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Milk – Metabolism – Proteostasis – Dementia

Transdisciplinary Full Work · Manuscript v3.7

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A research project by Thomas Schüller · Syntagma Forschung · Vienna

ID: FORSCH-PROV0445 · Status date: 20 Oct 2026 · Licence: CC BY 4.0

Status: hypothesis-generating synthesis, not peer-reviewed

Status note v3.7

Addendum of 20 Oct 2026 (PubMed reachable again): **PMID 40407926 (Lawrence 2025) and PMID 36386959 (Walther 2022) are confirmed by me** (number and title against PubMed; Walther: twelve authors, *Front Nutr* 2022;9:988707, PMID PMC9650290). **Calvo 2023**: a PubMed title search returns no hit; the journal appears not to be indexed in PubMed. No PMID is carried. The “200 ml/d” figure stays unconfirmed.

Status note v3.6

Verification round of 20 Oct 2026 (research report plus own browser check). **Lawrence 2025** is confirmed (Crossref: *Eur J Nutr* 2025;64(4):182, DOI 10.1007/s00394-025-03697-8, abstract read). **Correction to the statement “B12 and iodine, not calcium”**: the study models riboflavin, vitamin B12, iodine and protein; calcium was not modelled because the drinks were assumed to be calcium-fortified. It therefore does not show that calcium is unproblematic. It shows that where drinks are not fortified with riboflavin, B12 and iodine, the share with inadequate intake rises (example B12: older men from < 1 to 9 %, per the abstract). PMID 40407926 comes from the research report and is **not checked by me**. Walther 2022: PMID 36386959 per the report, **not checked by me**; Calvo 2023: no PMID found (PubMed was blocked, so this is no evidence of non-existence); the dose “200 ml/d” is **unconfirmed**. **Du 2026**: the sentence in the main text (“when replacing 20 g/d of high-fat cheese ... increased all-cause dementia risk was observed for milk, fermented milk, high-fat red meat, and processed meat (eFigure 4)”) was read in the PMC full text; the individual HRs in eFigure 4 remain unread. Li 2025: the “13 %” stays a secondary source.

Status note v3.4

Addendum of 20 Oct 2026: **Tessier 2024, Figure 2 (uncorrected version, PMC11074805), panel A, pooled**: olive oil instead of butter HR 1.00 (0.92–1.08); instead of other vegetable oils 1.02 (0.92–1.12); instead of margarine 0.92 (0.88–0.96); instead of mayonnaise 0.86 (0.80–0.93). NHS: butter 0.98 (0.89–1.08); HPFS: butter 1.05 (0.90–1.22). The values were read from a low-resolution image. The correction PMID 38916897 concerns the HRs printed beside panel A; **the corrected version was not read**, so the values are provisional. The statement stays “no difference for butter”; grade C.

Status note v3.3

Verification round of 20 Oct 2026 with browser access (PubMed and PMC were reachable). **Read and integrated**: (1) Li 2025 full text (PMC11735148): the paper studies red meat; low-fat dairy is one of the tested replacement partners, but its HR appears only in eTable 9 and the figure, not in the text. Text-confirmed: nuts/legumes HR 0.81 (0.75–0.86), fish 0.72 (0.64–0.80), poultry 0.84 (0.77–0.91). The Editors' Note (PMID 42546256) belongs to this paper; it is a letter without abstract, its content remained unread; two Reader Responses (PMID 42546255, 42546258) and an Author Response (PMID 42546257) accompany it. (2) Kim 2026 (PubMed abstract): the beverages studied are sugar-sweetened and artificially sweetened beverages, juice, coffee and tea; **milk is not an exposure per the abstract**, so no milk-specific substitution HR exists there (full text not read). The letter PMID 41610626 (Wang H.) is confirmed against its title. (3) Tessier 2024: PMID 38709531; 3,473 deaths in NHS and 1,278 in HPFS; pooled model olive oil > 7 g/d HR 0.72 (0.64–0.81). **Still open**: Tessier Figure 2 (butter → olive oil, image only), Du eFigure 4, Li eTable 9, Deng 2023 B12/iodine. The values were not refuted, they were not read.

Status note v3.2

Verification round of 19 Oct 2026 on the open items from v3.1. **None of the five requested substitution values with a dementia endpoint could be retrieved as a number with a confidence interval from the primary source** (Du eFigure 4, Kim milk HR, Tessier Figure 2, Li low-fat dairy, Ortega case count); PMC, PubMed, ScienceDirect and neurology.org blocked automated access. The numbers sit in supplements and figures and have to be added manually in a browser. Until then only the direction or the lack of significance per the text applies. **The values were not refuted; they were not found.**

Corrections in v3.2:

1. **Zhou 2023** has no dementia endpoint (all-cause mortality, CVD). It is removed from the dementia table in chapter 18.2 and kept as a side note.
2. **Ortega 2024**: the endpoint is the Clinical Dementia Rating (n = 1,334), not incident dementia. PMID

38388110 is confirmed through a University of Bern repository (secondary source).

3. **Du 2026:** the methods and the results text disagree. Methods list white, red and processed meat, desserts/snacks and margarine/mayonnaise as replacements; the results text adds milk and fermented milk. The statement "cheese → milk: higher risk" is therefore not to be cited until eFigure 4 is checked. Restricted to people without dietary change (n = 18,296) the cheese association fell to HR 0.89 (0.77–1.02) and was no longer significant.
4. **Tessier 2024:** 4,751 dementia deaths per the primary source (press releases give 4,571). A correction exists for Figure 2 (*JAMA Netw Open* 2024;7(6):e2424366, PMID 38916897); the butter → olive oil HR is to be taken from it. The text calls the effect not significant.
5. **Li 2025:** an Editors' Note was published (*Neurology* 2026;107(5):e218339, PMID 42546256). Its content was not read. Check before any citation.
6. **PMID 39096926** belongs to the 2024 Livingston report; the 2020 report has PMID 32738937.
7. **Bibliography:** Kiesswetter 2024 PMID 38779038; Salomé 2025 *Am J Clin Nutr* 122(4):1052–1060; Gorelick 2011 *Stroke* 42(9):2672–2713, PMID 21778438; Borkar AS confirmed as first author of PMID 42398769. Lawrence AS 2025 was not found in this round (not evidence of non-existence).

Evidence grades after this round: "Milk as a beverage is not associated with dementia in European cohorts": **B**. "High-fat cheese is inversely associated": **C**. "Replacing milk with a plant drink changes dementia risk": **not substantiated**; no study found, Scopus, Web of Science and medRxiv not searched.

Note on sources: several statements of this round come from abstracts, repositories and secondary reports; they are marked as secondary in the reference list.

Status note v3.1

Research round of 14.10.2026 on whether substitution analyses with dairy products and a dementia or cognition endpoint exist. **Result:** They exist but are thin — three analyses, each from a single cohort, none with a plant drink as the replacement, none adjusting for vitamin B12, iodine, calcium or total protein (Chapter 18.2). The statement "the substitute determines the sign" is therefore **Grade A for cardiometabolic endpoints and Grade C for the dementia endpoint** (one cohort, Du 2026). Version 3.0 carried it in Chapter 31 as Grade A without that restriction; this is corrected.

Further corrections in v3.1:

1. **Lawrence 2025 is not a microsimulation** but a dietary-intake model (usual-intake model, NCI method). The microsimulation is Salomé et al., *Am J Clin Nutr* 2025 (French adults).
2. **Erlich 2024:** The LDL effect comes from 10 of the 17 trials (n = 312), not from all 17. The work was funded by the United Soybean Board and the Canadian Institutes of Health Research; several authors declare ties to food, soy and dairy industries.
3. **Source review and reference list** carried three journal names wrongly (Kiesswetter: *Curr Dev Nutr*, not *Adv Nutr*; Erlich: *BMC Med*, not *Am J Clin Nutr*; Ford & Almeida: *Drugs Aging*, not *J Alzheimers Dis*). The manuscript itself was correct; the accompanying files are aligned.
4. **First author of PMID 42398769** is Aishwarya S. Borkar (Borkar, Todorova, Markey).

Not locatable, which is not evidence of non-existence: PubMed, PMC, Europe PMC (HTTP 429) and ScienceDirect were blocked or throttled in this round. Still open are the individual hazard ratios in supplementary figure eFigure 4 (Du 2026) and the milk-specific substitution values from Kim 2026.

Status note v3.0

With this version **all** chapters left open in v1.2/v1.3 are sourced. Added relative to v2.0: substitution and nutrient profiles (18), the agricultural and market system (20), health claims, EFSA assessments and the BSE regime (22), industry funding (23.3), animal welfare and antibiotics (24). There are no unsourced chapters left in this work; the remaining gaps are individual, explicitly named data points (Chapter 29).

Three corrections that change the state of the work:

1. **PMID 38718740 was wrongly attributed.** The number belongs to Libri I, Silvestri C, Caratozzolo S et al., "Association of APOE genotype with blood-brain barrier permeability in neurodegenerative

disorders," *Neurobiol Aging* 2024;140:33-40 — a paper **without** an insulin-resistance component. The axis APOE4 × insulin resistance × BBB now rests on Padovani et al. 2025 alone.

2. **The AGE strand does have an intervention study after all.** PMID 34250935 is Lotan R, Ganmore I, Livny A et al., "Effect of Advanced Glycation End Products on Cognition in Older Adults with Type 2 Diabetes," *J Alzheimers Dis* 2021;82(4):1785-95 — a pilot RCT with an AGE-reduced diet and a cognitive endpoint. The v2.0 downgrade stands, but now rests on two intervention studies instead of one.
3. **The strongest substitution evidence in the work is an RCT meta-analysis** that was missing in v2.0: soy drink in place of cow's milk lowers LDL by 0.19 mmol/l (LDL from 10 of 17 RCTs, n = 312, GRADE high). The substitution question thus has a randomised anchor for the first time.

Governing rule unchanged: No citation without verification. Three items remain with a check note (Chapter 0 of the source review).

Evidence scale

Grade	Meaning
A	Established / very robust evidence
B	Well supported, but incomplete or not consistent across populations
C	Plausible, testable hypothesis with relevant but incomplete data
D	Speculative / insufficient human or dose evidence
E	Strong form contradicts the data or is mechanistically/quantitatively rejected

Method rules (binding for all chapters)

1. Strictly separate observation, correlation, mechanism and causality.
2. Never use analogy as proof.
3. Account for real doses, Cmax, half-life, target-tissue concentration, EC50/IC50; mark missing figures explicitly as data gaps.
4. Always compare exogenous intake against endogenous production or pool (Exogenous-to-Endogenous Ratio, EER).
5. Always test milk specificity against non-dairy controls.
6. Label human, animal-model and in-vitro evidence separately.
7. Treat negative findings on par with positive ones; actively seek counter-hypotheses.
8. Define subgroups (APOE, metabolic state, sex, LCT) in advance, never post hoc.
9. Every hypothesis carried forward requires a hard falsification criterion.
10. Cite every source with its study design; mark unverifiable entries as "not locatable" rather than adopting them.

PART I — FOUNDATIONS AND ARCHITECTURE

1. Question and principal finding

The project began with the speculative question of whether rennet coagulation, "set protein," protein deposits in the brain, thrombosis and chronic metabolic disease rest on related physico-chemical principles. That intuition was progressively decomposed into testable sub-hypotheses, repeatedly corrected, and in parts rejected.

Principal finding: The direct chain *milk protein/rennet* → *brain amyloid* → *dementia* is **not** supported (Grade E for the strong form, D for the direct Aβ/tau pathway). The remaining, currently most plausible research direction is indirect:

Cow state + processing + product matrix → defined human exposure → ApoB/LDL, blood pressure, insulin resistance, inflammation, vascular function → BBB/neurovascular unit and possible clearance modification → possible dementia modification.

This architecture carries **Grade C**: coherent, mechanistically supported at several points, not causally demonstrated as a whole chain.

Refinement in v3.0: With the research complete, the dairy question must be framed as a question of **matrix and vascular mediation**, not of bioactive single compounds with brain effects. The latter already fail on pharmacokinetics: for none of the six postulated bioactive milk constituents does a published chain from product dose through Cmax to brain concentration exist (Chapter 29).

1.1 The most robust partial findings

- Dairy products are **not a uniform exposure (A)**.
- Animal health, mastitis, ketosis, negative energy balance, feed, heat stress and nitrogen efficiency alter the proteome, peptidome, lipidome and metabolome of milk (**A**).
- The **matrix effect on LDL** is the best-supported product-specific human finding: 40 g milk fat/day for 8 weeks as whipping cream (MFGM intact) raised LDL by 0.04 mmol/l, as butter oil by 0.36 mmol/l (**B**).
- Milk-derived peptides are partly detectable in plasma after consumption — inconsistently and in very small amounts (**C**).
- Brain cholesterol is largely its own compartment (**A**); individual oxysterols form a molecular bridge (**A-B**).
- In late-onset Alzheimer's disease, **reduced Aβ clearance** is a central mechanism (**A-B**).
- Dementia in old age is frequently **mixed (A)**.
- **New in v3.0:** Mendelian randomisation via the LCT instrument yields largely null findings for drinking milk (cognition, mortality) (**B** for the null).
- **New in v3.0:** Milk contributes only a small fraction of the daily dietary AGE load; a four-week high-AGE RCT produced no metabolic effects. The AGE strand is downgraded to **D**.

2. Chronology of hypothesis development

Phase	Content	Outcome
1	Initial intuition: shared state transitions	retained as abstract question
2	Model critique (sphere models vs. electron densities, energy landscapes)	refined
3	Separation of denaturation / aggregation / amyloid / fibrin / casein coagulation	common core only in the abstract
4	Metabolism and thrombosis	linear chain sugar→fat→fatty liver→thrombus rejected
5	Dairy cow and production system	formulated as measurable variables
6	Genetics/epigenetics, lactase persistence, APOE	disposition / imprinting / transfer separated
7	Nitrogen (rumen ammonia, urea, MUN)	direct hyperammonaemia hypothesis rejected
8	Cow state → milk profile	supported; biomarker ≠ effector
9	Product matrix	established as its own main axis
10	Gut–liver–vessel–brain	shift to a metabolic-vascular pathway
11	Survival-to-systemic-exposure	introduced as a mandatory filter
12	Competitive testing of main axes	prioritisation produced
13	Reverse causal mapping	backwards from the endpoint
14	Butter vs. cheese	matrix effect decomposed mechanistically
15	ApoB/LDL → brain	vascular route + oxysterol bridge
16	Clearance	clearance network as the central node
17 (v1.1)	Aging as common denominator	proteostasis/clearance as the ground, not the dairy lever
18 (v3.0)	Source repair, biomarkers, MR, substitution, transdisciplinary layers	single-compound hypotheses fail on pharmacokinetics; matrix/vascular route remains

3. Physico-chemical core

The defensible abstract idea is not that the diseases discussed share one molecular process, but a **dynamic homeostasis model**:

$$dX/dt = R_{\text{formation/damage}} - R_{\text{degradation/repair/clearance}}$$

X may represent amyloid mass, oxidised lipids, vascular lesions, fibrotic tissue or lost synapses. The common denominator is the **ratio** of formation to removal, not the chemistry of any single process.

Process	Molecular core	Do not conflate with
Rennet coagulation	chymosin cleaves κ-casein; casein micelles aggregate	Alzheimer amyloid
Fibrin coagulation	thrombin → fibrin from fibrinogen; factor XIII stabilises	protein misfolding
Atherosclerosis	ApoB particle retention, lipids, immune cells, matrix	acute thrombus
Amyloid formation	nucleation-dependent cross-β fibrils	any denaturation
Biomolecular phase separation	condensates, local concentration, liquid/gel/solid	any form of coagulation

Prions as the real limit of the analogy. BSE/vCJD shows that cross-species pathological protein misfolding is possible in principle. This implies **no** general prion action of milk proteins (**E** for milk as a relevant BSE transmission route). For each candidate, structural compatibility, dose, digestive resistance, tissue access and seeding activity must be demonstrated **separately**.

4. Integrated system model

Production state:

$Z_{\text{cow}} = \{\text{genetics, lactation, feed, energy balance, MUN, SCC, BHB, NEFA, heat stress, medication}\}$

Product chemistry:

$X_{\text{product}} = f(Z_{\text{cow}}, \text{pasteurisation, UHT, fermentation, ripening, storage, light, } O_2)$

Human exposure (per candidate j):

$dP_j/dt = \text{absorption}_j - \text{hepatic clearance}_j - \text{renal clearance}_j - \text{degradation}_j - \text{tissue uptake}_j$

Brain-damage dynamics:

$dD/dt = \alpha \cdot A + \beta \cdot T + \gamma \cdot V + \delta \cdot M + \varepsilon \cdot I - \rho \cdot R$

with A = amyloid biology, T = tau, V = vascular damage, M = metabolic burden, I = inflammation, R = reserve/resilience.

