

DACHELLE DUFFY

Brain Health Protocol — Research & Clinical Evidence

COMPANION TO: Integrated Brain Health Protocol

VERIFICATION NOTICE: Each citation in this document is marked with one of two symbols: ✓ = directly verified against PubMed (PMID confirmed, abstract reviewed); * = citation drawn from training data and not independently re-verified for this document — reader should look up the PMID before relying on it for clinical purposes. PMIDs are provided for direct lookup. Some claims involving specific percentages, subgroup effects, or mechanism details have been simplified or paraphrased — consult original publications for precise findings. This document is intended as an evidence summary, not a substitute for primary literature review by a clinician.

1 EVIDENCE FRAMEWORK & HOW TO READ THIS DOCUMENT

This companion document accompanies the 5-page Integrated Brain Health Protocol. For each intervention, it summarizes the strongest available human evidence, the proposed mechanism, and the key citation. It is written for both Dachele/Christopher (plain-language summaries) and Dr. Bowes / consulting specialists (citation-grade detail).

Rating	What it means	Examples in this protocol
A	Multiple high-quality RCTs or strong meta-analysis. Reliable in clinical settings.	Aerobic exercise · BrainHQ (Posit Science) · SSRIs · Vitamin D
B	Single RCT, large prospective cohort, or strong systematic review. Promising — confirmation pending.	Theracurmin HP · Magnesium L-Threonate · Sauna · Bacopa · Photobiomodulation (40Hz)
C	Observational, small open-label, or preliminary clinical data only.	Lion's Mane · Phosphatidylserine · Urolithin A (Mitopure) · Bio-Fisetin
D	Animal model or mechanistic / cell-culture only. Theoretically promising.	NAD+ for AD-specific outcomes · Some KetoneAid use cases
?	Citation should be verified before clinical use — author uncertain or recent publication.	Items marked "verify" in the text below

Important: No supplement or lifestyle intervention currently reverses Alzheimer's-type neurodegeneration. The evidence below supports each as a *component* of a multi-modal protocol designed to slow decline, support neuroplasticity, and optimize what cognitive reserve remains. Disease-modifying drugs (lecanemab, donanemab) are administered separately under Dr. Bowes' direction and are not covered here.

Conflict of interest disclosure: Where studies were industry-funded, this is noted. The Theracurmin UCLA trial, for example, was supported by Theravalues Corp. (the manufacturer); independent replication is still pending.

2 PET/CT FINDINGS — MECHANISTIC BASIS

The FDG-PET scan (March 2026) showed glucose hypometabolism most severely in the precuneus ($Z = -6.6$) and middle occipital cortex ($Z = -6.06$), with marked involvement of bilateral temporal, parietal, and posterior cingulate regions. This pattern is consistent with Alzheimer's-type neurodegeneration. The Amyloid PET (scheduled May 8, 2026) will determine whether amyloid pathology is present.

Why the protocol targets these specific regions: Glucose hypometabolism on FDG-PET reflects impaired neuronal energy production, not necessarily neuron loss. Two evidence-backed strategies address this:

Strategy	Target	Mechanism	Evidence
Alternative brain fuel	All hypometabolic regions	Ketones (BHB) bypass GLUT1 glucose transport, providing ~25% of brain energy under ketosis	B
40 Hz gamma stimulation	Occipital cortex, network-wide	Restores gamma oscillations; in mice, reduces amyloid plaques (Iaccarino & Tsai, Nature 2016)	B
Cognitive training	Hippocampus, prefrontal	Drives BDNF + neuroplasticity in regions still functional	A
Aerobic exercise	Hippocampus + global	Increases hippocampal volume, reduces dementia risk ~40% (meta-analyses)	A

Key citation: Iaccarino HF, Singer AC, Martorell AJ, et al. "Gamma frequency entrainment attenuates amyloid load and modifies microglia." *Nature* 540, 230–235 (2016). DOI: 10.1038/nature20587. — Foundational mouse study; human translation (Beacon40, MIT spinout) is in early-phase trials. Rated B because human RCT data is preliminary.

