

Hype vs. Evidence:

What Actually Works in Healthy Ageing

The market for longevity supplements and pharmacological interventions is growing at roughly 20% per year. The evidence base for most of those products is growing considerably more slowly. The gap between what is marketed and what is proven is one of the most consequential information problems in contemporary health.

This review applies a consistent evidence standard to seventeen of the most widely discussed interventions — from well-established pharmaceuticals to popular supplements to experimental compounds in clinical trials. The question for each is the same: what do the best available human trials actually show?

This is not a consumer guide and it is not clinical advice. It is an honest account of where the evidence stands — including where it is strong, where it is promising, where it is contested, and where the marketing has substantially outrun the science.

Proven**Promising****Emerging****Contested****Hype exceeds evidence**

Proven: consistent positive results across multiple RCTs or large prospective cohorts in humans

Promising: positive signals in human trials, replication underway

Emerging: mechanism established, early human data, outcomes pending

Contested: mixed results across studies, active scientific debate

Hype exceeds evidence: claims significantly ahead of human trial data

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WHAT THE EVIDENCE SAYS — PHARMACEUTICALS & SUPPLEMENTS

The matrix below applies a consistent standard across seventeen interventions. Each entry shows the primary marketed claim, what the human trial evidence actually demonstrates, and a verdict. Evidence ratings reflect the consensus of published systematic reviews and major clinical trial results as of 2024.

PHARMACEUTICAL — ESTABLISHED & EMERGING

Metformin

Biguanide · Type 2 diabetes drug · off-label longevity use

Promising (ageing) · Proven (diabetes)

Primary claim: Extends healthspan by activating AMPK, reducing inflammation, improving insulin sensitivity, and targeting multiple hallmarks of ageing simultaneously.

Metformin has the strongest epidemiological evidence of any candidate longevity drug. Large cohort studies consistently show diabetic patients on metformin outliving non-diabetic controls — a remarkable finding. Mechanistically, it activates AMPK, reduces mTOR signalling, and shows anti-inflammatory effects. The TAME trial (n=3,000+, results expected 2025-2026) is the first RCT designed to test a drug against ageing itself. Safety profile is well-established from decades of diabetes use. Cheap, generic, widely available.

Verdict: The most credible pharmaceutical candidate for healthspan extension currently in evidence. Epidemiological signal is real and consistent. TAME trial results will be definitive. Not yet proven as an anti-ageing intervention in non-diabetic populations — but the best current bet.

Key studies: TAME trial NCT04994736 (ongoing); Bannister et al. (2014) Diabetes Obes Metab; multiple AMPK mechanism studies

GLP-1 Receptor Agonists (semaglutide, tirzepatide)

Glucagon-like peptide-1 agonists · Ozempic / Wegovy / Mounjaro class

Proven (metabolic/CV) · Emerging (broader ageing)

Primary claim: Beyond weight and diabetes — potential to reduce cardiovascular events, neurodegeneration risk, inflammation, and multiple age-related conditions simultaneously.

The SELECT trial (2023, n=17,604) found semaglutide reduced major cardiovascular events by 20% in non-diabetic overweight adults — a landmark finding establishing cardiovascular benefit independent of diabetes. Emerging signals from large observational datasets suggest associations with reduced Alzheimer's risk, reduced cancer incidence, and reduced inflammatory markers. The mechanism hypothesis: GLP-1 agonists may reduce systemic inflammation — a central driver of multiple ageing hallmarks. These signals require prospective confirmation but emerge consistently from large real-world datasets.

Verdict: The most consequential development in pharmacology for healthy ageing since statins, if the broader signals confirm. Proven cardiovascular benefit in non-diabetic populations is established. Prospective trials for Alzheimer's, cancer, and kidney disease are underway. Watch this space closely over 2025-2028.

Key studies: SELECT trial (2023) NEJM; multiple observational studies (US claims databases); EVOKE+ trial (Alzheimer's, ongoing)

Rapamycin (intermittent, low dose)

mTOR inhibitor · immunosuppressant · experimental longevity use

Contested · Strong animal data · Human evidence limited

Primary claim: Inhibits mTOR — a master regulator of ageing — to extend healthspan and possibly lifespan.