Lifetime burdens as integrals:

$B_{\text{ApoB}} = \int \text{ApoB}(t) dt \cdot B_{\text{BP}} = \int \text{blood pressure}(t) dt \cdot B_{\text{Gly}} = \int \text{glycaemia}(t) dt$

Interpretation: On current evidence, diet attaches to **V, M and I**, not directly to A or T.

PART II — THE MECHANISTIC CHAIN

5. Animal production and milk phenotype

$X_{\text{milk}} = f(\text{genetics, lactation, feed, energy balance, MUN, mastitis, heat stress, medication, housing})$

It is established that the cow's physiological state measurably influences the milk profile (**A**).

5.1 Heat stress (newly sourced)

Heat stress lowers milk protein synthesis beyond the reduction in feed intake. In an integrated metabolomic/proteomic analysis of 18 cows (no, mild, moderate heat stress), ribosomal proteins (RPS23, RPS8, RPS25) and heat shock proteins were significantly downregulated, with significantly reduced milk protein yield ($p < 0.001$). Source: Zeng et al., *J Anim Sci Biotechnol* 2026;17:28, DOI 10.1186/s40104-025-01338-y. **Animal study.**

5.2 Nitrogen efficiency and MUN (newly sourced)

A meta-analysis of 48 studies (2004–2024) found a mean nitrogen use efficiency of 29.6 % (range 15.7–43.0 %) and a negative correlation between MUN and nitrogen use efficiency ($r = -0.43$). Source: Zhao et al., *J Dairy Sci* 2025;108(5):4851–4862, DOI 10.3168/jds.2024-25656.

The genetic architecture of milk urea concentration is lactation-stage dependent, with a pleiotropic DGAT1 locus (GWAS, *J Dairy Sci* 2026, PMID 42480924). Heritability estimates for MUN range from 0.22 (New Zealand) to 0.44–0.59 (Ontario). **Counter-finding:** other work finds only weak correlations between MUN and individual nitrogen efficiency (−0.01 to 0.06) and no genetic correlation ($< |0.12|$).

Verdict: MUN is a useful feeding and environmental indicator at **herd level**, a weak efficiency marker at **individual-animal level** — and in no case a human health marker.

A MUN phenotype comparison (faecal microbiome, faecal metabolome, serum metabolome in cows of differing MUN phenotype) exists: Zhao X, Song L, Li N et al., *J Dairy Sci* 2026;109(7):6926–6940, DOI 10.3168/jds.2025-27914. **Animal study — do not use as human evidence.**

5.3 The survival question

Cow-state feature	Survives pooling?	Survives heating?	Survives fermentation/storage?	Human relevance shown?	Grade
Fatty acid profile (pasture: more CLA, omega-3, 15:0/17:0)	partly (seasonal, regional)	yes (heat-stable)	yes	biomarker level yes, endpoints no	C
Milk urea (MUN)	diluted, herd mean	yes	partly (microbial degradation)	no; neurotoxicity rejected	E
Heat-stress proteome (ribosomal proteins, HSPs)	strongly diluted	largely denatured	largely degraded	no data	D
Mastitis inflammatory proteins / SCC	limited by SCC thresholds in the bulk tank	partly denatured	data gap	no data	D
Drug residues	limited by withdrawal periods and controls	partly stable	partly stable	no dementia data	data gap
Ketosis / negative energy balance	diluted	-	-	no data	D
Organic vs. conventional	yes (fatty acid profile)	yes	yes	no hard endpoint data	data gap

Hard limit: That milk molecularly reflects the cow's state proves no health effect in humans. **Milk amyloid A is not Alzheimer amyloid (E).** "The cow's suffering as a targeted epigenetic message" has no evidence (E).

Falsification criterion: If no heat-stress proteome signature with more than a two-fold change is detectable in pooled, UHT-treated bulk milk, any "cow state → human proteostasis via the proteome" hypothesis is rejected.

Outstanding: mastitis multi-omics, ketosis proteomics, drug residue data 2024–2026, quantitative pasture-vs-barn fatty acid data.

6. Processing, product matrix and exposure

The category "dairy product" is scientifically too coarse (A).

Product	Dominant matrix/processing	Main research variable
Pasteurised milk	fat-in-water emulsion, casein micelles	gastric coagulation, peptide/amino-acid kinetics
UHT milk	stronger whey-protein denaturation, complex formation	digestion, storage chemistry, glycation
Lactose-free UHT	cleaved lactose + UHT	Maillard/cross-linking chemistry
Yoghurt/kefir	acid gel, fermentation, microbial proteolysis	lactose, metabolites, gut response
Cheese	concentrated casein network, ripening	fat release, calcium, peptides, MFGM
Butter	water-in-fat system, MFGM reorganised	milk fat without intact protein matrix
Milk powder	heat + drying + storage	oxidation, glycation, cross-linking

6.1 The mandatory filter: survival-to-systemic-exposure

processing → digestion → absorption → plasma (Cmax, t½) → target tissue → target engagement

A molecule not demonstrated to traverse this chain is **not admissible** as a causal candidate.

6.2 Quantitative processing chemistry (newly sourced)

Furosine is the most sensitive indicator of the early Maillard reaction, CML an advanced AGE. A storage study (*Eur Food Res Technol* 2026, DOI 10.1007/s00217-026-05111-x) and a kinetic modelling study (*J Agric Food Chem* 2026;74(20):15776, PMC13220311) supply the dose basis.

Product	Furosine (mg/kg protein)	Furosine (mg/kg product, calculated)	CML (mg/kg protein)	CML (mg/kg product, calculated)	Lactulose
...	...	...	...	...	...

Raw milk	< 400	< 13	1.76	~0.06	absent
Pasteurised milk	1040 (model study)	~34	0.11 (LC-MS/MS)	~0.004	low
UHT milk, fresh	3070-4370	~100-145	1-10.1 (LC-MS/MS) or 70.7 (other analytics)	~0.03-0.33 or ~2.3	409 ± 161 mg/l
UHT milk, 6 months stored	-	-	178.6	~5.9	-
Sterilised condensed milk	4910	data gap	data gap	data gap	1997 ± 658 mg/l
Milk powder	2750-4480 (secondary source only)	data gap	data gap	data gap	data gap
Soy drink, fresh → 6 months	340-1780	-	60.8 → 143.9	-	-
Cheese, butter, cream	data gap	data gap	data gap	data gap	data gap
MG-H1, all dairy products	data gap	-	-	-	-

Conversions to mg/kg product are the author's own calculations using 33 g protein/kg milk and are not published.

Three findings from this table:

1. **For CML, storage is as important a driver as heating.** In UHT milk, CML rose from 70.7 to 178.6 mg/kg protein over 6 months.
2. **AGE formation is not milk-specific.** In the soy drink, CML rose over the same period from 60.8 to 143.9 mg/kg protein — the same order of magnitude. Protein + reducing sugar + heat + time generates AGEs regardless of origin. This is the chapter's central non-dairy control.
3. **Published CML values span more than an order of magnitude** (1-10.1 vs. 34-179 mg/kg protein). Causes: analytics (ELISA vs. isotope-dilution LC-MS/MS), reference basis, storage state. Only LC-MS/MS values should be used for the dose basis.

Proposed furosine limits: 8 mg/100 g protein (pasteurised), 20 mg/100 g protein (high-heat), 250 mg/100 g protein (UHT) per Clawin-Rädecker and Schlimme; Italy 8.6 mg/100 g protein for raw and pasteurised milk; China 12 and 190 mg/100 g protein for premium pasteurised and premium UHT milk.

6.3 Dose context and downgrade of the AGE strand

In the controlled AGE intervention trial (Linkens et al., *JCI Insight* 2022, PMC8986074, NCT03866343; 4 weeks, individuals with obesity), daily intake in the low-AGE group was 2.63 mg CML, 1.69 mg CEL and 13.44 mg MG-H1; in the high-AGE group 7.02 mg CML, 9.03 mg CEL and 49.67 mg MG-H1. **Result: no effects on insulin sensitivity, vascular function, inflammation or lipids.**

A glass of UHT milk (250 ml, ~8.25 g protein) delivers about 0.28 mg CML at 34 mg/kg protein, about 1.5 mg for long-stored product (179 mg/kg protein). **Even in the worst case, that is a subset of the variation that produced no effect in the RCT.**

Statement	Old grade	New grade	Rationale
Analytics of Maillard products in milk	-	A	LC-MS/MS data available
Milk AGE dose relevant to human insulin resistance / vascular function	C	D	4-week RCT with 2.7- to 5.3-fold AGE difference, no effect; older positive findings ELISA-based and often confounded with caloric restriction
AGE/RAGE effect is milk-specific	D	D (confirmed)	soy drink shows the same CML increase

A second intervention study, not yet assigned in v2.0: Lotan R, Ganmore I, Livny A et al., "Effect of Advanced Glycation End Products on Cognition in Older Adults with Type 2 Diabetes: Results from a Pilot Clinical Trial," *J Alzheimers Dis* 2021;82(4):1785-95, DOI 10.3233/JAD-210131 — pilot RCT, n = 75, type 2 diabetes, 6 months, two arms (standard care versus standard care plus an AGE-reduced diet), endpoints cerebral blood flow and cognition. For the first time the AGE strand therefore has an intervention with a **cognitive** endpoint. Its pilot character and the population restricted to type 2 diabetes limit its weight; the downgrade of the milk AGE strand to **D** stands, but now rests on two independent interventions instead of one.

Falsification criterion: If an RCT comparing stored UHT with freshly pasteurised milk (same matrix, ≥ 3 -fold CML dose difference, ≥ 12 weeks) shows no change in protein-bound plasma CML, insulin sensitivity (clamp) and endothelial function, the milk AGE strand is finally rejected (**E**).

Outstanding: oxysterol content of milk powder and cheese; MG-H1 in all dairy products; lipid oxidation under light and oxygen exposure.

7. Nitrogen: ammonia, urea, uric acid

Ruminants possess a pronounced microbial nitrogen cycle: feed protein/NPN $\rightarrow$ rumen ammonia $\rightarrow$ microbial protein; excess ammonia $\rightarrow$ liver $\rightarrow$ urea, partly recycled into the rumen.

Urea is normally present in cow's milk; MUN is an established metabolic and feeding marker (**A**).

Quantitatively, the urea taken in with normal milk is small relative to daily endogenous human urea production — the EER test is unambiguous.

Falsified strong pathway (E/D): rumen ammonia $\rightarrow$ milk $\rightarrow$ relevant hyperammonaemia in healthy humans $\rightarrow$ Alzheimer's.

Hyperammonaemia itself is clearly neurotoxic (liver failure, urea-cycle defects) — a **different** mechanism from Alzheimer amyloid (**A** for the neurotoxicity, **E** for the milk bridge). The ammonia-astrocyte axis belongs in the neighbouring work NEUROMETABOLICA (Chapter 25), not here.

Uric acid is a purine degradation product and must not be confused with urea. In human studies milk is associated with **lower** rather than higher uric acid (**E** for the opposite claim).

8. Genetics, epigenetics, lactase persistence, APOE

Prenatal conditions can influence development and epigenetic patterns long-term (**A-B**). This implies **no** stable transgenerational inheritance of arbitrary dietary effects.

Lactase persistence is a strong real example of gene-culture co-evolution (**A**) — the historical depth of this finding is developed in Chapter 19. It concerns lactose digestion primarily and is **not** an instrument for all milk constituents; as an MR instrument it measures **drinking milk**, not cheese, butter or cream (Chapter 16).

APOE is far more relevant to the dementia question: APOE- $\epsilon 4$ affects lipid transport, A β processing, immune responses and vascular biology (**A**). A **milk-specific** APOE interaction is a single-study finding (Chapters 14, 27) and remains **C**, pending replication closer to **D**.

Bovine extracellular vesicles and microRNA: systemic uptake and functional gene regulation after ordinary milk consumption in adults are contradictory or weakly supported (**D/E**).

9. Gut, microbiome and fermented dairy

product $\rightarrow$ gut/microbiome $\rightarrow$ portal vein/liver $\rightarrow$ metabolism/inflammation $\rightarrow$ vessels/BBB $\rightarrow$ brain

9.1 What dairy interventions actually do to the microbiome (newly sourced)

A systematic review of milk and dairy derivatives (*Gut Microbes* 2020, PMC7524346) found that, with one exception, **no** study reported a change in bacterial diversity from dairy interventions; one study even showed decreased diversity. A systematic review of kefir (Hamsho et al., *MicrobiologyOpen* 2026; 8 human studies from 2,743 hits) found only minor shifts at phylum and class level and **no** significant effect on the Firmicutes/Bacteroidetes ratio. A meta-analysis of fermented dairy and inflammatory markers (14 studies, 15 arms: yoghurt 9, fermented milk 4, kefir 2) reported reduced CRP and increased IFN- γ , with no effect on IL-6, IL-10 and IL-12.

9.2 The decisive non-dairy control

The key reference for the milk-specificity test is Wastyk et al., "Gut-microbiota-targeted diets modulate human immune status," *Cell* 2021, PMID 34256014: a diet rich in fermented foods increased microbiome diversity and lowered inflammatory markers. **The intervention, however, mixed yoghurt, kefir and cottage cheese with kimchi, sauerkraut and kombucha.** The effect therefore belongs to a **fermentation class**, not to dairy. No arm comparing dairy ferments alone with plant ferments alone exists per this search.

Strand	Human evidence	Milk-specifically tested?	Grade
Diversity change from milk/yoghurt/kefir	mostly null	no	C (for small effects)
CRP reduction from fermented dairy	meta-analysis, 14 studies	no	C
Mixed fermented diet → diversity ↑, inflammation ↓	Cell 2021	no (mixed)	B for fermentation class, D for the dairy share
Endotoxaemia/LPS from MFGM milk	crossover vs. soy lecithin, no detriment	yes (lecithin control)	C
SCFA, TMAO, bile acids from dairy	no human primary data found	-	data gap
Microbiome-brain axis milk → cognition	no human study with a cognitive endpoint	-	D

9.3 Liver and systemic inflammation

A general "leaky gut" caused by milk is **not supported (D/E)**. Randomised human trials on liver fat, insulin resistance and inflammation give neutral, favourable and unfavourable findings depending on product and population; a general hepatotoxic dairy effect is **not supported (E)**.

Falsification criterion: If in a three-arm RCT (dairy ferment vs. isoenergetic plant ferment vs. unfermented control) the CRP and diversity effects do not differ between dairy and plant ferment (equivalence margin ± 0.3 mg/l CRP), a milk-specific microbiome effect is rejected.

10. Butter vs. cheese: the matrix effect

Randomised trials show that comparable milk fat delivered as **intact cheese** produces a smaller LDL increase than butter or deconstructed cheese components (**B**).

10.1 The core finding in figures

Study	Design	Intervention	Result
Rosqvist et al., <i>Am J Clin Nutr</i> 2015, NCT01767077	single-blind parallel RCT, 8 weeks, n = 57 overweight adults	40 g milk fat/d as whipping cream (MFGM intact) vs. butter oil	LDL +0.04 vs. +0.36 mmol/l (p = 0.024); ApoB:ApoA-I -0.05 vs. +0.03 (p = 0.007)
<i>Am J Clin Nutr</i> 2021;114(5):1729, PMID 34477812	crossover RCT	Cheddar / homogenised / MCI drink / MCI gel	matrix-dependent postprandial response
<i>Food Funct</i> 2024, PMID 39017657	6-week RCT	~40 g milk fat as melted, unmelted or deconstructed cheese	matrix effect confirmed

The Rosqvist result is the quantitative basis of the entire matrix axis: **a ninefold difference in LDL increase at identical milk fat intake.**

10.2 MFGM — reversing the v1.2 downgrade

The sources listed as "not locatable" in v1.2 exist:

PMID	Work	Design	Result
42398769	Systematic review with meta-analysis, <i>Adv Nutr</i> 2026;17(9):100694, DOI 10.1016/j.advnut.2026.100694, PMC13470189 (co-author Oonagh Markey; first authorship unconfirmed)	SRMA of RCTs, GRADE, RoB 2.0; total cholesterol 10 RCTs, n = 600	TC WMD -0.18 mmol/l; LDL -0.12 mmol/l in sensitivity analysis; TC:HDL -0.17; ApoA-I no effect
42251897	Randomised, double-blind crossover RCT, whole-room calorimetry, NCT06340412	n = 12 healthy adults; isocaloric spreads with intact, disrupted or absent MFGM (40 g milk fat)	Triglyceride iAUC unchanged; GIP higher with MFGM (p = 0.02); free fatty acids higher for intact vs. disrupted MFGM (p = 0.01)

Further verified MFGM evidence: *Foods* 2024;13(17):2725 (meta-analysis, 6 RCTs, n = 464: TC SMD -0.259); Vors et al., *Gut* 2020;69(3):487, PMID 31189655 (RCT, n = 58, 0/3/5 g milk polar lipids/d); *JCI Insight* 2021, PMID 33857018 (ceramides/sphingomyelins); *Nutrients* 2023;15(14):3259 (crossover against soy lecithin — a non-dairy control, no adverse endotoxaemia).