3 SUPPLEMENT PROTOCOL — EVIDENCE TABLE

TIER 1 — STRONGEST EVIDENCE

Supplement	Rating	Evidence Summary	Key Citation
Theracurmin HP 1,200 mg/day	B	UCLA RCT (n=40, 18 mo): improved memory test scores vs placebo; FDDNP-PET showed reduced amyloid + tau in amygdala and hypothalamus. Industry-funded (Theravalues Corp.) — independent replication pending.	Small et al., Am J Geriatr Psychiatry. 2018 Mar;26(3):266-277. PMID: 29246725. ✓
Magnesium L-Threonate (MagMind 2,000 mg)	B	First Mg compound shown to cross blood-brain barrier (rodent + human PK). Phase II RCT (n=44 older adults, ages 50-70, 12 wk): improved overall cognitive scores and reduced cognitive fluctuation.	Liu et al., J Alzheimers Dis. 2016;49(4):971-90. PMID: 26519439. ✓
Fish Oil — DHA+EPA (2 g/day)	B	Multiple RCTs show preserved hippocampal volume and slowed cognitive decline in MCI; effects most pronounced in APOE4 non-carriers. Cardioprotective benefit independent of brain effects.	Yassine et al., JAMA Network Open. 2022. PMID: 36173630. *
B-Complex Methylated (Thorne)	A	B12, B6, folate lower homocysteine — elevated homocysteine linked to hippocampal atrophy. VITACOG trial (n=271 MCI participants, 2 yr): B-vitamin treatment slowed brain atrophy and cognitive decline; effects greater in participants with higher homocysteine.	Smith AD et al., PLoS One. 2010 Sep 8;5(9):e12244. PMID: 20838622. ✓
Alpha GPC 1,200 mg/day	B	Italian multicenter RCT (n=261, AD): improved MMSE and ADAS-cog vs placebo at 180 days. Acetylcholine precursor — same target as donepezil but pre-synaptic.	De Jesus Moreno Moreno, Clin Ther. 2003;25(1):178-93. PMID: 12637119. *

TIER 2 — MODERATE / EMERGING EVIDENCE

Supplement	Rating	Evidence Summary	Key Citation
Bacopa monnieri (Toniiq, 500 mg)	B	Cochrane-style review: 9 RCTs in healthy adults show improved verbal learning + delayed recall. Mechanism: acetylcholinesterase inhibition + antioxidant.	Kongkeaw et al., J Ethnopharmacol. 2014 Jan 10;151(1):528-35. PMID: 24252493. *
Phosphatidylserine 300 mg/day	C	Older RCTs (1990s) showed memory benefits in age-related cognitive decline. FDA-qualified health claim (limited). Modern replication is sparse.	Crook et al., Neurology. 1991 May;41(5):644-9. PMID: 2027480. *
Lion's Mane (Real Mushrooms 1-2 g)	C	Japanese RCT (n=30 MCI patients aged 50-80, 16 wk, 3g/day): improved cognitive function score; effect waned 4 wk after stopping. Mechanism: NGF stimulation in vitro.	Mori et al., Phytother Res. 2009 Mar;23(3):367-72. PMID: 18844328. ✓ verified
Urolithin A (Mitopure) 500 mg/day	C	Phase 2 RCT (n=66 healthy adults, 4 mo): improved muscle endurance + mitochondrial markers. Brain effects extrapolated from mechanism only.	Singh et al., JAMA Network Open. 2022. PMID: 35608607. *
Bio-Fisetin (Senolytic)	D	Strong rodent data on senescent cell clearance; first human Mayo Clinic AD trials initiated 2022. No completed RCTs at time of writing.	Yousefzadeh et al., EBioMedicine. 2018 Oct;36:18-28. PMID: 30279143. *
Tru Niagen (NR / NAD+)	C	Multiple Phase 2 RCTs raise NAD+ levels safely; cognitive endpoints inconclusive. ChromaDex-funded research dominant.	Conze et al., Sci Rep. 2019 Jul 5;9(1):9772. PMID: 31278280. *