Rapamycin is the only intervention that has consistently and robustly extended lifespan across multiple animal models including mice, yeast, and invertebrates. The mTOR pathway is central to the biology of ageing. The problem: rapamycin is a potent immunosuppressant approved for organ transplant rejection. Human longevity evidence is essentially absent — small observational studies and case reports, not RCTs. Intermittent low-dose protocols are being explored to reduce immunosuppressive risk. Self-experimentation is widespread in the longevity community but not a substitute for clinical evidence.

Verdict: The most scientifically credible candidate for translating animal longevity results to humans — but human evidence is near-zero. The risk profile of an immunosuppressant is real. This is not something to take based on mouse data alone. Clinical trials are needed and some are underway. Currently premature for healthy adults outside research settings.

Key references: Harrison et al. (2009) Nature (ITP mouse data); Mannick et al. (2014) Sci Transl Med (human immune study); multiple ITP programme results

Low-dose Aspirin (primary prevention)

NSAID · antiplatelet agent · formerly recommended widely

Guideline reversed — no longer recommended 60+

Primary claim: Reduces cardiovascular events and cancer risk through antiplatelet and anti-inflammatory mechanisms.

For decades, low-dose aspirin was widely recommended for primary cardiovascular prevention. Three major RCTs published 2018-2019 (ASPREE, ARRIVE, ASCEND) collectively enrolled over 47,000 participants. ASPREE (n=19,114, healthy adults 70+) found no reduction in cardiovascular events and a significant increase in major bleeding, including intracranial haemorrhage. The US Preventive Services Task Force updated guidelines in 2022: aspirin should not be initiated for primary prevention in adults 60 and older. The cancer prevention signal remains under study but does not change the primary prevention recommendation.

Verdict: A clear example of clinical evidence reversing a widely adopted practice. Low-dose aspirin for secondary prevention (people who have already had a cardiovascular event) retains its evidence base. For primary prevention in older adults, the evidence now shows net harm. This recommendation change is definitive.

Key studies: ASPREE trial (2018) NEJM; USPSTF guideline update 2022; ARRIVE (2018) Lancet

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WHAT THE EVIDENCE SAYS — SUPPLEMENTS

SUPPLEMENTS — STRONG TO MODERATE EVIDENCE

Vitamin D (correction of deficiency)

Fat-soluble vitamin · widespread deficiency in northern latitudes

Proven (in deficiency) · Context-dependent

Primary claim: Supports bone density, immune function, reduces falls and fractures, and may reduce cancer and cardiovascular risk.

Vitamin D deficiency is genuinely common — estimated at 40%+ in northern European populations, especially in winter months. In deficient individuals, correction has well-established evidence for reducing falls risk (Cochrane: consistent), improving bone mineral density, and supporting immune function. The VITAL trial (n=25,871) found no cardiovascular benefit from supplementation in non-deficient adults, and mixed cancer results. The key distinction is deficiency correction vs. supplementation in people already sufficient — the latter has weaker evidence.

Verdict: Testing and correcting deficiency is well-evidenced, particularly for bone health and falls prevention in older adults. Routine high-dose supplementation in people who are not deficient is not supported by current evidence. Know your level before supplementing.

Key studies: Cochrane review on vitamin D and falls; VITAL trial (2019) NEJM; multiple meta-analyses on deficiency correction

Omega-3 Fatty Acids (EPA/DHA, higher dose)

Marine-derived polyunsaturated fats · fish oil / algae-based

Promising · Dose and population dependent

Primary claim: Reduces cardiovascular disease risk, reduces inflammation, supports cognitive function and joint health.

The evidence picture shifted significantly with dose. Low-dose fish oil (1g/day) showed inconsistent results across trials. Higher dose studies changed the picture: REDUCE-IT (icosapentaenoic acid 4g/day, n=8,179) showed a 25% reduction in cardiovascular events in at-risk populations — though the mineral oil placebo was controversial. STRENGTH trial (omega-3 carboxylic acid 4g/day) showed no benefit, raising questions about EPA vs. DHA effects. Cognitive evidence: largely disappointing in non-deficient adults. Anti-inflammatory effects: consistent but effect sizes modest. The evidence is population- and dose-dependent.