Methodological critique that limits the finding:

- A letter to the editor (*Adv Nutr* 2026, article 100721) criticises that the "moderate certainty" rating for LDL rests on a **single study**.
- The acute crossover study (42251897) shows that **acute effects are not the mechanism**. The chronic LDL matrix effect remains plausible; the postprandial route does not.

10.3 MFGM and cognition — a null result

The largest intervention study to date: *Am J Clin Nutr* 2025;122(5):1161-1173, DOI 10.1016/j.ajcnut.2025.09.005, PMID 40939691. Multicentre, double-blind, placebo-controlled parallel RCT, **n = 263**, aged 55-75, subjective memory complaints without MCI, 50 g/d milk powder with 1.7 g or 4.0 g phospholipids/d against rice starch, 16 weeks.

Result: no effect on objective cognition. Secondary: alertness preserved (high dose), TC and LDL reduced, TNF-α reduced (high dose), active B12 increased, homocysteine reduced (high dose).

Decisive methodological critique: The control was **rice starch, not MFGM-poor milk powder**. Lipid, B12 and homocysteine effects are therefore not MFGM-specific and may be attributable to the milk powder as a whole (protein, B12, calcium). For the milk-specificity principle this is a material confounder — and at the same time an indication that **nutrient effects (B12) can mediate cognition-adjacent markers** (Chapter 18).

A subgroup finding (Calvo et al., *J Funct Foods* 2023; 200 ml/d MFGM-enriched milk, 14 weeks, older adults) showed improved episodic memory **only in women** — hypothesis-generating, not robust.

Ongoing, citable only as registry entries: NCT05939544 (Loughborough, MFGM and cardiometabolic/cognitive endpoints), NCT06953232 (acute, ~5 g milk polar lipids, postmenopausal women with overweight).

10.4 Assessment and grade correction

Statement	v1.3	v3.0	Rationale
Intact matrix alters LDL relative to butter	A-B	B	Rosqvist + cheese matrix RCTs
MFGM/milk polar lipids lower TC/LDL	C→D	B	SRMA 2026 (TC -0.18 mmol/l), meta 2024; LDL single-study driven
MFGM affects cognition in adults	C→D	D	RCT null result, n = 263
MFGM affects proteostatic endpoints	C→D	D	never measured

The butter-cheese difference is probably not explained by a single "protective molecule" but by several coupled matrix mechanisms: casein network (spatial entrapment of fat), calcium (faecal fat excretion via insoluble soaps), MFGM/polar lipids (intestinal cholesterol and lipoprotein processes), fermentation/ripening. Fat globule size alone does not explain the human response. Acute triglyceride response and chronic ApoB/LDL effect are **not identical** — the 2026 crossover study demonstrates this directly.

11. Peripheral ApoB, brain cholesterol, oxysterols, BBB

The brain synthesises most of its cholesterol itself. Plasma LDL does not freely cross an intact BBB. "LDL deposits directly in the brain" is mechanistically **false (E)**.

Peripheral ApoB acts primarily through the arterial wall:
particle retention → atherosclerosis → stenosis/plaque event/thrombosis → cerebral ischaemia or embolism (**A**).

Oxysterols form a genuine molecular bridge: 24S-hydroxycholesterol passes from brain into blood; peripherally generated 27-hydroxycholesterol can cross the BBB in the opposite direction (**A**). Dietary oxidised cholesterol demonstrably appears in human lipoproteins (*J Lipid Res* 2003;44(4):705, PMID

12562864, **A-B**). **The EER test is unfavourable, however:** the endogenous oxysterol pool dominates, and oxysterol levels in milk powder and cheese remain unquantified to this day (data gap, Chapter 29).

APOE acts in separate peripheral and central pools, yet the same genotype is present in both. APOE-ε4 can therefore simultaneously influence peripheral lipid metabolism, BBB/neurovascular biology and Aβ pathology (**A**).

CAA (cerebral amyloid angiopathy) is Aβ deposition in cerebral vessel walls, **not** fat/LDL deposition. Atherosclerosis and CAA are distinct vascular diseases but burden the same neurovascular unit. Two neuropathology findings support the separation: PMID 41566952 reports roughly 28-fold higher odds of severe CAA in APOE-ε2 carriers without AD at high plaque and tangle burden; and an autopsy-confirmed cohort from Beijing (Yin XS, Sun J, Wang X et al., *Alzheimers Dement (Amst)* 2025;17(2):e70100, DOI 10.1002/dad2.70100, n = 483 brain-bank donors) quantifies the overlap: CAA without AD 11 %, AD without CAA 16 %, **both 20 %**, neither 53 %. One case in five therefore carries both pathologies — the clinical category "dementia" routinely conceals two distinct vascular and deposition processes.

12. Amyloid clearance as the central node

Direct human kinetic data (stable-isotope SILK; Mawuenyega et al., *Science* 2010;330:1774, PMID 21148344) show **reduced Aβ clearance** in late-onset Alzheimer's disease without correspondingly increased production (**A-B**).

$$dA/dt = P - k_{BBB} \cdot A - k_{cell} \cdot A - k_{PV} \cdot A - k_{CSF} \cdot A - k_{agg} \cdot A^n$$

Route	Mechanism	Evidence level
BBB transport	LRP1 (efflux), RAGE (influx/inflammation)	human + animal (PMID 19275634, 15459432)
Microglia	Aβ uptake and phagocytosis	human pathology after immunotherapy
Astrocytes/lysosomes	uptake/degradation, possible overload	predominantly animal model
Perivascular drainage	Aβ distribution matches drainage routes; CAA impedes drainage	human pathology + imaging
CSF/meningeal-lymphatic/"glymphatic"	tracer and imaging studies	human, slower than in mouse
Sleep	SWS-dependent Aβ/tau dynamics	human RCT (PMID 40830882) + PET (PMID 29632177)
Vascular mechanics/hypertension	BBB permeability	human (PMID 41091964; higher BBB permeability with hypertension, DCE-MRI, n = 59 vs. 21)

Significance for the dairy project: A dairy product would not need to *generate* more amyloid to be relevant — it could become relevant if it modified vascular/metabolic factors over the long term such that clearance parameters fall. For a **direct** product→Aβ-clearance effect in humans there is no evidence (**D**).

13. Aging as the common denominator

The aging/clearance axis is **not a milk-specific mechanism** but the physiological ground on which any dietary effect can become operative at all.

13.1 Proteostasis

Directly measured in humans is above all **chaperone-mediated autophagy (CMA)**: age-dependent LAMP2A decline in human fibroblasts (Cuervo & Dice, *J Biol Chem* 2000;275:31505) and in human skeletal muscle (*Nature Metabolism* 2025). The "global loss of ubiquitination" is shown primarily in *C. elegans* (*Nature* 2021).

- "Proteostatic capacity declines with age in humans": **B**
- "Proteostasis decline → dementia in humans (causal)": **C**

13.2 Autophagy and lysosomes

Human evidence exists mainly for CMA; TFEB/mTORC1/AMPK, lysosomal acidification and lipofuscin are predominantly animal/in-vitro (**C**). Mechanistically connectable: **leucine inhibits autophagy** via acetyl-CoA, EP300-dependent raptor acetylation and mTORC1 (Son et al., *Nat Commun* 2020;11:3148 — in

vitro/neuronal culture). In humans, high-protein meals activate monocyte mTORC1 and reciprocally inhibit autophagy; the threshold is around 300 μ M leucine, with a marked step between 100 and 300 μ M (PMC11448845).

13.3 Mitochondria and NAD⁺

Raising circulating NAD⁺ with NR/NMN is robustly and dose-dependently established (Conze, Brenner & Kruger, *Sci Rep* 2019;9:9772, RCT n = 140: +22 %, +51 %, +142 % at 100/300/1000 mg; **A**). **Clinically relevant endpoints are largely negative or inconsistent; no NAD⁺ precursor RCT has reached a dementia or A β /tau clearance endpoint (D).**

13.4 Senescence and senolytics

Human studies with dasatinib + quercetin (SToMP-AD, open-label phase 1, *Neurotherapeutics* 2023; STAMINA, single-arm n = 12, *eBioMedicine* 2025) show safety and CNS penetrance (**B**) but **no controlled efficacy evidence (D)**. A phase-2 RCT is running.

13.5 Clearance aging: sleep, vessels, BBB

- **Animal-model basis:** Kress/Iliff, *Ann Neurol* 2014;76(6):845, PMID 25204284 — in old mice A β clearance impaired by 40 %, arteriolar pulsatility reduced by 27 %, loss of perivascular AQP4 polarisation. **Not quantitatively transferable to humans.**
- **Human imaging 2025:** MT spin-labelling MRI (*NeuroImage* 2025), diffusion-prepared ASL (*bioRxiv*, preprint) and dynamic ¹⁸F-FDG PET (*medRxiv*, preprint) independently show an age-dependent decline in BBB water exchange and CSF clearance (**B**).
- **Sleep:** One night of sleep deprivation measurably increases A β burden by about 5 % in hippocampus and thalamus (Shokri-Kojori et al., *PNAS* 2018;115(17):4483, n = 20). SWS lowers CSF A β and tau (randomised crossover, n = 12, PMID 40830882). Partial sleep restriction **without** SWS loss did not change the biomarkers — indicating a threshold character of clearance resilience.

13.6 Non-linearity and tipping point

Finding	Dataset
Inflection of plasma GFAP, NfL, p-tau181 at $\approx$ 68–72 years	Mayo Clinic Study of Aging, n = 2082, breakpoint analysis
Estimated onset age $\approx$ 49 y (A β 42/40), $\approx$ 51.6 y (p-tau181); $\sim$ 6 y earlier in APOE- ϵ 4	BIOCARD, n = 384
"Indolent phase then sharp rise in accumulation rate"; ϵ 4 shifts amyloid by 6.1 y, tau by 2.6 y; amyloid $\rightarrow$ tau lag 13.3 y	accelerated failure time model, PMID 34333107
Ordered cascade: A β (precuneus > 20 y before symptoms) $\rightarrow$ metabolism $\rightarrow$ atrophy	DIAN

Non-linear acceleration is supported (**B**). The stronger claim of a **single common tipping point** at which several clearance and repair systems fail *simultaneously* is not demonstrated as a simultaneous collapse — **C**, in its strong form **D**.

13.7 Can diet modify human proteostasis?

Candidate	Human finding	Dose / EER	Milk specificity	Grade
Fasting/caloric restriction	CALERIE-2 (11.7 % CR, 2 y): autophagy/stress-response/sirtuin genes upregulated in muscle; IGF-1/IGFBP-1 $-$ 42 %	transcriptional only, no in-vivo flux assay	opposite of dairy	B
Spermidine	SmartAge (<i>JAMA Netw Open</i> 2022;5(5):e2213875, NCT03094546; n = 100, 0.9 mg/d, ages 60–90 with SCD): no significant effect on the primary memory endpoint	0.9 mg/d low vs. dietary intake ($\sim$ 10–15 mg/d) and the endogenous polyamine pool	not milk-specific (wheat germ in the RCT)	D
Leucine/whey $\rightarrow$ mTOR $\rightarrow$ autophagy inhibition	monocyte mTORC1 activation and autophagy inhibition in humans; threshold $\sim$ 300 μ M	plasma Cmax reaches this range; brain target concentration = data gap	not milk-specific	C
MFGM sphingolipids/ceramides	3–5 g/d alters circulating ceramide/sphingomyelin species	lysosomal/autophagic function never measured	partly milk-specific	D
Milk fat $\rightarrow$ mitochondria	no human evidence	data gap	—	D

Core quantification gap: For spermidine, leucine (brain), ceramides and oxysterols, Cmax and above all **target-tissue (brain) concentrations** are missing.

14. Disease-specific evidence

Dementia is a clinical syndrome and in old age frequently the result of several concurrent pathologies (A).

14.1 The Swedish 25-year cohort

Du Y, Borné Y, Samuelsson J et al. (senior author Emily Sonestedt, Lund University), "High- and Low-Fat Dairy Consumption and Long-Term Risk of Dementia: Evidence From a 25-Year Prospective Cohort Study," *Neurology* 2026;106(2):e214343, DOI 10.1212/WNL.00000000000214343, Epub 17 Dec 2025, PMC12720290. Malmö Diet and Cancer, n = 27,670, aged 45–73, enrolment 1991–1996, 3,208 incident dementia cases over a median of 25 years.

Product	Finding
Milk, fermented milk, butter	no association with all-cause dementia
High-fat cheese ≥ 50 g/d	all-cause dementia HR 0.87 (0.78–0.97); vascular dementia HR 0.71
High-fat cream ≥ 20 g/d	HR 0.84 (0.72–0.98), i.e. 16 % lower risk
APOE	$\epsilon 4$ modification of the cheese-AD association (inverse only in non-carriers, HR 0.87; p-interaction 0.014)

Observational design — no causality (C). Residual confounding by education, social status and overall diet is not excluded; exposure was assessed once in 1991–1996, leaving 25 years of change unaccounted for.

Epidemiology thus contradicts a strong universal theory of "more milk fat $\rightarrow$ more dementia" (E). Conversely, "high-fat cheese is causally protective" is likewise **not** supported (D).

A secondary source (an interview with Sonestedt) reports an association of ≥ 40 g/d butter with higher AD risk; this is **not** verified against the original paper and must not be adopted (D, check required).

Substitution analysis in the same cohort (post hoc, as of the 14.10.2026 research round). Modelled was the replacement of 20 g/d high-fat cheese (> 20 % fat) or high-fat cream (> 30 % fat) by the same amount of another food, estimated from coefficient differences. According to the authors, replacing high-fat cheese with milk, fermented milk, high-fat red meat or processed meat was associated with higher all-cause dementia risk; for cream this held for more foods. **The individual HRs appear only in eFigure 4 of the supplement and were not retrievable.** The authors' own limits: single baseline diet assessment; restricted to people without dietary change, the cheese finding attenuated (HR 0.89; 0.77–1.02); cream reproducibility $r = 0.42$ – 0.48 ; E-value for the cheese finding 1.56. Vitamin B12, iodine, calcium and total protein are not adjusted. Placement in Chapter 18.2.

14.2 Other endpoints

Endpoint	Impression for dairy	Grade
Alzheimer diagnosis	mostly neutral/heterogeneous	C–D; D for direct A β /tau pathway
Vascular dementia	few data; 2026 data rather neutral/inverse	C
Ischaemic stroke	neutral to slightly inverse, regionally heterogeneous	B–C
LDL/ApoB	clear matrix differences in RCTs	B
Blood pressure	no consistent harm signal	B–C
Diabetes/insulin resistance	product-, dose- and population-dependent	B–C

Further verified cohort/meta evidence: Villos et al., *Adv Nutr* 2024;15(1):100160, PMID 38043604 (dose-response meta-analysis); Lu et al., *Eur J Nutr* 2023;62(7):2751, PMID 37335358 (Ohsaki, n = 11,637).

Central evidence gap: Direct human intervention data on dairy product $\rightarrow$ A β 42/40, p-tau217, tau-PET or amyloid-PET are largely absent.

14.3 Flanking risk-factor evidence

Livingston G, Huntley J, Liu KY et al., "Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission," *Lancet* 2024;404(10452):572–628, DOI 10.1016/S0140-6736(24)01296-0, PMID 39096926 (the 2020 report has PMID 32738937): 14 modifiable risk factors, 45 % attributable fraction combined; **high midlife LDL at 7 %**. This supports the project axis matrix $\rightarrow$ ApoB/LDL $\rightarrow$ vascular $\rightarrow$ dementia without making it milk-specific.

On the vascular dementia burden: Smith EE, Aparicio HJ, Gottesman RF et al., "Vascular Contributions to Cognitive Impairment and Dementia in the United States: Prevalence and Incidence," *Stroke* 2025;56(10):e317–e330, DOI 10.1161/STR.0000000000000494. For definitions, use the original statement Gorelick et al. 2011, *Stroke*, DOI 10.1161/STR.0b013e3182299496. **No 2026 update exists; the title "... and Brain Health" carried in the working inventory corresponds to no real statement and has been struck.**

15. Biomarkers of dairy intake (new)

Self-reported dietary data are the weakest point of the entire milk-dementia epidemiology. Objective fatty acid biomarkers partly circumvent this error.

15.1 The evidence

Trieu et al., *PLoS Med* 2021;18(9):e1003763 (cohort with systematic review and meta-analysis): serum 15:0 in cholesteryl esters in 4,150 Swedish 60-year-olds over a median 16.6 years — higher 15:0 linearly associated with lower CVD risk (HR 0.75 per interquintile range; 0.61–0.93). In the meta-analysis of 18 studies, 15:0 (RR 0.88; 0.78–0.99) and 17:0 (RR 0.86), but not t16:1n-7, were inversely associated with total CVD; for all-cause mortality there was no association (≤ 3 studies per biomarker).

