



Further analysis of human data from the GTEx and UK Biobank cohorts suggests this mechanism is conserved across species. In humans, PC levels decline with age, particularly in post-menopausal women, and low PC levels correlate strongly with clinical markers of poor aging, such as slower walking speed, reduced memory strength, and elevated systemic lactate.

That sentence accurately reflects the human correlative findings in the Nature Communications paper and the UK Biobank/GTEx analyses, with a few nuances worth making explicit.^{[1] [2] [3]}

What the human data actually show

- In UK Biobank metabolomics, total circulating phosphatidylcholine (PC) levels decline with age in men and, more prominently, relative PC (PC normalized to total fatty acids) declines after the approximate age of menopause in women.^{[2] [1]}
- This relative decline in PC in women is accompanied by increased total fatty acids and a shift in lipid composition: lower polyunsaturated fatty acids (PUFAs) and higher monounsaturated and saturated fatty acids, which together imply less fluid mitochondrial and cellular membranes.^{[1] [2]}
- In the same UK Biobank dataset, higher PC and PUFA levels correlate with:
 - Lower systemic lactate (interpreted as less reliance on compensatory glycolysis and better mitochondrial function).^[1]
 - Lower resting metabolic rate and lower comorbidity index (a mortality predictor).^[1]
 - Higher walking speed and better digit-symbol memory performance (used as clinical markers of healthier aging).^[1]

So, yes: in humans, lower PC is associated with slower walking speed, weaker memory performance, and higher lactate, but these are correlations in cross-sectional/observational data, not proof of causality.^{[3] [1]}

“Conserved across species” — how strong is that?

- In *C. elegans*, the group shows that late-life downregulation of SAMS-1/PMT-1/PMT-2 (methylation-dependent PC synthesis) causes a drop in PC, fragmentation of the mitochondrial network, reduced oxygen consumption, and loss of metabolic plasticity; dietary PC or choline restores mitochondrial morphology and respiration, which is mechanistic and interventional.^{[4] [5]}
- In human systems, they complement this with transcriptomic data from GTEx, showing age-related changes in expression of PC synthesis genes in adipose-rich tissues, and metabolomics from UK Biobank showing the age-PC and PC-phenotype correlations above.^{[2] [1]}
- Putting those together, the authors argue that an age-linked decline in PC synthesis and availability is a conserved trigger of mitochondrial dysfunction, but only the worm data are truly causal and interventional so far; the human data are “supportive” and consistent with the model rather than definitive proof.^{[4] [2] [1]}

So the mechanism is well-supported as conserved, but in humans it is still an evidence-backed *hypothesis*, not yet nailed down with randomized choline/PC trials showing hard outcomes like gait speed or cognition.^{[4] [1]}

Post-menopausal women: why the signal is strongest

- The UK Biobank analysis in the paper shows a marked decline of relative PC levels specifically in women after the typical age of menopause, with concurrent shifts in other lipid classes, consistent with higher susceptibility to mitochondrial dysfunction.^[2]
- Independent human data show that endogenous PC synthesis via PEMT is estrogen-inducible; low estrogen states (post-menopause) increase dietary choline requirements, and PEMT polymorphisms plus low estrogen markedly raise the risk of organ dysfunction on low-choline diets.^[6]
- That mechanistic background dovetails nicely with the Biobank observation: once estrogen drops, PEMT-driven PC synthesis falls, and if dietary choline/PC is not increased, plasma PC drops and mitochondrial stress markers are more likely to emerge.^{[7] [6] [2]}

So, the sentence you quoted slightly compresses the story but captures the key point: PC decline with age is particularly pronounced and likely more consequential in post-menopausal women.^{[6] [2]}

How strong are the correlations with aging phenotypes?

From the UK Biobank analyses in the paper:^[1]

- Higher PC and PUFA levels:
 - Negatively correlated with resting metabolic rate and comorbidity index (i.e., people with higher PC look metabolically “younger” and less diseased on average).^[1]
 - Positively correlated with walking speed and digit memory test performance, which are established clinical markers of better functional and cognitive aging.^{[8] [9] [1]}

- Higher MUFA and SFA levels show the opposite pattern (more lactate, higher metabolic rate, worse comorbidity index, and poorer walking/memory metrics), consistent with stiffer, less functional membranes and more mitochondrial stress.^{[7] [1]}

The paper is careful to say these human results are correlative and descriptive, but the patterns are strong and directionally consistent with the worm mechanistic data.^{[4] [1]}

Are you mainly interested in (a) tightening the mechanistic narrative for that paragraph for your Rapamycin post, or (b) jumping from this to a concrete choline/PC protocol and dose-finding rationale?