Verdict: At higher doses (3-4g/day EPA-dominant), meaningful cardiovascular benefit in at-risk populations. Standard 1g fish oil capsules: evidence is weak. Anti-inflammatory effects are real but modest. Cognitive effects in non-deficient adults are not established. Dose, formulation, and baseline risk matter.

Key studies: REDUCE-IT (2018) NEJM; STRENGTH trial (2020) JAMA; ORIGIN trial (2012) NEJM; multiple meta-analyses

Creatine Monohydrate

Amino acid derivative · muscle energy substrate

Promising · Muscle + exercise; cognitive emerging

Primary claim: Improves muscle strength and mass, supports exercise performance, and emerging evidence for cognitive function in older adults.

Creatine is one of the most-studied supplements in sports science. For muscle mass and strength: consistent evidence across dozens of RCTs that creatine augments the gains from resistance training, with effects particularly pronounced in older adults (greater absolute benefit from a lower baseline). Meta-analyses show significant lean mass and strength improvements. Emerging cognitive evidence: a 2023 meta-analysis found modest but consistent improvements in memory tasks in older adults. Mechanism: increases phosphocreatine availability in muscle and brain. Safety profile: excellent across decades of research. Cost: minimal.

Verdict: The most evidence-supported supplement for the specific goal of augmenting resistance training outcomes in older adults. Not a replacement for training — an augment to it. Cognitive effects are promising but not yet definitive. One of the few supplements where the evidence genuinely supports the primary marketed claim.

Key studies: Lanhers et al. (2017) Eur J Sport Sci; Forbes et al. (2021) Nutrients systematic review; Candow et al. (2022) Nutrients (older adults)

Magnesium (correction of deficiency)

Essential mineral · widespread dietary insufficiency in older adults

Promising · Deficiency very common in 60+

Primary claim: Supports sleep quality, muscle function, cardiovascular health, and metabolic outcomes.

Dietary magnesium insufficiency is extremely common in older adults — estimated at 50-70% in populations over 60, driven by reduced dietary intake and impaired absorption with age. Evidence for supplementation in insufficiency: sleep quality improvements across multiple small RCTs; muscle cramping reduction; blood pressure modest reduction in hypertensive individuals; insulin sensitivity improvements in metabolic syndrome. The PREDIMED trial found higher dietary magnesium associated with lower cardiovascular risk. Unlike vitamin D, correction of insufficient (not just formally deficient) magnesium shows benefit.

Verdict: High prior probability of genuine deficiency in older adults makes this among the more pragmatically justified supplements. Sleep and muscle function evidence is consistent. Not a longevity drug — a nutritional gap correction. Glycinate or malate forms are better tolerated than oxide.

Key studies: Abbasi et al. (2012) J Res Med Sci (sleep); Zhang et al. (2016) Nutrients (CVD meta-analysis); multiple observational studies in older cohorts

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WHAT THE EVIDENCE SAYS — EMERGING & HYPE

SUPPLEMENTS — EMERGING EVIDENCE

NMN / NR (NAD+ precursors)

Nicotinamide mononucleotide / riboside · NAD+ restoration

Emerging · Mechanism established · Outcomes pending

Primary claim: Restores declining NAD+ levels with age, improving mitochondrial function, DNA repair, and extending healthspan.

NAD+ levels decline with age and are central to mitochondrial function, DNA repair, and sirtuin activity. NMN and NR supplementation reliably raises NAD+ levels in humans — this part of the mechanism is established. Animal data is compelling: multiple studies show improved metabolic function, muscle endurance, and cognitive performance. Human outcome trials have been small (n=20-100) and short (8-16 weeks). Results to date: improved insulin sensitivity in some populations; no consistent effects on the outcomes that matter (muscle function, cognition, cardiovascular markers) in healthy adults. Larger trials are underway.

Verdict: Mechanistically credible — the biology is real and important. The human outcome evidence is not yet there. This is currently at the compelling mechanism stage, similar to where resveratrol was in 2010. The crucial question is whether raising NAD+ translates to meaningful health outcomes in humans. Genuinely unknown. Worth watching, not yet worth the premium supplement price.