Imamura et al., *PLoS Med* 2018, DOI 10.1371/journal.pmed.1002670 (pooled analysis of 16 prospective cohorts): comparing the 90th with the 10th percentile, 20 % (15:0) and 35 % (17:0) lower T2D risk.

The biomarkers correlate with self-reported milk fat intake at $r = 0.4$ – 0.7 .

Biomarker	Specificity for milk fat	CVD	T2D	Mortality	Cognition/dementia
15:0 (pentadecanoic acid)	high	RR 0.88	–20 % (P90 vs. P10)	no association	data gap
17:0 (heptadecanoic acid)	medium (fibre, endogenous)	RR 0.86	–35 %	no association	data gap
t16:1n-7	medium (also ruminant meat)	no association	inverse in CHS/MESA	no association	data gap

15.2 Limits

17:0 and partly 15:0 are also influenced by fibre fermentation (propionate) and endogenous α -oxidation; in a post-myocardial-infarction cohort, circulating odd-chain fatty acids also correlated with fibre intake. Fish and ruminant meat contribute as well. **15:0 is the more specific, 17:0 the less specific marker.** In US cohorts (CHS, MESA) the OCFAs were not associated with T2D, while t16:1n-7 was inverse — consistency across populations is limited.

An inverse association is no proof of causation: 15:0 may be a marker of lifestyle, fibre intake or overall diet quality.

Grade: biomarker-cardiometabolic association **B**; biomarker-dementia **data gap** (no biomarker-based dementia cohort locatable). This is one of the most important gaps in the whole work, because existing biobank samples could generate evidence here comparatively quickly.

Falsification criterion: If in a pooled analysis (≥ 10 cohorts with stored plasma, dementia follow-up ≥ 10 years, $\geq 5,000$ cases) the HR for dementia per standard deviation of 15:0 lies between 0.95 and 1.05, "milk fat protects against dementia" is falsified at the biomarker level.

16. Mendelian randomisation (new)

MR is the only realistic route to a causal statement without a decades-long RCT.

16.1 Instrument strength

In EPIC-InterAct each additional T allele of rs4988235 (LCT-13910 C/T) was associated with 17.1 g/d (10.6–23.6) more milk intake, explained 2 % of variance, F-statistic 515. Other cohorts report F-statistics from 1,366 (Sweden) to 3,887 (Austria). **Weak-instrument bias is unlikely for drinking milk.**

Decisive limitation: In the Swedish Malmö material, rs4988235 was strongly associated only with **unfermented drinking milk** and only weakly with other dairy products. The instrument measures drinking milk — **not cheese, butter or cream**. MR therefore provides no information on precisely those products for which the cohort (Chapter 14) shows inverse associations.

16.2 Results

Study	Design	Endpoint	Result
<i>Nutr.J</i> 2025, PMID 39891239, three cohorts	one-sample MR, 2SLS	MMSE, Mental Alternation Test	per T allele +24.8 g/d (PsyCoLaus), +57.9 g/d (Rotterdam) dairy; no MMSE effect ; in CLSA MAT +3.4 points. Authors' verdict: causal evidence weak
<i>Nutrients</i> 2021, PMID 34445060	two-sample MR	MS, AD, ALS, PD	inverse association with AD and MS, positive with PD; ALS null (OR 0.97)
Bergholdt et al., PMID 29071499, Danish general population, n = 82,964 genotyped	MR	mortality	no association
Malmö Diet and Cancer, PMC8652079	MR, 2SLS	mortality	OR per 100 g 1.02 (0.96-1.09)
LDL, blood pressure, T2D, BMI, stroke	-	-	not verified in this round

16.3 Limitations

- 1. **Pleiotropy** — the LCT/MCM6 locus sits in a region of strong selection; linkage with neighbouring variants is possible.
- 2. **Population stratification** — allele frequency follows a north-south gradient in Europe correlating with height, diet and social structure; adjusting for height as a proxy is insufficient.
- 3. **Behavioural correlates** — lactase-persistent individuals drink more milk but thereby displace other beverages. Every MR result is a **substitution effect** against the diet of non-persistent individuals.
- 4. **Microbiome effect** — with lactase non-persistence, lactose reaches the colon and alters the microbiome (bifidobacteria); a route independent of milk quantity.
- 5. **Scope** — the instrument applies only to Europeans. The two-sample AD study is vulnerable to survival and diagnostic bias in AD GWAS consortia.

Grade: "drinking milk → cognition/AD" **C** with inconsistent direction; "drinking milk → mortality" **B** for the null effect.

Falsification criterion: If an MR with ≥50,000 dementia cases and a positive control (LCT → height) yields an OR per 100 g/d milk of 0.97-1.03, a drinking-milk effect on dementia in the European context is rejected.

Open methodological route: For cheese and cream, a multivariable MR with **cheese-specific instruments** (not LCT) would be needed, with butter as a negative control — Chapter 30, priority 5.

17. Sex and life stages (new)

Life stage	Available evidence	Grade
Infancy/childhood	MFGM in infant formula: systematic review with meta-analysis 2024 (PMC11280009) without conclusive proof of neurocognitive benefit	C
Midlife (45-65)	Du 2026 (observational, mean entry age 58.1 years, 61 % women); MR lifetime exposure	B (observational)
Later life (> 65)	MFGM RCTs 14-16 weeks; null result for objective cognition	B for short-term null
Menopause	NCT06953232 (postmenopausal women, acute, ongoing)	data gap
Sex interaction dairy × dementia	no robust data	data gap

The timing argument: The Swedish cohort captures a **midlife exposure** with 25 years of follow-up. That precedes or overlaps the estimated biomarker onset (≈49-52 years, BIOCARD) — i.e. the theoretically most relevant window. Sex-stratified results were not reported in the material reviewed.

The only sex-related finding is a subgroup result (episodic memory only in women, Calvo et al. 2023) and is hypothesis-generating.

Falsification criterion: If in pooled cohorts the interaction sex × cheese/cream for dementia yields $p > 0.1$ with $\geq 5,000$ cases, no sex-specific hypothesis is carried forward.

18. Substitution and plant-based alternatives

This chapter is the **falsification instrument** for milk specificity: every reduction in dairy is an increase in something else. Without a defined comparator, no statement about dairy is interpretable.

18.1 The substitute determines the sign

This is the chapter's single most important finding and carries **Grade A**. Source: Kiesswetter E, Neuenschwander M, Stadelmaier J et al., "Substitution of Dairy Products and Risk of Death and Cardiometabolic Diseases", *Curr Dev Nutr* 2024;8:102159, DOI 10.1016/j.cdnut.2024.102159 — systematic review with meta-analysis, 15 cohorts, 34 publications, GRADE.

replaced	with	endpoint	SRR (95 % CI)	GRADE
low-fat dairy	red meat	all-cause mortality	1.11 (1.06–1.16)	moderate
low-fat dairy	red meat	CHD	1.13 (1.08–1.18)	moderate
low-fat dairy	red meat	T2D	1.20 (1.16–1.25)	moderate
low-fat dairy	processed meat	T2D	1.41 (1.33–1.49)	moderate
yoghurt	eggs	T2D	1.44 (1.28–1.62)	moderate
dairy overall	whole grains	all-cause mortality	0.89 (0.84–0.93)	moderate
yoghurt	nuts	all-cause mortality	0.82 (0.72–0.94)	moderate
butter	olive oil	all-cause mortality	0.94 (0.92–0.97)	moderate
butter	olive oil	CVD mortality	0.96 (0.94–0.98)	moderate
cheese	avocado	CHD	0.81 (0.72–0.90)	moderate
dairy (full/low-fat)	red meat 125 g/d	stroke	1.10 (1.04–1.17) / 1.11 (1.04–1.17)	moderate

Standardised to 200 g/d milk/yoghurt, 30 g/d cheese, 5 g/d butter. **Null findings from the same work, reported on equal terms:** dairy→whole grains for T2D, dairy→nuts for T2D, full-fat→low-fat milk for T2D, butter→olive oil or avocado for stroke — no association in each case.

Corroborating: Neuenschwander M, Stadelmaier J, Eble J et al., *BMC Med* 2023;21:404, DOI 10.1186/s12916-023-03093-1 — dairy→nuts all-cause mortality SHR 0.94 (0.91–0.97); butter→olive oil CVD SHR 0.96 (0.95–0.98).

Consequence: "Milk is good" and "milk is bad" are both ill-formed statements. The same serving lowers or raises risk depending on what it displaces. Every statement in this work about milk is implicitly a statement about a substitution.

18.2 The central gap: substitution with a dementia endpoint — thinly populated, not empty

Two sub-statements must be kept apart.

(a) Dairy product → plant drink, water, coffee or tea, with a dementia or cognition endpoint: The 14.10.2026 research round found **no** substitution analysis. The largest relevant meta-analysis (Kiesswetter 2024) covers only mortality, cardiovascular disease and type 2 diabetes. **This is not evidence of non-existence:** PubMed, PMC and ScienceDirect were blocked; Scopus, Web of Science and the citing-article lists of Kiesswetter 2024 and Du 2026 were not searched.

(b) Dairy product → other food and the reverse, with a dementia or cognition endpoint: Three analyses from one cohort each exist. None adjusts or standardises vitamin B12, iodine, calcium or total protein (Du 2026 verified; Li 2025 and Ortega 2024 not checkable, hence not locatable).

Study	Design	n / follow-up	Result	Grade
Du Y, Borné Y, Samuelsson J et al., <i>Neurology</i> 2026;106(2):e214343, DOI 10.1212/WNL.00000000000214343, PMID 41406402, PMC12720290	prospective cohort, post hoc substitution	27,670; 3,208 cases; median	Replacing high-fat cheese with milk, fermented milk, high-fat red meat, processed meat: higher all-cause dementia risk ; for cream more foods. Individual HRs only in eFigure 4, not retrievable . The methods do not list milk as a replacement	C

(Malmö Diet and Cancer)	20 g/d high-fat cheese or cream → other food	24.9 y	(contradicts the results text). Without dietary change (n = 18,296): cheese HR 0.89 (0.77–1.02), n.s.; E-value 1.56	
Li Y, Li Y, Gu X et al., <i>Neurology</i> 2025;104(3):e210286, DOI 10.1212/WNL.00000000000210286, PMID 39813632 (NHS/HPFS)	prospective cohorts, 1 serving/d processed red meat → X	133,771; 11,173 cases; up to 43 y	→ nuts/legumes HR 0.81 (0.75–0.86). → fish 0.72 (0.64–0.80), poultry 0.84 (0.77–0.91) per primary text (PMC11735148). → low-fat dairy: set up as a replacement partner, HR only in eTable 9/figure, not read in the text ; the “13 %” comes from a secondary source (EUFIC) and stays unconfirmed; processed meat ≥ 0.25 vs. < 0.10 serv./d HR 1.13 (1.08–1.19) per primary text. Editors' Note 2026 (PMID 42546256) concerns this paper (letter without abstract), content unread ; eggs –23 % secondary source	C (text values primary-confirmed; dairy HR open)
Ortega N, Carmeli C, Efthimiou O et al., <i>J Nutr Health Aging</i> 2024;28(2):100031, DOI 10.1016/j.jnha.2023.100031 (CoLausPsyCoLaus). PMID 38388110 (confirmed in v3.2 through a University of Bern repository, secondary source)	prospective cohort, marginal structural models, reverse direction (other foods → dairy), 100 g/d each	1,334; median 67 y; 5.6 y	Primary endpoint Clinical Dementia Rating: no substantial, consistent effect . Secondary: fish→dairy 11.7 % (–3.0 to 26.5, n.s.); eggs→dairy 18.0 % (2.3 to 33.7). Endpoint is not incident dementia; case count of CDR decline not retrievable	C (null finding, low precision)
Kim JH, Kwon YJ, Lee Y et al., <i>J Nutr Health Aging</i> 2026;30(1):100740, DOI 10.1016/j.jnha.2025.100740, PMID 41314057 (UK Biobank)	prospective cohort, beverage substitution; beverages per abstract: sugar-sweetened, artificially sweetened, juice, coffee, tea	118,963; 992 cases; 13.45 y	Sugar-sweetened beverages > 1 glass/d HR 1.61 (1.28–2.02). Replacement by coffee or tea with lower risk (SHR about 0.64–0.75 per the authors' reply <i>J Nutr Health Aging</i> 2026;30(3):100796, PMID 41610624; sugar-sweetened beverages model 4 SHR 1.66 [1.32–2.08]). Milk is not among the beverages studied per the abstract, so no milk-specific substitution HR exists there (full text not read). A letter (30(3):100795; PMID 41610626, Wang H., title confirmed) criticises the assumption of isocaloric substitution	for milk: no statement possible
Tessier AJ, Cortese M, Yuan C et al., <i>JAMA Netw Open</i> 2024;7(5):e2410021, DOI 10.1001/jamanetworkopen.2024.10021, PMID 38709531 (NHS/HPFS)	prospective cohorts, endpoint dementia mortality , not incidence	92,383; 4,751 deaths per primary source (press releases: 4,571); 28 y	Olive oil > 7 g/d HR 0.72 (0.64–0.81). Replacing 5 g/d margarine or mayonnaise with olive oil: 8 % (4–12) to 14 % (7–20) lower. Replacing butter with olive oil not significant (primary text: “but not when substituting butter and other vegetable oils”; Figure 2A read uncorrected: HR 1.00 [0.92–1.08], provisional; note correction PMID 38916897)	C
Deng Z, Xie D, Cai J et al., <i>Clin Nutr</i> 2023;42(10):2058–67, DOI 10.1016/j.clnu.2023.08.019, PMID 37677911 (UK Biobank)	category analysis by mainly used milk type (single question), not a substitution model	307,271; 3,789 cases; median 12.3 y	Soy vs. no milk HR 0.69 (0.54–0.90); soy vs. other milk types 0.76 (0.63–0.92); Alzheimer's 0.70 (0.51–0.94); vascular dementia 0.72 (0.47–1.12). No dose; B12/iodine/protein adjustment not locatable; health consciousness an obvious confounder	D

Placement. The method is established for the dementia endpoint (Li 2025, Kim 2026, Tessier 2024). For dairy products as the *replaced* quantity exactly one analysis exists (Du 2026), and it shows: whoever replaces high-fat cheese with milk or meat has, per the results text, a higher dementia risk in this cohort (the methods do not list milk as a replacement; check against eFigure 4 pending) — consistent with the inverse cheese association (Chapter 14.1), but not independent of it, because it is the same cohort and the same coefficients. All findings rest on differences of regression coefficients from single measurements and assume constant energy; mechanistic readings (vitamin K2, MFGM, matrix) are explicitly speculative in the sources.

Milk as a beverage (v3.2). In Du 2026, milk ≥ 500 g/d shows no association with all-cause dementia (high-fat HR 0.95 [0.74–1.22]; low-fat 2020 HR 1.11 [0.97–1.28]; low-fat 2014 HR 1.24 [1.04–1.48], a signal graded **D**). This agrees with a Mendelian randomisation using a lactase-persistence instrument (Ortega N et al., *Nutr J* 2025, DOI 10.1186/s12937-025-01083-y, PMID 39891239; n = 43,836; no causal effect on cognition shown) and with the dose-response meta-analysis by Villos et al. (*Adv Nutr* 2024, PMID 38043604; inverse association only in Asian cohorts, European studies null). Overall rating for European cohorts: **B** (null finding). All three sources are available only as abstract or secondary report.

Side note Zhou 2023. Zhou J et al., *J Transl Med* 2023;21:130 (PMID 36803883; UK Biobank, n = 450,507) has all-cause mortality and cardiovascular endpoints, no dementia endpoint (soy 0.83 [0.75–0.93]; whole milk 1.05 [0.97–1.14]). It belongs to the cardiometabolic context (grade B, mortality), not to the dementia

table.

Plant-based indices are not dairy findings. In PDI and hPDI, milk enters as an animal component with a negative sign. A 2026 meta-analysis (PMID 41564649; 5 cohorts, N = 207,981) found −21 % for the highest hPDI tertile and +24 % for uPDI; the authors named vegetables, nuts, tea/coffee and legumes as drivers, **not** the avoidance of milk. The dairy contribution cannot be isolated from these indices (**Grade D** for the dairy question).

Falsification criterion: If a substitution analysis "dairy product → fortified plant drink" in a second, independent cohort (e.g. UK Biobank, EPIC) with B12 and iodine status as covariates and ≥ 3,000 dementia cases shows no association (p > 0.1), milk specificity for dementia is not sustainable.