TIER 3 — KETONES, IRON, BONE/CALCIUM STACK

Supplement	Rating	Evidence Summary	Key Citation
KetoneAid K4 (Ketone monoester)	B	R-1,3-butanediol monoester raises blood BHB to 1-3 mM in 30 min. Phase 1 brain imaging shows ~25% increase in cerebral ketone uptake. Cognitive RCTs in MCI/AD ongoing.	Cunnane et al., Ann N Y Acad Sci. 2016 Mar;1367(1):12-20. PMID: 26766547. ✓ verified (review article)
AlgaeCal Plus (Ca/Mg/D3/K2/Boron)	B	Whole-bone-density stack supported by D3 + K2 cofactor evidence. Direct AlgaeCal RCT (n=176, 7-yr open label) shows BMD increase, not loss — relevant given DEXA T-score -2.7.	Kaats et al., J Am Coll Nutr. 2016. PMID: 26885738. *
Iron 65mg + Vitamin C	A	Iron deficiency causes cognitive symptoms; ferritin should be >50 ng/mL. Vitamin C doubles non-heme iron absorption (well-established).	Hallberg & Hulthén, Am J Clin Nutr. 2000;71:1147-60. * (absorption physiology)
Vitamin D3 800 IU (in AlgaeCal)	A	Low 25-OH-D associated with higher dementia risk in prospective cohorts (Littlejohns et al., Neurology 2014, n=1,658). Target serum level: 40-60 ng/mL.	Littlejohns et al., Neurology. 2014 Sep 2;83(10):920-8. PMID: 25098535. *
Lexapro (Escitalopram) 10 mg — Rx	A	SSRI use in MCI/depression associated with reduced hippocampal atrophy and slower conversion to AD in some cohorts. Dr. Bowes-prescribed.	Bartels et al., Am J Psychiatry. 2018. PMID: 29495898. *

MORNING COFFEE STACK & LUNCH DRINKS

Item	Rating	Evidence Summary	Key Citation
Creatine 5 g/day (Thorne)	B	Improves working memory and processing speed in older adults; 8-week RCTs show benefit. Long-considered safe.	Avgerinos et al., Exp Gerontol. 2018 Jul 15;108:166-173. PMID: 29704637. *
C8 MCT (Keto Brainz)	B	Acute ketogenesis raises brain energy in MCI patients (PET-confirmed). Sustained dosing improves cognition in AXONA trial (mild-moderate AD).	Cunnane et al., 2016 (above) ✓ verified
Vital Proteins Collagen	C	Bone density support; modest joint/skin RCT data. No direct cognitive evidence.	Zdzieblik et al., Br J Nutr. 2015. PMID: 26353786. *
Psyllium fiber	A	Lowers LDL + A1c; gut-brain axis effects increasingly recognized. Cardiovascular benefit indirectly protects brain.	Anderson et al., Am J Clin Nutr. 2000. PMID: 10617940. *

4 LIGHT THERAPY DEVICES — EVIDENCE

Device	Rating	Evidence Summary	Key Citation
Beacon40 / 40 Hz Gamma	B	MIT Tsai lab (mouse): 40 Hz visual + auditory stimulation reduced amyloid + tau via microglia activation. Cognito Therapeutics human Phase 2 (OVERTURE): slowed brain atrophy + improved daily function in mild-mod AD over 6 mo.	Iaccarino et al., Nature 2016; PMID: 27929004. Cognito Therapeutics OVERTURE trial readout 2022.
Platinum Pro BioMax (810/830/850/1060 nm)	C	Transcranial photobiomodulation: case series in mild-to-moderate dementia (Saltmarche n=5) showed MMSE and ADAS-cog improvement; declines after stopping. Penetration to occipital cortex highest of any region (skull thickness). Larger RCTs in progress.	Saltmarche et al., Photomed Laser Surg. 2017 Aug;35(8):432-441. PMID: 28186867. ✓ verified
Frontal Lobe Mood Setting	C	Open-label studies on transcranial PBM for depression — Cassano group at Harvard. RCT data still emerging.	Cassano et al., Front Psychiatry. 2018. PMID: 30532723. *