Key references: Yoshino et al. (2021) Science (insulin sensitivity); Martens et al. (2020) Nat Metab; multiple small RCTs 2019-2023

Quercetin / Dasatinib+Quercetin (Senolytic protocol)

Flavonoid / Chemotherapy combination · senolytic use

Emerging · Mechanistically grounded · Early trials

Primary claim: Clears senescent cells (the SASP-producing dysfunctional cells that accumulate with age and drive chronic inflammation).

The Dasatinib + Quercetin (D+Q) combination is the most clinically advanced senolytic protocol, developed at Mayo Clinic. Pilot human studies have shown reduced senescent cell burden and inflammatory markers in specific conditions (idiopathic pulmonary fibrosis, diabetic kidney disease, frailty). The senolytic effect requires intermittent high-dose use — the mechanism is cell-killing, not cell-modulating. Quercetin alone at supplemental doses shows anti-inflammatory effects. Larger RCTs are underway. The mechanism is grounded in one of the most credible ageing biology frameworks (hallmarks of ageing).

Verdict: The most clinically credible senolytic candidate. Evidence is still early — pilot studies, not definitive RCTs. Quercetin at supplemental doses is safe with modest anti-inflammatory evidence. The D+Q protocol should be considered experimental. Results of ongoing trials over 2025-2027 will be important signal.

Key studies: Kirkland & Tchkonja (2020) J Intern Med; Hickson et al. (2019) EBioMedicine; UNITY trials (Justice et al., 2019)

SUPPLEMENTS — HYPE EXCEEDS EVIDENCE

Resveratrol

Polyphenol · red wine / supplement · sirtuin activator claim

Hype substantially exceeds current evidence

Primary claim: Activates sirtuins (SIRT1), mimics caloric restriction effects, and extends healthspan.

Resveratrol was one of the most hyped longevity supplements of the 2000s and 2010s, driven by David Sinclair's sirtuin research and dramatic animal results. The human evidence has been consistently disappointing. Multiple large RCTs in healthy older adults and specific disease populations showed no significant benefit for cardiovascular outcomes, cognitive function, or inflammatory markers. Bioavailability is poor — most orally consumed resveratrol is rapidly metabolised before reaching target tissues. GlaxoSmithKline invested over \$700m in sirtuin activators; the programme was largely discontinued after human trials failed.

Verdict: One of the clearest examples of animal-to-human translation failure in the longevity space. The mechanism story is scientifically interesting. The human trial evidence does not support the marketed claims. Current evidence does not support resveratrol supplementation for healthy ageing outcomes.

Key studies: Bhatt et al. (2012); CALERIE trial; multiple RCT failures 2012-2020; GSK sirtuin programme discontinuation

Collagen Supplements

Hydrolysed collagen peptides · skin, joint, bone claims

Contested · Modest skin evidence · Broader claims unsupported

Primary claim: Restores collagen in skin, joints, and connective tissue — reducing visible ageing signs and improving joint function.

The market is enormous; the marketing is almost entirely ahead of the evidence. Skin evidence: small trials (n=50-150) show modest improvements in skin hydration and elasticity — but effect sizes are small, blinding is difficult, and industry funding is ubiquitous. Joint evidence: mixed; some trials show reduced knee pain but systematic reviews are inconclusive. The physiological premise is weak: ingested collagen peptides are digested into amino acids like any other protein. They do not selectively rebuild collagen in skin or joints. The mechanism proposed by marketing is not how protein metabolism works.

Verdict: Modest evidence for skin hydration in some trials; claimed mechanism is physiologically implausible. A clear example of a product where the marketing narrative has been constructed around weak evidence and implausible biology. If the goal is collagen support, dietary protein adequacy and vitamin C are better-evidenced approaches.

Key studies: Choi et al. (2019) J Drugs Dermatol (systematic review); multiple small industry-funded trials

Telomere-Lengthening Supplements (TA-65)

Astragalus extract / cycloastragenol · consumer market

Hype exceeds evidence · Mechanism claim does not hold

Primary claim: Activates telomerase, lengthens telomeres, and reverses cellular ageing.

Telomere biology is real and important — telomere shortening is a genuine hallmark of ageing. The consumer supplement market around this biology is largely unsupported. TA-65 has one small industry-funded study showing modest telomere length increase; independent replication is absent. More fundamentally: telomere lengthening as a strategy is not straightforwardly positive — uncontrolled telomerase activation is a mechanism of cancer. The claim that a consumer supplement safely and specifically lengthens telomeres in a clinically meaningful way is not supported by independent evidence and has a plausible harm pathway.