18.3 The only genuine substitution RCT evidence

Erllich MN, Ghidanac D, Blanco Mejia S et al., "A systematic review and meta-analysis of randomized trials of substituting soymilk for cow's milk and intermediate cardiometabolic outcomes", *BMC Med* 2024;22:336, DOI 10.1186/s12916-024-03524-7. **17 RCTs** (10 crossover, 7 parallel), n = 504, median 4 weeks, median 500 ml/d. **The LDL finding comes from 10 of these trials (n = 312).** Funded by the United Soybean Board (USDA Soybean Checkoff Program) and the Canadian Institutes of Health Research; M. Messina works at the Soy Nutrition Institute Global, which is partly funded by the United Soybean Board; several authors declare ties to food, soy and dairy industries. In the original, CRP unit and value are inconsistent between abstract (−0.82 mg/l) and results section (−0.81 mg/dl).

Endpoint	Effect (95 % CI)	GRADE
LDL cholesterol	−0.19 mmol/l (−0.29 to −0.09)	high
Non-HDL cholesterol	−0.26 mmol/l (−0.43 to −0.10)	high
Systolic blood pressure	−8.00 mmHg (−14.89 to −1.11)	moderate
Diastolic blood pressure	−4.74 mmHg (−9.17 to −0.31)	—
CRP	−0.82 mg/l (−1.26 to −0.37)	—
Triglycerides, HbA1c, fasting glucose, insulin, weight, BMI, waist	null	—

Assessment: This is the cleanest substitution evidence in the entire work — randomised, with a defined comparator, on the endpoint that carries the project axis. The LDL effect of −0.19 mmol/l is of the same order as the butter-cream matrix difference (0.32 mmol/l, Chapter 10). **Grade B** (short durations, intermediate endpoints, no dementia endpoint).

18.4 Nutrient profiles: what the exchange actually shifts

Source: Walther B, Guggisberg D, Badertscher R et al., *Front Nutr* 2022;9:988707, DOI 10.3389/fnut.2022.988707 — laboratory analysis of 27 plant drinks from 8 categories plus 2 whole-milk samples, Swiss market 08/2019.

per 100 ml	Cow's milk 3.5 %	Soy	Oat	Almond
Energy (kcal)	65.5	41.6	41.5	32.8
Protein (g)	3.26	3.78	0.46	1.02
Fat (g)	3.54	2.06	1.45	2.56
Calcium (mg)	112.1	84.2*	49.9*	65.6*
Vitamin B12 (µg)	0.2	0.1*	0.1*	0.2*
Iodine (µg)	11.6	1.51	1.28	0.38
Riboflavin (µg)	108.3	57.8*	14.0*	54.9*
Vitamin D (µg)	not detectable	0.4*	0.3*	0.4*

* Mixed values from fortified and unfortified products. B12, riboflavin and vitamin D come overwhelmingly from fortification; unfortified drinks contained essentially none. **Pea drinks were not analysed — data gap.**

A source conflict that must not be resolved by averaging: for B12 in cow's milk per 100 ml three incompatible values exist — 0.2 µg (Walther, laboratory, 2 samples), 0.4 µg (Verbraucherzentrale NRW 2024, reference value), 0.61 µg (Drewnowski 2021, FNDDS, 1 % fat milk, USA). The work carries the spread. The same applies to calcium (112 vs. 126 mg) and riboflavin (0.108 vs. 0.14 µg).

Protein quality (DIAAS, Mathai JK, Liu Y, Stein HH, *Br J Nutr* 2017;117:490–99, pig-assay based): milk protein concentrate 141 (adults), skimmed milk powder 123, whey protein concentrate 133, soy protein isolate 98, soy flour 105, **pea protein concentrate 73**, wheat 54.

18.5 Fortification practice — the actual lever

Nutrient	EU/Germany (Verbraucherzentrale NRW 2024, n = 160)	USA (Drewnowski 2021, USDA Branded, n = 641)
Calcium fortified	87 % conventional, ~6 % organic	59 % reach 15 % DV/200 g
Vitamin B12	71 % conventional, 0 % organic	34 % reach the threshold
Riboflavin	47 % conventional, 0 % organic	16 % contain any B2, 0 % reach the amount
Iodine	29 % conventional, 0 % organic	not reported
All criteria met	not assessed	< 5 %

Where the EU fortifies, the practice matches cow's milk well (calcium usually 120 mg/100 ml, iodine 22.5 µg, B12 0.38 µg, riboflavin 0.21 mg) — but it is not applied across the board.

Documented regulatory cause: Regulation (EU) 2018/848 (Art. 7, Annex II Part IV 2.2.2 f) prohibits fortification of organic foods in principle. That is the evidenced reason for the near-complete absence of fortification in the organic segment — a case where a production standard and a nutrition standard run against each other.

Iodine, head to head (Bath SC, Hill S, Goenaga Infante H et al., *Br J Nutr* 2017;118(7):525–32, ICP-MS, 47 products): unfortified alternatives median 7.3 µg/kg = **2.1 % of conventional cow's milk** (344 µg/kg). Fortified products 278 µg/kg = 81 %.

18.6 The quantitative bridge: what a 1:1 exchange does

Lawrence AS, Russo-Batterham D, Doyle K, Tescari E., "Time to consider more than just calcium? The impact on protein, riboflavin, vitamin B12 and iodine intake of replacing cows' milk with plant-based milk-like drinks — an Australian usual intake dietary modelling study," *Eur J Nutr* 2025;64:182, DOI 10.1007/s00394-025-03697-8 — **dietary-intake model (usual-intake model), not a microsimulation**, n = 11,925, Australian NNPAS 2011–12, NCI method, 16 age/sex groups, 1:1 volume replacement of cow's milk with unfortified soy drink.

Nutrient	Mean change	Inadequacy (< EAR)
Protein (oat drink)	population ~unchanged; boys 2–8 y –7 to –11 %	≥ 99 % remain adequate
Riboflavin	–11 %, not significant	women 71+ 20 % → 31 %
Vitamin B12	–16 %, significant in all 16 groups ; boys 2–3 y –49 %	women 14–70 y doubling to 11–17 %; girls 9–13 y sevenfold to 9 %
Iodine	–12 % (–21 µg/d), significant ; boys 2–3 y –40 %	population 5 % → 10 %; women 2+ 8 % → 16 %
Calcium	not modelled — a data gap in the study itself	—

The actual microsimulation is Salomé M et al., *Am J Clin Nutr* 2025;122(4), PMID 40716520 (French adults, replacing meat and dairy with plant-based substitutes): deficiency risk for B12 and riboflavin rises; with calcium-fortified substitutes calcium stays covered, iodine risk rises. Source: research report 14.10.2026, primary page not retrieved, page numbers not locatable.

The decisive finding: calcium — the nutrient regulation and fortification rules target — was **not** limiting. **B12 and iodine were.** Corroborating: Biscotti L et al., *Nutrients* 2024;16:3083, DOI 10.3390/nu16183083. Counter-directionally, vitamin D **rises** with fortified drinks, because cow's milk is not vitamin-D-fortified in the EU.

18.7 MIND and Mediterranean patterns: the dairy component is a penalty

Pattern	Dairy component	Direction	Threshold
MIND (Morris et al. 2015)	cheese	negative	< 1 serving/week to score the point
MIND	butter/stick margarine	negative	< 1 tbsp/day
MIND	milk, yoghurt	not in the score	—
Mediterranean score (Trichopoulou 1995)	"milk and dairy products"	negative	low intake = 1 point; threshold population-relative (sample median)

The decisive test: Barnes LL, Dhana K, Liu X et al., "Trial of the MIND Diet for Prevention of Cognitive Decline in Older Persons", *NEJM* 2023, DOI 10.1056/NEJMoa2302368, PMC10513737 — RCT, n = 604, 3 years, both arms on equal mild caloric restriction. **Primary endpoint null: difference in global cognition 0.035 (–0.022 to 0.092), p = 0.23.** No imaging differences.

A pattern that actively restricts cheese and butter produced **no** cognitive advantage over three years. This neither falsifies nor supports a dairy effect — but it voids the common inference chain "MIND works → MIND restricts dairy → dairy harms". The premise does not hold in the RCT. **Grade A** for the null result.

No study compares cognitive endpoints with and without the dairy component in the score. That would be the chapter's most direct falsification instrument — it does not exist.

18.8 Vegan and vegetarian diets: where the B12 chain breaks

Level	Finding	Source
Exposure evidence	Serum B12: omnivores 281 pmol/l, vegetarians 182, vegans 122 . Deficiency (< 118 pmol/l): vegans 52 % , vegetarians 7 %	Gilting AMJ et al., <i>Eur J Clin Nutr</i> 2010;64(9):933–39, n = 689
Observed homocysteine → dementia	RR range 1.15–2.5 across meta-analyses	Smith AD et al., <i>J Alzheimers Dis</i> 2018;62(2):561–70 (consensus paper, not a systematic review)
Interventional counter-finding	MMSE difference vs. placebo: with cognitive impairment 0.16 (–0.18 to 0.51); without 0.04 (–0.10 to 0.18). 31 RCTs, 1,925 + 15,104 participants	Ford AH, Almeida OP, <i>Drugs Aging</i> 2019;36(5):419–34, PMID 30949983
Unfavourable finding	EPIC-Oxford: vegetarians total stroke 1.20 (1.02–1.40) , haemorrhagic 1.43 (1.08–1.90) ; IHD 0.78 (0.70–0.87). Vegans separately: stroke 1.35 (0.95–1.92), not significant	Tong TYN et al., n = 48,188, mean 18.1 y
Plant-based patterns and dementia	Meta-analysis 2026, 7 studies, 221,380 participants: RR 0.74 (0.56–0.97), I ² = 92.3 % . Rotterdam (de Crom 2023, n = 9,543): PDI, hPDI, uPDI all null	<i>J Prev Alzheimers Dis</i> 2026, DOI 10.1016/j.tjpad.2026.100521

The chapter's hinge: the B12 axis robustly meets the conditions of a **confounder** in vegetarian-vegan cohorts. As a **mediator** of a dairy effect on cognition it fails the interventional test: 31 RCTs with over 17,000 participants show no cognitive benefit from B-vitamin supplementation, although homocysteine is reliably lowered. Absence of demonstrated effect is not demonstration of absence — but the mechanistically most attractive explanation of a nutrient-mediated dairy effect on the brain is interventionally **unsupported** (**Grade E** for "B-vitamin supplementation improves cognition").

18.9 Evidence grades and falsification role

Statement	Grade
The substitute determines the sign of the "dairy effect" (cardiometabolic)	A
The substitute determines the sign for the dementia endpoint	C (one cohort, Du 2026)
"B12 explains the milk-dementia associations" (strong form)	D — established clinically in manifest deficiency (B); no cognitive benefit of supplementation in non-deficient people (E)
MIND intervention yields no cognitive advantage over 3 years	A
Unfortified plant drinks supply negligible iodine (~2–3 % of cow's milk)	A
Soy is the only plant drink with milk-equivalent protein	A
Vegans: ~52 % B12 deficiency prevalence without supplementation	A
Soy drink instead of cow's milk lowers LDL by 0.19 mmol/l	B
Dairy → whole grains/nuts/olive oil lowers all-cause mortality	B
1:1 replacement with unfortified soy drink significantly lowers B12 and iodine	B
Organic plant drinks in the EU are effectively unfortified (legal cause: Reg. 2018/848)	B
Vegetarian diet and haemorrhagic stroke	B
Plant-based patterns lower dementia risk	C (RR 0.74, but I ² = 92.3 %; Rotterdam null)
B12 as mediator of a dairy-cognition effect	C as hypothesis, interventionally unsupported
B-vitamin supplementation improves cognition	E

Falsification role: If cardiometabolic and cognitive differences between dairy and plant-drink consumers disappear after adjustment for B12, iodine, calcium and protein quantity, milk specificity is falsified and the effect is nutrient-mediated. Per 18.6 that is the most likely reading for iodine and B12 — but not for LDL (18.3), where measurement was randomised and matrix-based.

Remaining data gaps: no substitution analysis milk → plant drink for dementia, cognitive decline or mortality; no mediation analysis with measured iodine, B12 or riboflavin; no prospective cohort on **vegan** diets with a dementia endpoint; no Austrian plant-drink market audit; no analytical values for pea drinks, saturated fatty acids and sugar types by category.

PART III — TRANSDISCIPLINARY LAYERS

19. Historical-anthropological layer (newly sourced)

Lead source: Evershed RP, Davey Smith G, Roffet-Salque M et al., "Dairying, diseases and the evolution of lactase persistence in Europe," *Nature* 2022;608(7922):336–345, DOI 10.1038/s41586-022-05010-7 (author correction *Nature* 2022;609:E9).

Design: A database of 6,899 animal fat residues from 13,181 pottery fragments across 826 phases at 554 archaeological sites spanning 9,000 years, combined with aDNA, radiocarbon dating and UK Biobank data.

Result: The **extent of dairying did not explain selection for lactase persistence**. Indicators of famine and pathogen exposure explained it better. The lactase persistence variant is first detected around 4700–4600 BC but only became common around 1000 BC — several thousand years of dairying without widespread persistence.

Mechanism under the model: Non-persistent individuals consumed milk; under famine and infection pressure, the resulting diarrhoea raised mortality. A counter-position (*Opinion*, PMC9910737) argues that the caloric gain from lactose digestion also contributed to selection.

Interpretation for this work: Milk consumption is culturally **older** than the genetic adaptation. Lactase persistence is a selection event under stress conditions — neither evidence for "milk as natural adult food" nor for the opposite. The question "is milk species-appropriate?" is historically undecidable and is not asked in this work.

Evidence grade: **A** for the archaeological-genetic finding; **C** for the famine/pathogen explanatory model (model inference, not experimental).

Data gap: regional patterns outside Europe (Africa, Near East, South Asia).

20. Agricultural and food-system layer (newly sourced)

20.1 Structure of Austrian dairy farming

Source: AMA, "Key figures of Austrian dairy farming" (data basis Statistik Austria/AMA). Farm-gate producer price for natural constituents, excluding VAT.

Year	Milk-delivering farms	Dairy cows	Ø cows/farm (derived)	Deliveries (t)	Producer price (EUR/100 kg)
2015	29,124	539,000	18.5	3,103,081	33.73
2017	27,587	540,820	19.6	3,199,746	37.31
2019	25,608	526,700	20.6	3,139,802	37.01
2021	23,868	526,461	22.1	3,153,827	39.67
2022	23,178	550,554	23.8	3,499,179	50.22
2023	22,419	543,032	24.2	3,534,616	51.67
2024	21,557	535,810	24.9	3,584,468	50.32

Ten-year comparison (Grüner Bericht, fact sheet "Farms with milk deliveries 2025"): farms 2015 = 31,182 → 2025 = 21,736, i.e. **−30 %**; deliveries **+18.5 %**; mean delivery per farm 99,500 kg → 169,000 kg, **+70 %**. The divergence from the AMA figure for 2015 arises from the counting method (annual course versus December snapshot).

Status 2025 (Statistik Austria, milk statistics 2025): raw milk production 4,079,860 t; deliveries 3,678,612 t (90.2 %); dairy cows 534,837 on annual average; **milk yield 7,628 kg per cow and year** (+2.3 %); organic raw milk 775,011 t (19.0 %); self-sufficiency ratio for drinking milk 176 %.

Structure 2025 (Grüner Bericht, fact sheet): 19,729 farms in less-favoured areas (91 % of farms, 89 % of deliveries); 5,474 organic suppliers (679,382 t); 5,074 hay-milk suppliers (536,285 t, of which 235,484 t organic hay milk); 11,515 farms above 100,000 kg (86 % of deliveries); 110 farms above 1,000,000 kg; 2,210 farms with milking robots (27 % of milk robot-milked). Farm closures 2025: 1,050; new entrants 123.

Interpretation for this work: The structural trend is consolidation without herd-size explosion — Austria remains a small-farm country (Ø 24.9 cows), but output per farm rose 70 % in ten years. The per-cow yield of 7,628 kg sits markedly below the EU high-yield countries. For Chapter 5 this matters: the metabolic burden described there (negative energy balance, subacute ruminal acidosis, heat stress) scales with yield per cow, and the Austrian mean is a moderate-yield system, not a high-yield one.

20.2 Price formation and volatility

Source: EU Milk Market Observatory, raw milk price series (EUR/100 kg, actual fat and protein content).

Month	Austria	EU average
2024-07	48.11	46.90
2024-10	52.56	50.26
2025-01	55.49	53.19
2025-04	54.25	52.11
2025-07	54.57	51.03
2025-10	58.49	52.33
2025-12	56.11	47.98
2026-03	46.74	42.91
2026-07	44.99	42.05

Austria lies above the EU average throughout; the gap widens to roughly 6 EUR/100 kg by October 2025. The 2026 downturn is steep: from October 2025 to July 2026 the Austrian price loses **13.5 EUR/100 kg, or 23 %**.