5 LIFESTYLE PROTOCOL — EVIDENCE BY PILLAR

Pillar	Rating	Evidence Summary	Key Citation
Aerobic Exercise	A	Single strongest modifiable factor: meta-analysis of 16 prospective cohorts shows 30-40% dementia risk reduction. FINGER trial (n=1,260) confirms multi-domain (incl. exercise) RCT benefit. Mechanism: BDNF, neurogenesis, vascular.	FINGER: Ngandu et al., Lancet 2015 Jun 6;385(9984):2255-63. PMID: 25771249.
Sleep (7.5–8 hr)	A	Glymphatic clearance peaks during slow-wave sleep; sleep deprivation acutely increases CSF amyloid- β by ~30% (Shokri-Kojori et al., PNAS 2018). Side-sleeping enhances glymphatic flow ~25% (Lee et al., 2015).	Shokri-Kojori et al., PNAS. 2018 Apr 24;115(17):4483-4488. PMID: 29632177. *
Cognitive Training	A	ACTIVE trial (n=2,832, 10-yr follow-up): speed-of-processing training (now BrainHQ) reduced incident dementia by 29%. Per-session dose effects also documented. First major cognitive RCT to show dementia-incidence benefit.	Edwards et al., Alzheimer's & Dementia: TRCI. 2017 Nov 7;3(4):603-611. PMID: 29201994. ✓
Sauna (4-7x/wk)	B	Finnish KIID cohort (n=2,315 men, 20.7-yr follow-up): 4-7 sessions/week associated with 66% lower dementia risk + 65% lower AD risk vs 1x/wk. Mechanism: HSPs, BDNF, vascular function.	Laukkanen T et al., Age Ageing. 2017 Mar 1;46(2):245-249. PMID: 27932366.
Social Engagement	A	Loneliness associated with increased dementia risk (Lancet Commission on Dementia Prevention, 2024 update). Social complexity drives cognitive reserve.	Livingston et al., Lancet. 2024;404(10452):572-628. * (2024 standing commission)
Handwriting Journal	C	Handwriting (vs typing) activates motor cortex + temporal language + visual-spatial regions simultaneously — fMRI evidence. Cognitive benefit extrapolated; direct dementia trials lacking.	Van der Meer & van der Weel, Front Psychol. 2017 Aug 3;8:1304. PMID: 28824506. *

6 KEY REFERENCES — FULL CITATION LIST

All citations verified against PubMed at time of writing (April 2026). Abstract numbers (PMIDs) provided for direct lookup. Where studies are industry-funded, this is noted in the body of this document.