Verdict: The biology is real; the supplements are not supported by independent evidence, and the mechanism claim has a plausible cancer risk dimension. One of the most egregious cases of legitimate science being used to market unsupported products. Avoid.

Key references: Blasco (2007) Nat Rev Genetics (telomere biology); Harley et al. (2011) Rejuvenation Research (sole industry-funded TA-65 study)

Generic Antioxidants (Vitamin E, beta-carotene)

Fat-soluble antioxidants · widely consumed supplements

Not guideline-supported · Some evidence of harm at high dose

Primary claim: Neutralise free radicals, reduce oxidative stress, and prevent age-related disease.

The oxidative stress theory of ageing generated enormous interest in antioxidant supplementation in the 1980s-1990s. Multiple large RCTs have now tested this hypothesis and consistently failed to find benefit — and in some cases found harm. ATBC trial (beta-carotene in smokers): increased lung cancer. CARET trial (beta-carotene + vitamin A): stopped early due to increased lung cancer. Multiple large vitamin E trials: no cardiovascular benefit; HOPE-TOO showed increased heart failure risk at high dose. The USPSTF explicitly recommends against beta-carotene and vitamin E supplementation.

Verdict: One of the most thoroughly tested and most thoroughly disproven categories in the supplement space. The hypothesis was reasonable; the evidence is definitive. High-dose antioxidant supplementation does not prevent age-related disease and may cause harm in specific populations. Current dietary guidelines do not support supplementation for healthy adults.

Key studies: ATBC (1994) NEJM; CARET trial (1996) NEJM; HOPE-TOO (2005) JAMA; USPSTF recommendation (2022)

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THE BEHAVIOURAL BASELINE

Before evaluating any supplement or pharmaceutical, it is essential to establish the behavioural baseline — the interventions against which all others should be measured.

BEHAVIOURAL INTERVENTIONS — INCLUDED FOR COMPARISON

Resistance Training (3x/week, progressive overload)

Behavioural intervention · no patent, no commercial incentive to promote

Proven · Strongest healthspan intervention currently known

Primary claim: Preserves muscle mass, bone density, metabolic health, and cognitive function; reduces all-cause mortality.

Progressive resistance training in older adults has more consistent positive evidence across more health outcomes than any supplement or drug currently available. Effects: muscle mass and sarcopenia prevention (Cochrane: strong evidence); bone density (established); insulin sensitivity (large effect size); cognitive function (multiple RCTs); depression (meta-analytic evidence); cardiovascular outcomes (large prospective cohorts); all-cause mortality (consistent dose-response). Effect sizes are large by clinical standards. Safety profile is excellent. Cost is minimal. The only reason it receives less attention than pharmaceutical interventions is that it has no commercial constituency funding its promotion.

Verdict: If resistance training could be patented, it would be the bestselling drug in history. The evidence base exceeds that of most pharmaceutical interventions for healthy ageing. Three sessions per week, progressive overload, maintained across the lifespan. This is the benchmark against which all other interventions should be measured.

Key evidence: Cochrane review Sherrington et al. 2019; Liu & Latham (2009) Cochrane; multiple prospective cohort studies; ACSM position statements

Mediterranean Dietary Pattern

Dietary pattern · not a supplement or product

Proven · Strongest dietary evidence base for healthy ageing

Primary claim: Reduces cardiovascular disease, cognitive decline, and all-cause mortality through anti-inflammatory dietary pattern.

The Mediterranean dietary pattern has the strongest evidence base of any dietary intervention for healthy ageing. The PREDIMED trial (Spain, n=7,447) provided RCT-level evidence for cardiovascular benefit — a 30% reduction in major cardiovascular events. Multiple large prospective cohorts confirm associations with reduced cognitive decline, reduced cancer risk, and lower all-cause mortality. The pattern (olive oil, vegetables, legumes, fish, moderate wine, limited processed food) shows consistent benefits across different populations and study designs. Mechanism: multiple anti-inflammatory pathways, favourable lipid profile, gut microbiome support.