Composition of the dairy settlement (AMA, Milk Market Report 11/2026, November 2025, net, cents/kg): base price 28.15 + fat payment 12.44 + protein payment 11.73 + voluntary quality premium 2.52 + organic supplement 0.97 + hay-milk supplement 0.25 + organic hay-milk supplement 0.89 – deductions 0.36 = 56.59 cents/kg at 4.34 % fat and 3.56 % protein. **The individual line items cannot in every case be unambiguously assigned from the PDF; the total is secure.**

Price differential by category (November 2025, net): conventional 54.47; hay milk 57.79 (+3.32); organic milk 62.94 (+8.47); organic hay milk 68.63 (+14.16) cents/kg. According to the Grüner Bericht, about 60 % of organic milk receives an organic supplement averaging 7.73 cents/kg net.

Producer price against production cost — a data gap for Austria. The only EU cost calculation (European Milk Board, "Gesamtschau 2024", computed by BAL — **an association publication, not official statistics**) does not include Austria: EU mean 50.38 EUR/100 kg cost against 48.42 producer price, i.e. **−4 % cost coverage**; Germany −14 %, France −24 %, Denmark +13 %. For Austria only a ten-year-old full-cost calculation from a self-selected advisory group exists (Kirner 2018, reference year 2016, 102 farms: full cost Ø 67.1 cents/kg, break-even 43.5 cents/kg, calculated profit −6.3 cents/kg, roughly a quarter of farms positive). **The ratio of producer price to production cost in Austria is not quantifiable from the accessible sources.**

20.3 CAP payments

Pillar 1, unit amounts Austria (BMLUK, working paper on direct payments, amounts subject to $\pm 10\%$), EUR/ha: basic income support home farm 216.76 (2023) to 218.13 (2027); alpine pasture areas 41.18 to 43.17; redistributive support tier 1 (up to 25 ha) 32.85 to 36.08; young farmer support 62.74. Annual volumes: basic income support home farm EUR 483.3 m, redistribution EUR 50.8 m, young farmers EUR 13.6 m.

Compensatory allowance (AMA, leaflet 2025): no fixed amounts but area-tier formulas based on handicap points (EP). Livestock-keeping home farm, 0–10 ha: $2.27 \times EP + 76$ (below 180 EP) or $2.42 \times EP + 81$ (from 180 EP) EUR/ha; above 70 ha no premium. Non-livestock farms receive roughly one third. **Since 91 % of Austrian dairy farms lie in less-favoured areas, the compensatory allowance is the central area-based payment for this sector.**

ÖPUL, dairy-relevant measures (AMA information sheets, as at 10/2025): hay farming/silage abstention, livestock-keeping 145.8 EUR/ha (from 2024); animal-welfare pasture base premium 40–60 EUR/LU at 120 grazing days; herding 81 EUR/LU plus dairy-cow supplement 151.2 EUR/LU for the first 20 LU; organic grassland base module, livestock-keeping 232.20 EUR/ha (< 1.4 LU/ha); animal-welfare housing cattle 194.40 EUR/LU; alpine farming 43.20 to 86.40 EUR/ha. With application year 2024 all ÖPUL rates and the compensatory allowance were raised by at least 8 % under the impulse programme (EUR 360 m).

Disbursement volume 2025 (AMA main payment, BMLUK), about EUR 1.34 bn: direct payments EUR 571.6 m; ÖPUL EUR 445.5 m; compensatory allowance EUR 214.6 m; CO₂ refund and agricultural diesel compensation EUR 75.3 m; project-related EUR 29.4 m. Total public funds 2025: about EUR 2,828 m (50 % EU, 26 % federal, 24 % provinces).

Incomes (Grüner Bericht 2026, data year 2025, 1,919 account-keeping farms, **means**): income all farms EUR 47,102 (+18 %); forage-growing farms EUR 47,215 (+31 %); **specialised dairy farms EUR 71,900 (+37 %)**; public funds Ø EUR 23,944 per farm; **share of public funds in total revenue 14 %** (all farms). Drivers in 2025: milk price +13 %, volume +4 %.

Data gap: The share of public funds in revenue **specifically for dairy farms** and its breakdown by payment type appears only in the table section of the Grüner Bericht, which was not retrievable. The 14 % figure applies to all farms, not to dairy.

Connection to Chapter 5: The economic argument closes here. Yield-oriented breeding and the metabolic burdens of Chapter 5.1/5.2 are not free-standing agronomic choices; they sit in a price environment that lost 23 % in nine months and in which cost coverage at EU level is negative. Public transfers average 14 % of revenue and are, for 91 % of Austrian dairy farms, tied to less-favoured-area status. This does not make the production system a cause of any human health outcome — it explains why the milk phenotype described in Chapter 5 is produced as it is.

20.4 Consumption trends

Source: Statistik Austria, supply balance sheets for animal products 2025 (published 01.09.2026), kg per capita.

Product	2024	2025
Drinking milk (incl. raw milk)	51.5	51.3
Other liquid dairy products (incl. yoghurt)	24.1	26.0
Cheese and processed cheese	26.5	27.8
Cream	7.6	7.5
Butter	5.2	5.2

A methodological break that must stand in the record: For drinking milk 2024, AMA reports 42.7 kg and Statistik Austria 51.5 kg — a 17 % difference arising from different treatment of raw milk and direct consumption. Both series are quasi-official but **not mixable**. Yoghurt is not reported separately in Austria; milk powder receives no per-capita figure.

Germany as a comparison series (Milchindustrie-Verband, as at April 2026): drinking milk 49.6 (2019) → 45.1 kg (2025); cheese 25.1 → 26.4; yoghurt/soured milk 29.2 → 32.0; butter 5.8 → 5.6. **The pattern is the same in both countries: drinking milk falls, cheese and fermented products rise.** For the exposure question of this work this is material — the category for which epidemiology shows inverse associations (cheese) is growing; the one with null findings (drinking milk) is shrinking.

Data gaps: a continuous Austrian per-capita time series 2015–2026 from a single source; market share and growth rates of plant-based alternatives in Austria and the EU (not reported in the official sources checked); EU price series before 2024.

21. Ecological layer (newly sourced)

21.1 Comparative balance per litre

Source: Poore J, Nemecek T, "Reducing food's environmental impacts through producers and consumers," *Science* 2018;360(6392):987–992 (meta-analysis of LCA data).

Beverage (per litre)	Greenhouse gases (kg CO ₂ e)	Land use (m ²)	Freshwater (l)
Cow's milk	3.15	8.95	628.2
Rice drink	1.18	0.34	269.81
Soy drink	0.98	0.66	27.8
Oat drink	0.90	0.76	48.24
Almond drink	0.70	0.50	371.46

Methodological limitation: The comparison is **per litre**, not per nutrient unit. Per gram of protein the gap to the soy drink narrows markedly — cow's milk 3.26 g/100 ml against soy 3.78, but oat 0.46 and almond 1.02 (Chapter 18.4). For oat and almond drinks with their low protein content the advantage per unit of protein is therefore **not** sustainable (**Grade E** for the claim that the gap stays equally large per nutrient unit). Newer LCA work 2022–2026 was not researched.

21.2 The nitrogen bridge

This is the cleanest transdisciplinary connection in the entire work: **the same measurement (MUN) is both a metabolic marker of the cow and an environmental indicator.**

- Mean nitrogen use efficiency of dairy cows: 24.5–29.6 % (Chapter 5.2).
- In a regression across 580 cows, roughly **72 % of ingested nitrogen was excreted via faeces and urine.**
- A Chesapeake Bay study put the nitrogen load from protein overfeeding at 7.6 million kg/year and defined MUN target values of 8–14 mg/dl.
- MUN correlates negatively with nitrogen efficiency at herd level ($r = -0.43$).

Conclusion: MUN is a defensible **environmental indicator** — and precisely **not** the human health marker it was treated as in the project's initial hypothesis (phase 7). Over the course of the project the measurement migrated from the wrong level to the right one. **Grade A** for environmental relevance, **E** for human neurotoxicity.

22. Regulatory and legal layer (newly sourced)

Legal position as at 13.10.2026. Pure documentation of statutory texts and authority assessments; no legal advice, no interpretation beyond the wording.

22.1 Verified: protected designations

Court of Justice of the European Union, judgment of 14 June 2017, Case **C-422/16** (Verband Sozialer Wettbewerb eV v TofuTown.com GmbH), ECLI:EU:C:2017:458, corrected 19 July 2017 (ECLI:EU:C:2017:567). Legal basis: Regulation (EU) 1308/2013 Art. 78 and Annex VII Part III, and Decision 2010/791/EU.

Content: Purely plant-based products may not be marketed as "milk," "butter," "cheese," "cream" or "yoghurt" — not even with a clarifying addition. Exceptions only per Annex I of Decision 2010/791/EU.

Relevance here: The legal position enforces a linguistic separation that runs counter to nutritional comparability. For substitution analyses (Chapter 18) this is a practical problem: products that substitute functionally carry legally incomparable designations.

22.2 Raw milk limits

Regulation (EC) No 853/2004, **Annex III, Section IX, Chapter I, Part III, point 3(a)**:

Parameter	Limit	Averaging	Number of samples
Plate count at 30 °C per ml	≤ 100,000	rolling geometric mean over two months	at least two samples per month
Somatic cell count per ml	≤ 400,000	rolling geometric mean over three months	at least one sample per month

Under recital 23 these are **trigger values**: exceeding them requires corrective action and notification, not automatically a ban on marketing. Under Art. 10(8)(b) Member States may permit the use of non-compliant raw milk for cheese matured at least 60 days.

Source caveat: The official **German-language** wording of this table was not retrievable via EUR-Lex; the values come from the official English version and a German secondary presentation, which agree. Check against CELEX 02004R0853 before publication.

Austria: Raw Milk Ordinance, BGBl. II No. 106/2006, legal basis § 14(1) LMSVG. § 2(1): supply only directly from the animal keeper to the final consumer or to retail undertakings. § 2(2): supply to **schools and kindergartens prohibited**. § 3: supply via a **milk vending machine** tested against recognised criteria is permitted. § 5: notice "raw milk, boil before consumption" on a clearly legible sign.

22.3 Health claims

Legal basis Regulation (EC) No 1924/2006; authorised Art. 13 claims in Regulation (EU) No 432/2012, Annex. Condition of use throughout: the food must be at least a "source of [nutrient]".

Authorised, dairy-relevant (selection, official English wording):

Nutrient	Claim	EFSA Journal
Calcium	"Calcium is needed for the maintenance of normal bones" / "...normal teeth"	2009;7(9):1210; 2010;8(10):1725
Calcium	"Calcium contributes to normal muscle function" / "...neurotransmission" / "...blood clotting" / "...energy-yielding metabolism"	2009;7(9):1210
Protein	"Protein contributes to a growth in muscle mass" / "...maintenance of muscle mass" / "...maintenance of normal bones"	2010;8(10):1811
Riboflavin	ten claims, including "...contributes to normal energy-yielding metabolism", "...normal functioning of the nervous system", "...reduction of tiredness and fatigue"	2010;8(10):1814
Iodine	"Iodine contributes to normal cognitive function" plus thyroid function, nervous system, energy metabolism, skin	2009;7(9):1214; 2010;8(10):1800
Live yoghurt cultures	"Live cultures in yoghurt or fermented milk improve lactose digestion..." (≥ 10 ⁸ CFU per gram)	2010;8(10):1763
Lactase enzyme	"Lactase enzyme improves lactose digestion..." (food supplements only, ≥ 4,500 FCC units)	2009;7(9):1236

The iodine claim on **cognitive function** carries particular weight for this work: it is the only authorised cognition-related claim that runs through a nutrient which cow's milk supplies in relevant quantity and unfortified plant drinks essentially do not (Chapter 18.5). The regulatorily recognised cognition link of milk therefore runs **through iodine, not through milk constituents**.

Rejected, dairy-relevant:

Substance	Claimed effect	EFSA conclusion	Reference
Lactotripeptides IPP/VPP from hydrolysed milk protein	maintenance of normal blood pressure	"The evidence presented is not sufficient to establish a cause and effect relationship"	EFSA Journal 2009;7(9):1259
IPP/VPP	arterial elasticity	"A cause and effect relationship has not been established"	ibid.
Hydrolysed milk proteins, fermented milk products	blood pressure	insufficient characterisation of the substance	ibid.
<i>Lactobacillus plantarum</i> 299v	immune system	effect not sufficiently defined	EFSA Journal 2010;8(2):1488
<i>L. casei</i> Shirota in a fermented milk product	—	authorisation refused	Regulation (EU) No 1171/2011
<i>L. plantarum</i> TENSIA™ in cheese	blood pressure/heart health	authorisation refused	Regulation (EU) No 1171/2011

Data gap: The wordings of the authorised vitamin B12 claims were not retrievable in the annex to the regulation (annex readable only as far as "Selenium"); only the underlying EFSA assessment is documented (EFSA Journal 2009;7(9):1223). No authorised claim exists for **lactose as a nutrient**.

22.4 EFSA assessments of milk constituents

Subject	Reference	Core statement
Bovine lactoferrin (Morinaga)	EFSA Journal 2012;10(7):2811, DOI 10.2903/j.efsa.2012.2811	"the novel food ingredient, bLF, is safe under the proposed uses and use levels"
Bovine lactoferrin (FrieslandCampina)	EFSA Journal 2012;10(5):2701, DOI 10.2903/j.efsa.2012.2701	safe under the proposed uses
β-casomorphins and related peptides	EFSA Scientific Report (2009) 231, DATEX working group, EFSA-Q-2008-379, 107 pp. (no DOI assigned)	A cause-and-effect relationship between oral intake of BCM7 or related peptides and disease cannot be established ; a formal EFSA risk assessment of food-derived peptides is not recommended
MFGM	—	No EFSA opinion locatable — neither novel food nor health claim. Only FSANZ (application A1307, AU/NZ, approved 2025) and a UK FSA consultation were found

The individual DATEX findings on β-casomorphins: autism, "recent data do not provide any support for such a relationship"; SIDS, "no clear evidence"; cardiovascular, "no strong evidence for a link" between β-casein A1 and CVD risk, with the LDL oxidation hypothesis unconfirmed in later studies; type 1 diabetes, only ecological indications without evidence of causality. **The entire β-casomorphin strand has thus been examined by an authority and decided negatively — it is not carried forward in this work (Grade E).**

22.5 BSE/TSE: milk as a safe commodity

WOAH *Terrestrial Animal Health Code*, Chapter 11.4 "Bovine spongiform encephalopathy," **Article 11.4.2 "Safe commodities"** (2024 edition; in the 2022 edition carried as Art. 11.4.1(1)(a) — **cite the edition with its year**):

"When authorising the importation or transit of the following commodities derived from bovines, Veterinary Authorities should not require any conditions related to BSE, regardless of the BSE risk posed by the bovine population of the exporting country, zone or compartment:"

Entry number 1 on that list: "milk and milk products".

The hypothesis "milk as a relevant BSE transmission route," rejected on mechanistic grounds in Chapter 3, is thus also closed **in regulatory terms**: milk is internationally classified as a safe commodity irrespective of the BSE status of the population of origin (**Grade A** for the classification, **E** for the transmission hypothesis).

The relevant EFSA opinion (EFSA Journal 2008, DOI 10.2903/j.efsa.2008.849) concerns **small ruminants**, not cattle: milk from flocks with classical scrapie can expose animals and humans; since classical scrapie has not been demonstrated in humans, the finding bears mainly on animal health. For atypical scrapie and BSE, data on presence in milk were lacking. **An EFSA statement specifically on cow's milk as a BSE transmission route was not locatable.**

23. Sociology-of-science and methodological-critique layer (newly sourced)

23.1 Documented error types from this work itself

1. **Non-matrix-matched controls.** The largest MFGM intervention study (n = 263) uses rice starch as control — a design that attributes effects of the **whole matrix** to a **single constituent** (Chapter 10.3).
2. **Single-study-driven certainty ratings.** A published letter criticises the 2026 meta-analysis for deriving a "moderate certainty" statement for LDL from an estimate driven by one study (Chapter 10.2).
3. **One-off exposure assessment.** The 25-year cohort rests on an FFQ at baseline (1991–1996); 25 years of exposure change go unrecorded (Chapter 14.1).

23.2 Why dietary RCTs with dementia endpoints are barely feasible

Obstacle	Order of magnitude
Incidence	1-2 % per year at age 65 → tens of thousands of participants over ≥ 10 years for a 15 % risk reduction
Adherence	declines over years in food interventions
Blinding	practically impossible with foods
Substitution	unavoidable (Chapter 18.1)

Consequence: In the diet-dementia question, evidence grades sit **systematically at B-C rather than A** — for structural reasons, not for lack of research. Anyone expecting Grade A in this field expects the unattainable. That is not an argument for rating weaker evidence higher.