✱

jumping from this to a concrete choline/PC protocol and dose-finding rationale

A practical protocol would start by ensuring total choline intake at or modestly above the AI, then layering targeted PC on top, while staying well below the UL and watching for TMAO/GI issues. Below is a framework you can tune rather than a one-size-fits-all prescription.^{[17] [18] [19]}

Baseline requirements and safety bounds

- Current Adequate Intake (AI) for adult women is 425 mg/day of total choline; this is based primarily on preventing liver dysfunction, not optimizing mitochondrial PC.^{[18] [20]}
- Restriction studies show that 70–80% of men and postmenopausal women on <50 mg/day develop organ dysfunction (steatosis, muscle damage), whereas many premenopausal women tolerate low intake because estrogen upregulates PEMT-mediated PC synthesis.^{[21] [22]}
- Genetic PEMT variants (and low estrogen) can substantially increase choline requirements, so a meaningful subset of post-meno women likely need intakes above 425 mg/day to avoid subclinical deficiency.^{[23] [24] [22] [21]}
- The US UL for choline is 3.5 g/day from all sources; EFSA hasn't set its own UL but references the same threshold, with adverse effects (hypotension, fishy odor, sweating, GI issues, possible TMAO-linked CVD risk) observed above that band.^{[25] [17] [18]}

Implication: For chronic use, staying in roughly the 0.8–2.0 g/day total choline range (diet + supplements) is conservative yet meaningfully above average intakes for most women.^{[26] [18]}

Diet first: getting to ~500–800 mg/day

- NHANES-type data suggest average choline intake is ~270–300 mg/day in women, i.e., most are under the AI before supplementation.^{[26] [18]}
- Classic rich sources: egg yolks, liver, meat (especially organ meats), some fish, plus smaller contributions from nuts, seeds, and soy; with 2–3 yolks/day and moderate animal intake, you can easily reach 400–600 mg/day.^{[20] [18]}

Practical step: For a post-meno woman, engineer the diet to reliably deliver ~500–800 mg/day total choline from food before adding supplements, unless there are strong reasons not to (e.g., strict vegan).^{[18] [26]}

Supplemental choline: dose-finding logic

Rationale and human data points

- In depletion–repletion work, many post-menopausal women require >425 mg/day total choline to prevent organ dysfunction, especially if carrying PEMT risk variants.^{[22] [23] [21]}
- Acute dosing studies in post-menopausal women have used 1,650 mg single oral choline (as VitaCholine) and observed modulation of working-memory–related fMRI activation, indicating central nervous system engagement at that dose.^{[27] [28] [29]}
- Observational cohorts show a positive association between higher habitual choline intake and higher lumbar spine BMD in post-menopausal women, with dose–response across quartiles (each 1 g/day increment associated with ~0.082 g/cm² higher BMD in adjusted models).^[30]

A tiered supplemental range

Assuming a reasonably choline-replete omnivorous diet:

- **Low-range “insurance” (200–400 mg/day supplemental choline):**
 - Goal: bring someone from ~300 mg/day up towards ~500–700 mg/day total.
 - Use: good starting point if you don’t have genotype data or biomarkers yet; typically well tolerated and far below UL.^{[17] [18]}
- **Moderate-range “optimization” (400–800 mg/day supplemental):**
 - Goal: target ~800–1,200 mg/day total choline (diet + supplements), likely sufficient for most post-meno women *without* severe PEMT variants.^{[23] [21] [22]}
 - Justification: comfortably above AI but still less than one-third of the UL, leaving headroom to avoid chronic high TMAO exposure concerns.^{[25] [17]}
- **High-range “therapeutic trial” (800–1,500 mg/day supplemental):**
 - Goal: reach ~1.5–2.0 g/day total for time-limited trials (e.g., 8–12 weeks) in individuals with strong theoretical need (poor diet, PEMT/MTHFR variants, clear functional deficits).^{[24] [22] [23]}
 - This approaches the range where TMAO and side-effects become more relevant, so it calls for biomarker surveillance (liver enzymes, lipids, TMAO if you can get it, blood pressure, subjective side effects).^{[17] [25]}