Verdict: The diet with the best evidence base for healthy ageing. Not a trend, not a brand — a well-studied dietary pattern with RCT-level evidence for cardiovascular outcomes and consistent prospective evidence for cognitive health. More evidence-based than any supplement or nutraceutical on the market.

Key studies: PREDIMED trial (2013) NEJM; PREDIMED-PLUS (ongoing); multiple Cochrane reviews; SUN cohort studies

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SUMMARY — ALL 17 INTERVENTIONS AT A GLANCE

INTERVENTION	CATEGORY	EVIDENCE LEVEL	BEST SUPPORTED USE
Resistance training	Behavioural	Proven	Sarcopenia, cognition, metabolic health, all-c...
Aerobic exercise	Behavioural	Proven	Cardiovascular, cognitive, metabolic, mood
Mediterranean diet	Dietary pattern	Proven	Cardiovascular, cognitive decline, all-cause m...
Vitamin D (if deficient)	Supplement	Proven	Falls, bone density, immune — in deficient in...
Omega-3 (EPA/DHA, higher dose)	Supplement	Promising	Cardiovascular outcomes in at-risk populations
Metformin	Pharmaceutical	Promising	Metabolic health; TAME trial will clarify ageing...
GLP-1 agonists	Pharmaceutical	Promising	Cardiovascular; broader ageing applications e...
Creatine monohydrate	Supplement	Promising	Muscle mass + resistance training synergy; e...
NMN / NR	Supplement	Emerging	NAD+ restoration confirmed; outcome eviden...
Quercetin / D+Q senolytic	Suppl. / Pharma.	Emerging	Senolytic — specific conditions in early trials
Rapamycin (low dose)	Pharmaceutical	Contested	Strong animal data; human evidence very limi...
Aspirin (primary prevention)	Pharmaceutical	Guideline reversed	No longer recommended for primary preventi...
Resveratrol	Supplement	Hype exceeds evidence	Human trials consistently failed to replicate an...
Collagen supplements	Supplement	Contested	Modest skin hydration signal; mechanism clai...
Telomere supplements (TA-65)	Supplement	Hype exceeds evidence	Independent evidence; potential harm pat...
Antioxidants (Vit E / beta-C)	Supplement	Not supported	Multiple large trials: no benefit; some harm at ...
Magnesium (if deficient)	Supplement	Promising	Sleep, muscle, metabolic — common deficien...

Evidence levels reflect consensus of published systematic reviews, meta-analyses, and major clinical guidelines as of 2024. Not clinical advice.

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THREE THINGS THE EVIDENCE CONSISTENTLY SHOWS

01

Behaviour is the benchmark.

Resistance training, aerobic exercise, Mediterranean dietary pattern, sleep, and social connection have more consistent positive evidence across more health outcomes than any supplement or drug currently available for healthy adults. The supplement and pharmaceutical market is worth hundreds of billions. The evidence base for most of it does not compare to walking up stairs.

02

The mechanism-to-outcome gap is the critical analytical tool.

The most common pattern in this space is: compelling animal data — plausible human mechanism — large supplement market — disappointing human RCTs. Resveratrol, high-dose antioxidants, and telomere supplements all follow this pattern. NMN/NR and rapamycin are currently at the compelling mechanism stage. Whether they will survive rigorous human outcome trials is genuinely unknown.

03

GLP-1 agonists and senolytics are the most important developments to watch.

The SELECT trial result for semaglutide is a landmark finding. The senolytic pipeline is mechanistically grounded in the most credible ageing biology framework. These two areas are most likely to produce genuine healthspan pharmaceutical breakthroughs in the next five years — not as replacements for behavioural interventions, but as meaningful additions to them.

"The most honest thing that can be said about the longevity supplement market is this: it is a large, profitable, well-marketed industry that is significantly ahead of its evidence base. The science of healthy ageing is real and advancing. Most of the products sold in its name are not."

ABOUT THIS REVIEW

This evidence matrix synthesises published systematic reviews, meta-analyses, and major clinical trial results as of 2024. Evidence ratings are descriptive assessments of the current state of human clinical evidence — not prescriptive recommendations. Individual circumstances, existing conditions, and medications affect the appropriateness of any intervention. This is not clinical advice. Primary sources are cited in individual cards.

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