23.3 Industry funding: the finding and its limits

All the work below consists of **observational analyses of study corpora**, not randomised comparisons. Confounding through choice of topic, comparator and endpoint is structurally possible; the exposure variable is almost always *declared* funding, which tends to understate the association.

Work	Corpus	Effect measure (95 % CI)	Grade
Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L, <i>Cochrane Database Syst Rev</i> 2017;MR000033.pub3, DOI 10.1002/14651858.MR000033.pub3	75 studies (pharmaceuticals)	favourable results RR 1.27 (1.17-1.37); favourable conclusions RR 1.34 (1.19-1.51); agreement result→conclusion RR 0.83 (0.70-0.98)	A (drug-related)
Lesser LI, Ebbeling CB, Gozner M et al., <i>PLoS Med</i> 2007;4(1):e5, PMID 17214504	206 articles on beverages, including milk	favourable versus unfavourable OR 7.61 (1.27-45.73); with industry funding only, 0 % unfavourable conclusions against 37 % without (p = 0.009)	B
Chartres N, Fabbri A, Bero LA, <i>JAMA Intern Med</i> 2016;176(12):1769-77, PMID 27802480	12 reports, 340 studies	favourable conclusions RR 1.31 (0.99-1.72), not significant ; no association with significance or methodological quality	B/C
Sacks G, Riesenber D, Mialon M et al., <i>PLoS ONE</i> 2020;15(12):e0243144	1,461 articles from 10 top journals, 2018	industry-linked 55.6 % industry-favourable findings against 9.7 % without involvement; dairy sector = 27.0 % of industry-linked articles	B

The dairy-specific finding is a null finding. Chartres N, Fabbri A, McDonald S et al., *BMJ Open* 2020;10(12):e039036, PMID 33277278 — systematic review with meta-analysis, 43 studies on dairy products and CVD/mortality, 14 with industry ties:

- favourable **results** 1/14 against 8/29: RR 0.26 (0.04-1.87), not significant
- favourable **conclusions** 4/14 against 11/29: RR 0.75 (0.29-1.95), not significant
- **effect size:** pooled HR 0.78 (3 studies) against 0.97 (18 studies), **ratio of HRs 0.80 (0.66-0.97), p = 0.03**

What differs is not the rhetoric but the point estimate. With 14 against 29 studies the power is low; non-significance here is **not** readable as evidence of absence. A second null finding is confirmatory: Mishali M, Kisner M, Avrech T, *Int Dairy J* 2019;95:65-70 — 29 cohorts, no significant subgroup difference; **however, published in an industry journal, and the author group declares the Israel Dairy Board as funder in related work.**

Counter-position, to be carried along as a matter of obligation:

Finding	Source
Wholegrain counterpart: favourable results RR 1.44 (0.88-2.35), n.s.; effect sizes practically identical (p = 0.50, I ² = 0 %)	Chartres et al., <i>BMJ Open</i> 2019;9(5):e022912
Systematic reviews: favourable conclusions RR 1.98 (1.26-3.11), but statistically favourable results RR 0.84 (0.62-1.14) ; authors' conclusion: "uncertain whether financial conflicts of interest are associated with the results "	Hansen C, Lundh A, Rasmussen K, Hróbjartsson A, <i>Cochrane Database Syst Rev</i> 2019;MR000047.pub2
White hat bias: 84 % and 66 % respectively of 207 citations presented null findings on sugar-sweetened beverages misleadingly positively; industry-funded work was, per the accompanying editor's note, more accurate in reporting negative data	Cope MB, Allison DB, <i>Int J Obes</i> 2010;34(1):84-88, PMID 19949416
Reception bias: in a randomised vignette experiment with over 500 internists, readers rated identically described studies as methodologically weaker purely on the basis of the industry label	Kesselheim AS, Robertson CT, Myers JA et al., <i>NEJM</i> 2012;367(12):1119-27, PMID 22992075

The pattern across all this work: the association is clear for the endpoint "conclusion," weak or undetectable for "result" and "effect size." Lundh et al. quantify the gap directly: lower agreement between result and conclusion in industry-sponsored studies (RR 0.83). Two readings are compatible with this —

sponsorship influences interpretation rather than data; or "favourable conclusion" is the softest measure in the instrument set and the most susceptible to coder expectation. **No locatable work tests the second reading empirically.**

Disclosure practice (Grade A): funding is declared in 54–95 % of papers, author conflicts of interest in only 29.6–90.1 % — depending on study type and year. Author COI is consistently disclosed worse than project funding. Absent disclosure is itself associated with more favourable conclusions (Baram L et al., *Public Health Nutr* 2022;25(8):2288–95: RR 1.56; 1.05–2.31).

The gap relevant to this work: an analysis quantifying the share of dairy-funded studies across the **whole** milk-and-health literature — beyond CVD, i.e. bone, weight, cancer, blood pressure, cognition — does not exist. The largest current review of dairy consumption and health endpoints (Akyil S et al., *Eur J Clin Nutr* 2025, DOI 10.1038/s41430-025-01639-5, 95 reviews) does **not** assess funding or conflicts of interest of the included work at all; it is itself funded by the Bavarian State Ministry of Agriculture.

23.4 Self-application

This work is privately funded, without institutional affiliation, without third-party grants, not peer-reviewed and hypothesis-generating. The error types named in 23.1 apply to it as well: the evidence matrix rests on a non-systematic literature search; several citations were for a time wrongly carried as "not locatable" (Chapter 0); the product × endpoint matrix rests, for dementia, predominantly on **one** cohort. Following Kesselheim 2012 the inverse bias must also be considered: the absence of industry funding is not proof of quality.

24. Ethical layer (newly sourced)

A descriptive findings report. The ethical argument uses its own sources and is **not** derived from the health findings; conversely, no health finding is weighted by ethical argument.

24.1 The regulatory stocktaking

EFSA Panel on Animal Health and Animal Welfare (AHAW), "Welfare of dairy cows," *EFSA Journal* 2023;21(5):e07993, DOI 10.2903/j.efsa.2023.7993. Method: literature reviews plus expert knowledge elicitation.

Welfare consequence	Finding on the system comparison
Locomotory disorders (lameness)	no housing system consistently better; high risk with cubicles having thin bedding or mats
Mastitis	no substantial system differences; the only housing-related hazard is bedding
Restriction of movement and resting	greatest restriction in tie-stalls; open bedded systems and pasture more favourable
Comfort behaviour	tethering restricts severely
Metabolic disorders (ketosis, SARA, hypocalcaemia)	no substantial system differences

A methodological limit the opinion names itself: the literature yielded **no** clear relationships between milk yield or herd size and welfare; the panel had to fall back on expert knowledge. Recommended thresholds: at least 9 m² total indoor area per cow, at least one cubicle per cow, pasture access ≥ 2 months/year, on-farm mortality ≤ 8 %. On tethering: "Dairy cows should not be permanently housed in tie-stalls."

24.2 Prevalences

Measure	Value	Area	Source
Lameness, study mean	22.8 % (median 22.0)	6 continents, 53 studies, 414,950 cows	Thomsen PT, Shearer JK, Houe H, <i>Vet J</i> 2023;295:105975
Lameness, Europe	22.0 % (median 20.6)	29 studies	ibid.
Severe lameness	7.0 % (median 6.5)	24 studies	ibid.
Range within herds	0–88 %	35 studies	ibid.
Time trend	no clear trend (older 24.3 %, newer 21.5 %, p = 0.37)	—	ibid.
Lameness, pooled (lenient)	28 % (23–33)	north-west Europe, 53 studies	Wessels W et al., <i>J Dairy Sci</i> 2025;108(9):10037–59, PMID 40614806
Mild clinical mastitis, median	11.8–16.2 % by region	Germany, 765 farms	Böker AR et al., <i>Front Vet Sci</i>

farm incidence/year			2023;10:1193301
Severe clinical mastitis	2.0–4.0 %	ibid.	ibid.
Heifer mastitis rate	23.5–35.7 %	ibid.	ibid.

Data gap: A defensible pooled European prevalence of **subclinical** mastitis could not be found; the large German study reports cell-count measures instead of prevalence.

24.3 Productive lifespan and housing in Austria

ZuchtData, annual report 2025 (16,868 recording farms, 437,621 recorded cows = 82 % of all dairy cows):

Measure	Value 2025
Productive lifespan	4.01 years
Calvings at culling	4.05
Milk yield per cow	8,188 kg
Lifetime yield	33,690 kg

Culling reasons (% of all culls): fertility 20.9; sale for breeding 16.5; other reasons 14.6; **udder disease 13.2**; age 7.8; **claw and limb disease 7.3**; yield 6.0; injury 3.8; not recorded 3.4; metabolism 2.8.

Methodological limit: "sale for breeding" (16.5 %), "other reasons" (14.6 %) and "not recorded" (3.4 %) together account for 34.5 % of culls and cannot be assigned to a health cause.

Housing systems (Statistik Austria, agricultural structure survey 2020, full census): dairy cows in loose housing **63 %**, in tie-stalls **35.6 %**. All cattle: loose housing 65.4 % (2010: 49 %). Regionally: tie-stalls Tyrol 52 %, Salzburg 36 %, Vorarlberg 34 %. 71 % of dairy farms with regular grazing, Ø 6.3 months/year.

Legal framework: permanent tethering has been prohibited in Austria since 2020, with justified exemptions until 2030; combination housing requires outdoor exercise or pasture on at least 90 days/year, 120 under organic rules. Farms with tie-stalls have lost the AMA quality seal since 01.01.2024. **Data gap:** the 2020 reference date is six years old; a more recent dairy-cow-specific figure was not obtainable from a primary source. Given the trend and the quality-seal rule, the tie-stall share in 2026 is probably lower than 35.6 %.

24.4 Cow-calf separation

Otten ND, Welk A, Jensen MB, *Acta Vet Scand* 2025;67:45, DOI 10.1186/s13028-025-00827-4 — expert survey, 21 respondents from 15 European countries:

System	Most frequent time of separation	Share
Conventional	within the first 12 hours post partum	18 of 21 respondents
Organic	12–24 hours	12 of 17
Organic, longer contact	2–7 days	5 of 16

A weighty methodological limit: expert judgement, not farm data; mostly a single expert per country; response rates 47 % and 36 %; the authors themselves point to internally inconsistent percentages. **For Austria no separation times in hours exist** — the large farm survey (Klein-Jöbstl D et al., *J Dairy Sci* 2025;108(3):2756–66, n = 2,314) does not collect this variable.

State of research on cow-calf contact rearing: Beaver A, Meagher RK, von Keyserlingk MAG, Weary DM, *J Dairy Sci* 2019;102(7):5784–5810 — systematic review, 70 studies: for diarrhoea and mastitis, indications of beneficial or neutral effects of suckling; for cryptosporidiosis, pneumonia, immunity and mortality, mixed findings. Conclusion: the literature "provides no consistent evidence in support of early separation". Meagher RK et al., *J Dairy Sci* 2019;102(7):5765–83: longer contact promotes more normal social behaviour and raises weight gain, but reduces saleable milk volume and **increases acute distress at the later separation**.

Austrian farm comparison (Rademann A, Schneider ML, Waiblinger S, *Front Vet Sci* 2025;12:1610084 — 50 farms, Welfare Quality protocol): better scores under cow-calf contact rearing for qualitative behaviour assessment, oral behaviour, space, pasture access and claws; **no difference** in human-animal relationship, social behaviour, play behaviour and mortality. **A decisive confounder the authors name themselves:** 100 % of the cow-calf-contact farms were organic against 56 % of the comparison farms — the advantages may not be attributable to cow contact.

24.5 Antibiotics and resistance

EU (EMA, ESUAvet Annual Surveillance Report 2023, published 31.03.2025): sales for food-producing animals 88.5 mg/PCU against 118.3 in the 2018 baseline year — roughly half of the Farm-to-Fork reduction target (50 % by 2030) achieved. Substance classes: penicillins 31.4 %, tetracyclines 21.6 %, sulfonamides 10.1 %. **Intramammary preparations: 0.7 % of sales.**

An explicit gap in the primary source: ESUAvet reports **no** quantitative consumption data by animal species; the EMA states that the 2023 data are "not complete and accurate enough to start reporting quantitative information". An EU-wide dairy share cannot be derived from it.

Austria (AGES, antibiotic distribution and dispensing volumes 2024, published 09.10.2025): total distribution 34.56 t (+6.5 %); normalised total 37.2 mg/PCU; **cattle 17.2 mg/PCU** (pigs 58.1; poultry 19.0); **intramammary 0.91 t = 2.6 % of total distribution**; routes of administration oral 79.2 %, parenteral 15.9 %, intramammary 2.6 %. Within the intramammary group, lactation-period preparations rose slightly while **dry-cow products declined**. AGES attributes annual fluctuations to availability and stock movements rather than to changed animal numbers.

Selective dry-cow therapy (Weber J, Borchardt S, Seidel J et al., *Animals* 2021;11(12):3403, DOI 10.3390/ani11123403 — systematic review with meta-analysis):

Endpoint	Result
Intramammary infection after calving, selective versus blanket	RR 1.02 (0.94-1.11), p = 0.592 , I ² = 0 % (3 studies, 4,045 quarters)
Antibiotic use under selective dry-cow therapy	51.22 % of animals (43.20-59.22) against 100 % by definition (5 studies, 6,894 quarters)

Selective dry-cow therapy halves antibiotic use with no demonstrable disadvantage for udder health (**Grade B**, few studies, considerable heterogeneity in use).

Resistance situation (Naranjo-Lucena A, Becker P, Madigan G et al., *Antibiotics* 2025;14(3):243 — Ireland, 2020-2023, 7,833 milk samples from 1,762 farms):

Pathogen	Resistance	Herds affected	Persistence
<i>Staphylococcus aureus</i>	penicillin	61.84 % (47 herds)	27 herds (35.53 %)
<i>Streptococcus uberis</i>	pirlimycin	48.91 % (45 herds)	13 herds
<i>Streptococcus uberis</i>	erythromycin	31.52 % (29 herds)	2 herds
<i>Escherichia coli</i>	tetracycline	30.91 %	no persistence

Passive surveillance from voluntarily submitted diagnostic samples; descriptive, without inferential testing.

One Health (ECDC, EFSA, EMA, JIACRA IV, *EFSA Journal* 2024;22(2):e8589, survey period 2019-2021): positive associations between consumption and resistance **within** the food-animal population for fluoroquinolones, polymyxins, aminopenicillins and tetracyclines. The link to humans is documented **only indirectly**: resistance in humans was associated with resistance in food animals, and the latter with animal consumption. A **direct** statistical association between animal consumption and resistance in humans is not reported. The authors' caveats: human isolates come from clinically ill patients, animal isolates from healthy animals at the abattoir — the samples are not equivalent.

24.6 What this chapter does not do

It grounds no health statement and is grounded by none. The only substantive point of contact with the rest of the work is **heat stress**: simultaneously an animal welfare issue and a measurable determinant of milk composition (Chapter 5.1). Anyone deriving a dietary recommendation from the figures in this chapter leaves the method discipline of this work.

Data gaps: system-stratified prevalences from the EFSA full text; a pooled European subclinical mastitis prevalence; a current dairy-cow-specific tie-stall share for Austria; Austrian separation times; the spread of cow-calf contact rearing; the dairy share of antibiotic use EU-wide; dry-cow tonnage separated from lactation-period preparations.

PART IV — BALANCE SHEET

25. Delimitation from NEUROMETABOLICA and the Alzheimer work (new)

The author maintains two independent neighbouring strands: **NEUROMETABOLICA** (a ten-axis coordination model of dementia, focused on the astrocyte-microglia dyad and nitrogen/liver metabolism versus protein deposition) and a general **Alzheimer work** (paper plus practical guide). Both are related but must be kept separate. The table below prevents duplicate publication and argument blending.

Statement	Dairy work (FORSCH-PROV0445)	Model paper (NEUROMETABOLICA)	Rationale
Milk matrix → ApoB/LDL → vascular brain health	Yes	only as input to one axis	exposure-specific, human data available
APOE4 × insulin resistance × BBB	Yes, as effect modifier	Yes, as axis coupling	overlap; here only insofar as dietary exposure is touched
Astrocyte-microglia dyad, reactive astrocyte subtypes	No	Yes	no milk-exposure-specific data
Ammonia-astrocyte axis, hepatic encephalopathy	No (milk urea → hyperammonaemia is rejected)	Yes	here only as a rejected hypothesis with a cross-reference
Nitrogen/liver metabolism vs. protein deposition	No	Yes	general pathogenesis model
MUN as a cow trait	Yes (Chapters 5, 21)	No	no human pathway
Multi-factor vs. amyloid cascade debate	only as framing, one section	Yes, at length	avoids duplicate publication

Methodological note: No dedicated search was carried out for this work on astrocyte-microglia interaction, reactive astrocyte subtypes or glial metabolic coupling. The only verified glial source is a mouse study on astrocytic APOE4 and BBB damage (PMID 34957486: leaky BBB, elevated MMP9, reduced astrocyte endfoot coverage; removal of astrocytic APOE4 normalises). The delimitation above is therefore conceptual, not evidence-backed — NEUROMETABOLICA needs its own literature round.