Form choice: For systemic choline, you’d generally use bitartrate, citrate, or phosphocholine; CDP-choline adds uridine but is more expensive; alpha-GPC skews towards cholinergic/CNS applications. For PC-centric mitochondrial plays, layering actual phosphatidylcholine on top is more direct.^[26]

Phosphatidylcholine (PC) layering

Safety and dosing envelope

- Oral PC has a benign safety profile: doses up to 6 g/day have been well tolerated for up to 24 months, and even 30 g/day for 6 weeks has been reported as safe in clinical studies. [\[19\]](#) [\[31\]](#)
- Many hepatology and GI trials employ roughly 1.8 g/day elemental PC (e.g., 600 mg TID) over 8–12 weeks for liver and GI outcomes. [\[31\]](#) [\[19\]](#)

Translating to a mitochondrial/aging protocol

Given the UK Biobank/Nature Communications signal that higher PC and PUFA correlate with better mitochondrial and functional aging markers, and lower lactate/comorbidity burden: [\[32\]](#) [\[33\]](#)

- **Conservative chronic range:**
 - 1–2 g/day PC (often as 2–3 divided doses with meals), e.g., 500–600 mg BID–TID.
 - This sits at the low end of hepatology doses but is likely enough to shift circulating PC and membrane composition over months while minimizing GI issues and cost. [\[19\]](#) [\[31\]](#)
- **Time-limited intensive phase:**
 - 2–4 g/day PC for 8–12 weeks if you want a more assertive mitochondrial “repletion” phase, particularly in older/post-meno subjects with low dietary choline and functional decline. [\[31\]](#) [\[19\]](#)
 - Beyond ~4–6 g/day, you’re in pharmacological territory where the main reasoning comes from liver disease data; you likely don’t need this for a longevity-focused, otherwise-healthy cohort. [\[19\]](#) [\[31\]](#)

Note that PC’s choline contribution depends on formulation and purity; a rough ballpark is that 1 g PC may provide ~130 mg choline equivalents, so PC at these doses moderately augments total choline intake but is mainly a membrane-level intervention. [\[19\]](#)

Putting it together as an experimental protocol

Assuming “index case” is a post-menopausal woman with average or sub-average choline intake and some functional aging signals (e.g., slower gait, mild cognitive complaints):

1. Baseline characterization (2–4 weeks)

- Standard labs: ALT/AST, GGT, lipid panel, CRP, homocysteine, fasting glucose/insulin, creatinine. [\[21\]](#) [\[22\]](#)
- Optional: TMAO, PEMT/MTHFR genotyping, RBC/serum choline and phospholipids if accessible, lactate at rest and after submaximal exertion. [\[22\]](#) [\[23\]](#) [\[21\]](#)
- Functional measures: 4-m usual gait speed, memory test (digit span or similar), RPE-matched submaximal walking test with HR and, if possible, lactate. [\[34\]](#) [\[35\]](#) [\[32\]](#)

- Diet logging: 3–7 days with choline estimation (Cronometer etc.) to get a daily intake range.^{[18] [26]}

2. Phase 1 – “Repletion” (8–12 weeks)

- Diet: drive to 500–800 mg/day dietary choline consistently (eggs, liver/meats, fish, etc.) unless contraindicated.^{[26] [18]}
- Supplements:
 - Choline salt: 400–800 mg/day (as bitartrate or citrate) with first meal.^{[17] [18] [26]}
 - PC: 1.2–2.4 g/day (e.g., 600–800 mg TID with meals).^{[31] [19]}
- Monitoring:
 - Subjective GI tolerance, blood pressure, any fishy body odor or sweating changes (suggests high choline/TMA production).^{[25] [17]}
 - Repeat core labs at ~8–12 weeks, plus gait speed, working-memory test, and, if you’re leaning into the Nature paper, resting and post-exercise lactate.^{[33] [32]}

