehensive understanding of how HDs might influence the pathophysiology of AD. To increase their translational relevance and scientific robustness, future preclinical studies should standardize dietary protocols, such as fat type, cholesterol content, and duration of exposure, and ensure the inclusion of female mouse models. Additionally, research should explore novel endpoints, including neurovascular integrity. Despite many studies suggesting detrimental effects of HD on cognitive function and AD-related pathology in animal models, wide heterogeneity and several methodological flaws significantly limit the strength of these conclusions. A more rigorous and comprehensive approach is essential to clarify the complex relationship between nutrition and neurodegeneration, considering also gender-specific characteristics, that could provide an appropriate basis to guide future preventive and therapeutic strategies.

Acknowledgements

The authors have no acknowledgments to report.

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Ethical considerations

Not applicable

Consent to participate

Not applicable

Author contribution(s)

Elena Carbone: Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review & editing.

Sofia Scibetta: Data curation; Investigation; Software; Writing – original draft; Writing – review & editing.

Marisa Cappella: Data curation; Investigation; Validation; Writing – original draft.

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Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the European Union—Next Generation EU –PNRR M6C2—Investment 2.1 Enhancement and strengthening of biomedical research in the NHS, under the project identification number PNRR-MAD-2022-12375822, CUP I55E22000560006; Ministero della Salute.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

Further inquiries can be directed to the corresponding author.

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