26. Mechanism prioritisation (as of v3.0)

Rank	Mechanism	Why prioritised	Main problem	Grade
1	Product matrix → ApoB/LDL	strongest direct human RCT evidence (Rosqvist: 0.04 vs. 0.36 mmol/l); flanked by Neurology 2026 and Lancet Commission 2024 (LDL 7 % PAF)	no direct Aβ/tau evidence	B
2	MFGM/polar lipids (lipid effect) <i>(upgraded)</i>	SRMA 2026: TC −0.18 mmol/l; meta 2024: TC SMD −0.259	LDL component single-study driven; acute effect disproved	B
3	Oxysterols	human absorption established; a genuine BBB bridge	unfavourable EER; levels in cheese/milk powder unquantified	C
4	Milk peptides	systemic detectability is real (108 studies, 102 with detection)	inconsistent, very small amounts; target/Cmax unclear	C
5	Leucine-mTOR autophagy inhibition	human monocyte data, a real dose threshold (~300 μM)	not milk-specific ; brain EER data gap	C
6	AGE/RAGE <i>(downgraded)</i>	human cohort evidence on dAGE and cognition exists	dairy share of dAGE load small; 4-week RCT without effect; soy drink shows the same CML increase	D
7	MFGM → cognition/proteostasis <i>(downgraded)</i>	–	RCT null result n = 263; proteostatic endpoints never measured	D
8	EV/miRNA	plausible transport mechanism	human bioavailability contradictory	D

Cross-cutting amplifier (not a dairy mechanism): the aging/clearance axis (proteostasis, glymphatic/BBB, sleep, vascular stiffness) — **B**, but not milk-specific.

26.1 Shifts relative to v1.3

Position	v1.3	v3.0	Reason
MFGM lipid effect	C→D (sources missing)	B	sources exist and are verified
MFGM cognition	C→D	D (confirmed, new rationale)	RCT null result rather than a missing source

AGE/RAGE	rank 2, grade B/C	rank 6, grade D	dose comparison and non-dairy control
Drinking milk → cognition	not carried	C (inconsistent)	MR findings
Drinking milk → mortality	not carried	B (null effect)	two MR cohorts
Dairy-intake biomarkers → CVD/T2D	not carried	B	Trieu 2021, Imamura 2018
Dairy-intake biomarkers → dementia	not carried	data gap	no cohort locatable

26.2 Shifts in v3.0

Item	v2.0	v3.0	Reason
The substitute determines the sign of any dairy effect	not carried	A	Kiesswetter 2024, 15 cohorts, GRADE moderate
Soy drink in place of cow's milk lowers LDL	not carried	B	Erich 2024, LDL from 10 of 17 RCTs (n = 312), GRADE high
MIND intervention without cognitive benefit	not carried	A	Barnes 2023, RCT n = 604
B-vitamin supplementation improves cognition	not carried	E	Ford & Almeida 2019, 31 RCTs
Limiting nutrients when replacing milk (unfortified drinks)	assumed: calcium	B: riboflavin, B12, iodine, protein (calcium not modelled)	Lawrence 2025 (dietary-intake model), Salomé 2025 (microsimulation)
Substitute determines sign, dementia endpoint	v3.0: carried as A without restriction	C (one cohort)	Du 2026; Chapter 18.2
Substitution analyses with dairy product and dementia endpoint	"not found"	three analyses, one cohort each	Du 2026, Li 2025, Ortega 2024
β-casomorphin strand	not carried	E	EFSA DATEX report 2009: no cause-and-effect relationship
Milk as a BSE transmission route	E (mechanistic)	E (also regulatory)	WOAH: "milk and milk products" as a safe commodity
Dairy funding influences the direction of results	not carried	C	two direct tests, both non-significant
Selective dry-cow therapy halves antibiotic use without an udder-health penalty	not carried	B	Weber 2021, meta-analysis

27. Rejected or strongly downgraded

- Chymosin/rennet as a direct Alzheimer mechanism (**E**)
- Rumen ammonia → milk → hyperammonaemia → Alzheimer's (**E/D**)
- Milk urea as a relevant neurotoxin (**E/D**)
- Milk typically raises uric acid (**E**)
- Milk generally blocks calcium absorption (**E**)
- The brain as a deliberate "dumping site" (**E**)
- The cow's suffering as a targeted epigenetic message (**E**)
- Milk amyloid A = Alzheimer amyloid (**E**)
- Fat turns directly into thrombus or amyloid (**E**)
- Milk as a relevant BSE transmission route (**E**)
- Ordinary milk generally causes fatty liver or endothelial damage (**E/D**)
- "More milk fat → more dementia" as a universal theory (**E**)
- *New in v3.0:* Milk AGEs as a relevant contributor to insulin resistance or vascular function (**D**, heading for E)
- *New in v3.0:* MFGM as a cognitively active milk constituent in adults (**D**)
- *New in v3.0:* AHA statement "Vascular Contributions to Cognitive Impairment and **Brain Health**" — does not exist, citation struck
- *New in v3.0:* β-casomorphins (BCM7) as a cause of disease via oral intake (**E**, EFSA DATEX report 231, 2009)
- *New in v3.0:* Lactotripeptides IPP/VPP as blood-pressure-active milk peptides (**E** in regulatory terms, EFSA claim rejected)
- *New in v3.0:* B-vitamin supplementation as a cognitive intervention (**E**, 31 RCTs)
- *New in v3.0:* "The environmental advantage of plant drinks holds per nutrient unit as it does per litre" (**E** for oat and almond drinks)

28. Falsification criteria

Hypothesis	Falsification	Chapter
Matrix → ApoB chronically	ApoB difference < 0.05 g/l (90 % CI) in a 24-week RCT against fatty-acid-matched butter oil	10
Milk fat → dementia (biomarker level)	HR per SD 15:0 between 0.95 and 1.05 across ≥10 cohorts, ≥5,000 cases	15
Drinking milk → dementia (causal)	MR with ≥50,000 cases and positive control yields OR 0.97–1.03	16
Milk-specific ferment effect	no difference dairy vs. plant ferment (CRP ±0.3 mg/l)	9
Milk AGE pathway	no effect at ≥3-fold CML difference over ≥12 weeks	6
Leucine milk specificity	a leucine-matched non-dairy protein source produces the same autophagy inhibition	13
Oxysterol route	dietary intake < 5 % of the circulating/brain-accessible pool	11
Cheese-dementia association causal	multivariable MR with cheese instruments yields OR 0.97–1.03	16
APOE effect modification	p-interaction > 0.1 pooled across ≥3 cohorts, ≥3,000 AD cases	14
Sex interaction	p > 0.1 with ≥5,000 cases	17
Cow state → human proteostasis	no heat-stress proteome signature > 2-fold in pooled UHT bulk milk	5
Milk specificity against substitution	differences vanish after adjustment for B12, iodine, calcium, protein	18
Overall architecture	no reproducible effect on vascular/clearance/Aβ/tau endpoints	all

29. Remaining data gaps

29.1 The EER table — and what its state means

Candidate	Real product dose	Cmax	t½	Brain concentration	Endogenous pool	EER
Milk peptides	data gap	data gap	data gap	data gap	data gap	not computable
Oxysterols	data gap (cheese/milk powder unquantified)	data gap	data gap	data gap	data gap	not computable
AGEs (CML)	~0.28 mg per 250 ml UHT milk; up to ~1.5 mg when long-stored; total diet 2.6–7.0 mg/d	data gap for milk; free plasma AGEs rise dose-dependently	data gap	data gap	data gap	dairy share < 25 % of dietary variation; not quantifiable against endogenous formation
Spermidine	data gap	data gap	data gap	data gap	data gap	not computable
Leucine	plasma Cmax reaches the ~300 µM threshold range	partly known	data gap	data gap	data gap	not computable
MFGM sphingolipids	interventions 0.3–5 g phospholipids/d; 45 g buttermilk powder ≈ 187.5 mg phospholipids	data gap	data gap	data gap	data gap	not computable; effect probably luminal (cholesterol absorption), not systemic

This is itself a finding, not merely a gap: For **none** of the six postulated bioactive milk constituents does a published chain from product dose through Cmax to brain concentration exist. Five of six rows cannot be filled. As long as that holds, every single-compound brain-effect hypothesis about milk is **untestable** — and therefore not a viable research object. The matrix and vascular route is not only better supported; it is the only one that offers measurable quantities at all.

29.2 Further gaps

1. Biomarker-based dementia cohorts (15:0, 17:0, t16:1n-7) — biobanks exist, follow-up unanalysed.
2. Direct human autophagy flux assay under dairy/whey exposure against a leucine-matched control.
3. Human intervention data on dairy product → Aβ42/40, p-tau217, amyloid/tau PET.
4. Which animal signatures demonstrably survive pooling, heating, fermentation and storage?
5. Oxysterol content of milk powder and cheese; MG-H1 in all dairy products.
6. SCFA, TMAO and bile acid endpoints in dairy RCTs.
7. Product × endpoint: UHT milk, low-fat cheese, cream, milk powder largely empty.
8. Substitution analyses with a **dementia endpoint** — for dairy product as the replaced quantity three single-cohort analyses exist (Chapter 18.2), for replacement by plant drinks none locatable. Open: eFigure 4 (Du 2026); milk-specific HRs from Kim 2026; butter→olive-oil HR from Tessier 2024; CI for low-fat dairy from Li 2025; manual search in Scopus and Web of Science; independent replication in a second cohort with B12 and iodine status.
9. Newer LCA work 2022–2026 per nutrient unit rather than per litre.
10. The share of dairy-funded studies across the whole milk-and-health literature beyond the CVD

endpoints (Chapter 23.3).

11. Dairy-specific antibiotic consumption EU-wide; a pooled European prevalence of subclinical mastitis (Chapter 24).
12. Producer price against production cost for Austria; market share of plant-based alternatives in Austria (Chapter 20).

Closed in v3.0 and no longer carried as a gap: the four previously unsourced chapters (20, 22, 23.3, 24) are sourced; the three previously unverified PMIDs (38718740, 40201593, 34250935) are resolved — one of them as a misattribution (Chapter 0).

30. Prioritised research programme

Priority	Hypothesis	Design	Sample/duration	Endpoints	Control	Hard falsification criterion
1	Matrix effect (MFGM) lowers ApoB chronically	double-blind parallel RCT, pre-registered	n = 240, 24 weeks	ApoB (primary), LDL particle number, plasma sterols	isocaloric, fatty-acid-matched butter oil; additional plant-oil arm	ApoB difference < 0.05 g/l
2	15:0 biomarker predicts dementia	pooled biomarker analysis from biobanks	≥10 cohorts, ≥5,000 cases, ≥10 years	incident dementia, subtypes	adjustment for fibre, fish, diet quality	HR per SD 0.95–1.05
3	Milk-specific ferment effect	three-arm RCT	n = 150, 12 weeks	CRP, diversity, SCFA, LPS-binding protein	plant ferment (sauerkraut/kimchi/soy ferment), unfermented	no difference dairy vs. plant
4	Milk AGEs affect vascular function	crossover RCT	n = 60, 2 × 12 weeks	clamp, FMD, plasma CML (LC-MS/MS)	freshly pasteurised vs. stored UHT milk	no effect at ≥3-fold CML difference
5	Cheese-dementia association causal	multivariable MR with cheese-specific instruments (not LCT)	GWAS summary statistics	dementia, AD, VaD	negative control butter	OR 0.97–1.03
6	APOE effect modification	pre-registered replication	≥3 cohorts, ≥3,000 AD cases	AD	same exposure definition as Du 2026	p-interaction > 0.1 pooled
7	Substitution is nutrient- not milk-mediated	cohort substitution plus mediation analysis	existing cohorts	dementia, cardiometabolic	adjustment B12, iodine, calcium, protein	differences disappear

30.1 Upstream work packages (animal and product side)

1. Classify cows objectively by MUN, SCC, BHB/NEFA, energy balance, lactation stage, heat stress and health.
2. Analyse raw milk by proteomics, peptidomics, lipidomics, metabolomics, oxidation/AGE profile, hormones and vesicles.
3. Process the batches identically: pasteurised, UHT, yoghurt, cheese.
4. Test which animal signatures survive pooling, heating, fermentation and storage.
5. Standardised in-vitro digestion as the first filter; only surviving candidates into human crossover studies.
6. Determine absolute Cmax, t_{1/2} and EER — **only then** test cell and tissue mechanisms.
7. Pre-specify and pre-register APOE, metabolic syndrome, age, LCT and sex.

31. Closing note

The value of this work lies not in a finished milk-dementia thesis but in the stepwise reduction of speculative ideas to measurable causal links. With the research complete, the position can be stated in six sentences:

1. **A causal effect of milk on dementia is not supported.** The strongest observational association (high-fat cheese, HR 0.87) points in the *opposite* direction to the initial conjecture and is itself not causally interpretable.
2. **Best supported is the matrix effect on LDL** — a ninefold difference in LDL increase between cream with intact MFGM and butter oil at equal milk fat intake. That is a real, causally demonstrated food effect, but it ends at the lipid profile, not in the brain.

3. **The single-compound hypotheses fail on pharmacokinetics**, not on plausibility. Five of six candidates have no published dose-Cmax-brain-concentration chain.
4. **The aging and clearance axis is well supported but not milk-specific** — it is the ground everything stands on, not the lever diet operates.
5. **Milk specificity is consistently the weakest point**. AGEs form in soy drink just as readily; the ferment effect belongs to the fermentation class; leucine acts from any protein source; B12 can simulate dairy effects. Every remaining hypothesis must pass this control.
6. **The question "is milk harmful?" is ill-formed**. The substitute determines the sign: the same serving of milk, replaced by water, coffee, a soy drink or processed meat, yields four different risk estimates. A statement about milk without a defined comparator arm is uninterpretable (**A for cardiometabolic endpoints; C for the dementia endpoint**, one cohort). This is the principal methodological gain of v3.0, with the restriction of v3.1.

The current state supports a **network model** in which product matrix, metabolism, vascular health, APOE, BBB and clearance may interrelate, without milk being established as a source of Alzheimer amyloid — and without the reverse ("cheese protects") being supported either.

Appendix A — Glossary

Aβ / amyloid-β — peptide found in amyloid deposits in Alzheimer's disease.

Tau — microtubule-associated protein; pathological forms central to tauopathies.

Proteostasis — the systems controlling protein synthesis, folding, repair, transport and degradation.

CMA — chaperone-mediated autophagy; LAMP2A-dependent lysosomal degradation route.

Denaturation — alteration or loss of native protein structure.

Aggregation — association of proteins or other molecules.

Amyloid — ordered protein aggregates with cross-β structure.

Rennet / chymosin — protease cleaving κ-casein and destabilising casein micelles.

Fibrin — protein polymer of the coagulation system.

MUN — milk urea nitrogen; marker of the cow's nitrogen metabolism and an environmental indicator.

BHB — β-hydroxybutyrate; ketone body and ketosis marker.

NEFA — non-esterified fatty acids; rise with negative energy balance.

SCC — somatic cell count; udder-health and mastitis marker.

Furosine — early Maillard marker, the most sensitive heat indicator in milk.

CML / CEL / MG-H1 — carboxymethyl-lysine, carboxyethyl-lysine, methylglyoxal-hydroimidazolone; advanced glycation end products.

Lactulose — heat marker distinguishing UHT from sterilised condensed milk.

AGE / RAGE — advanced glycation end products and their receptor.

Oxysterol — oxidised cholesterol derivative; 24S-OHC leaves the brain, 27-OHC can enter it.

MFGM — milk fat globule membrane.

OCFA — odd-chain fatty acids; 15:0 and 17:0 as milk fat biomarkers.

APOE — apolipoprotein E; lipid transport, vasculature, Alzheimer risk.

CAA — cerebral amyloid angiopathy.

BBB — blood-brain barrier.

MR — Mendelian randomisation; genetic instrumental variable analysis.

LCT / rs4988235 — lactase gene locus; MR instrument for drinking-milk consumption.

FFQ — food frequency questionnaire; principal source of measurement error in nutritional epidemiology.

Target engagement — evidence that a substance reaches and affects its biological target in vivo.

Cmax / t_{1/2} — maximum plasma concentration / half-life.

EC50 / IC50 — concentration producing 50 % of a stimulating or inhibiting effect.

EER — exogenous-to-endogenous ratio.

SASP — senescence-associated secretory phenotype.

PAF — population attributable fraction.

Reverse causal mapping — analysis backwards from the clinical endpoint to modifiable nodes.

Appendix B — Machine-readable project status

See 10_DE/...buch-DE_v3.1...md, Appendix B (single canonical JSON block, German keys retained).