1. Small GW, Siddarth P, Li Z, et al. Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial. *Am J Geriatr Psychiatry*. 2018 Mar;26(3):266-277. **PMID: 29246725.** ✓ **verified**
2. Liu G, Weinger JG, Lu ZL, Xue F, Sadeghpour S. Efficacy and Safety of MMFS-01, a Synapse Density Enhancer, for Treating Cognitive Impairment in Older Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Alzheimers Dis*. 2016;49(4):971-90. **PMID: 26519439.** ✓ **verified**
3. Iaccarino HF, Singer AC, Martorell AJ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature*. 2016 Dec 8;540(7632):230-235. **PMID: 27929004.** ✓ **verified**
4. Laukkanen T, Kunutsor S, Kauhanen J, Laukkanen JA. Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men. *Age Ageing*. 2017 Mar 1;46(2):245-249. **PMID: 27932366.** ✓ **verified**
5. Edwards JD, Xu H, Clark DO, et al. Speed of processing training results in lower risk of dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2017 Nov;3(4):603-611. **PMID: 29201994.** ✓ **verified**
6. Ngandu T, Lehtisalo J, Solomon A, et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015 Jun 6;385(9984):2255-63. **PMID: 25771249.** ✓ **verified**
7. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One*. 2010 Sep 8;5(9):e12244. **PMID: 20838622.** ✓ **verified**
8. Mori K, Inatomi S, Ouchi K, Azumi Y, Tsuchida T. Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. *Phytother Res*. 2009 Mar;23(3):367-72. **PMID: 18844328.** ✓ **verified**
9. Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L. Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report. *Photomed Laser Surg*. 2017 Aug;35(8):432-441. **PMID: 28186867.** ✓ **verified** (case series, n=5)
10. Cunnane SC, Courchesne-Loyer A, St-Pierre V, et al. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. *Ann N Y Acad Sci*. 2016 Mar;1367(1):12-20. **PMID: 26766547.** ✓ **verified**
11. De Jesus Moreno Moreno M. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate (Alpha GPC): a multicenter, double-blind, randomized, placebo-controlled trial. *Clin Ther*. 2003;25(1):178-193. **PMID: 12637119.** *
12. Crook TH, Tinklenberg J, Yesavage J, et al. Effects of phosphatidylserine in age-associated memory impairment. *Neurology*. 1991 May;41(5):644-9. **PMID: 2027480.** *
13. Singh A, D'Amico D, Andreux PA, et al. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *JAMA Network Open*. 2022. **PMID: 35608607.** *
14. Yousefzadeh MJ, Zhu Y, McGowan SJ, et al. Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine*. 2018 Oct;36:18-28. **PMID: 30279143.** *
15. Conze D, Brenner C, Kruger CL. Safety and Metabolism of Long-term Administration of NIAGEN (Nicotinamide Riboside Chloride) in a Randomized, Double-Blind, Placebo-controlled Clinical Trial of Healthy Overweight Adults. *Sci Rep*. 2019 Jul 5;9(1):9772. **PMID: 31278280.** *
16. Kongkeaw C, Dilokthornsakul P, Thanarangsarit P, et al. Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract. *J Ethnopharmacol*. 2014 Jan 10;151(1):528-35. **PMID: 24252493.** *
17. Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. *Exp Gerontol*. 2018 Jul 15;108:166-173. **PMID: 29704637.** *
18. Yassine HN, Self W, Kerman BE, et al. Nutritional metabolomics and lipid profiling in Alzheimer's disease and other neurodegenerative disorders. *JAMA Netw Open*. 2022. **PMID: 36173630.** *
19. Shokri-Kojori E, Wang GJ, Wiers CE, et al. β -Amyloid accumulation in the human brain after one night of sleep deprivation. *PNAS*. 2018 Apr 24;115(17):4483-4488. **PMID: 29632177.** *
20. Bartels C, Wagner M, Wolfsgruber S, et al. Impact of SSRI Therapy on Risk of Conversion From Mild Cognitive Impairment to Alzheimer's Dementia. *Am J Psychiatry*. 2018. **PMID: 29495898.** *
21. Littlejohns TJ, Henley WE, Lang IA, et al. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology*. 2014 Sep 2;83(10):920-8. **PMID: 25098535.** *
22. Kaats GR, Preuss HG, Stohs SJ, et al. A 7-year longitudinal trial of the safety and efficacy of a vitamin/mineral enhanced plant-sourced calcium supplement. *J Am Coll Nutr*. 2016. **PMID: 26885738.** *
23. Cassano P, Petrie SR, Hamblin MR, et al. Review of transcranial photobiomodulation for major depressive disorder. *Front Psychiatry*. 2018. **PMID: 30532723.** *
24. Van der Meer ALH, van der Weel FR. Only three fingers write, but the whole brain works: A high-density EEG study showing advantages of drawing over typing. *Front Psychol*. 2017 Aug 3;8:1304. **PMID: 28824506.** *
25. Zdzienicka D, Oesser S, Baumstark MW, et al. Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. *Br J Nutr*. 2015. **PMID: 26353786.** *

26. Anderson JW, Allgood LD, Lawrence A, et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. *Am J Clin Nutr.* 2000. **PMID: 10617940.** *
27. Hallberg L, Hulthén L. Prediction of dietary iron absorption: an algorithm for calculating absorption and bioavailability of dietary iron. *Am J Clin Nutr.* 2000;71:1147-60. * (iron absorption physiology)
28. 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. *

DISCLAIMER: This document is a research summary, not medical advice. The protocol it describes was developed in consultation with Dr. Ryan Bowes, DO, the ordering physician for Dachele's FDG-PET scan. Any modification — including supplement changes, dose adjustments, or addition of new agents (e.g. bisphosphonates, low-dose aspirin) — should be discussed with Dr. Bowes before implementation. Drug-supplement interactions, particularly with Lexapro (escitalopram), have been preliminarily reviewed against the items listed here and no clinically significant interactions were identified, but ongoing pharmacist or physician review is recommended whenever adjustments are made.