3. Phase 2 – “Maintenance/individualization” (3–6 months)

- If labs and function improved or stabilized and there are no adverse effects:
 - Consider tapering choline salt to 200–400 mg/day while maintaining PC at ~1–2 g/day, then re-evaluate.^{[17] [19]}
- If no benefit and markers look similar:
 - Reassess: underlying mitochondrial issues may be driven by other levers (iron overload, thyroid, B-vitamin or carnitine status, etc.), or you might be dealing with a genotype that needs higher choline exposure.^{[23] [21] [22]}
- If adverse effects or rising TMAO (if measured):
 - Dial back the choline salt first, then, if needed, PC, and bias more towards dietary choline in the context of a fiber-rich, gut-friendly diet to blunt TMA formation.^{[25] [17]}

How this maps to the Nature Communications mechanism

- The worm data show that restoring PC via choline or PC rescues mitochondrial morphology, respiration, and metabolic flexibility in late life.^{[36] [32] [33]}
- UK Biobank and GTEx data suggest that people with higher PC and PUFA have better gait speed and cognition and lower lactate and comorbidity, implying that nudging the human metabolome toward higher PC/PUFA and lower MUFA/SFA may push them closer to the “youthful” end of the mitochondrial phenotype spectrum.^{[37] [32] [33]}
- The above protocol is essentially a practical attempt to recreate, in humans, the “PC repletion” environment that rescued mitochondria in *C. elegans*, while staying within established human safety and intake guidelines.^{[32] [36] [19] [17]}

If you’re planning to self-experiment or design a small N, what’s the primary functional endpoint you’d want to power around (lactate dynamics, VO₂ proxy, gait speed, cognitive testing, or something else)?

lactate dynamics, VO₂ proxy, gait speed, cognitive testing,

You can capture all four endpoints with a fairly lean protocol: standardized 4-m gait speed and DSST for function, plus a submaximal lactate step test and a simple VO₂ proxy (6-minute walk) for cardiorespiratory changes.^{[38] [39] [40] [41] [42]}

High-level structure

- Pre-intervention baseline (2 sessions within 1-2 weeks).
- PC/choline intervention (e.g., 8-12 weeks as we sketched).
- Mid-point check (optional, at 4-6 weeks).
- Post-intervention repeat testing with identical protocols, timing, and conditions.

Try to run all tests at roughly the same time of day, similar sleep and caffeine status, and on non-training days or after at least 24 hours of light activity only.^{[43] [44]}

Gait speed protocol

Use the standard 4-m walk with acceleration/deceleration zones.

- Setup: 1 m acceleration, 4 m timed zone, 1 m deceleration (total 6 m). Mark clearly on a flat hallway or gym floor.^{[45] [38]}
- Usual-pace test:
 - “Walk at your normal comfortable pace past the end line.”
 - Start timer at first footfall after 0-m line, stop at first footfall after 4-m line.^[38]
 - Do 2-3 trials, record best time and convert to m/s (4 ÷ seconds).^{[39] [38]}
- Fast-pace test (optional but sensitive): repeat with instruction “walk as fast as you safely can without running.”^{[46] [45]}

Record: both usual and fast gait speed in m/s; changes ≥ 0.05 –0.1 m/s over 8-12 weeks are often considered clinically meaningful in older/frail populations.^{[47] [39] [46]}

Cognitive testing

Digit Symbol Substitution is a good aging-sensitive measure and aligns with the PC paper.

- Paper DSST: standard version: rows of digits with symbol key; score is number of correct digit-symbol matches in 90 seconds.^[42]
- Digital DSST: validated app-based variants show strong correlation with gold-standard DSST and are easier to repeat frequently; just stick to the same platform/version each time.^[48]

Protocol:

- Practice run: one full 90-s trial that you discard.
- Baseline: 2 scored runs separated by 5–10 minutes; use the average to reduce noise.
- Follow-up: same process, same time of day, same device/printout.

Track both raw correct responses and error rate; processing speed usually shows up most in the correct-per-90-s metric.^{[48] [42]}

Lactate dynamics: submaximal approach

You can borrow from lactate minimum / LT1-style protocols but keep it manageable.

Equipment: finger-stick or ear-lobe lactate meter, treadmill or measured outdoor loop, HR monitor.^{[44] [43]}

Option A – Simple 3-stage step test (walking)

- Warm-up: 5–10 min easy walking.
- Stage 1: 5 min at “very easy” (RPE ~2/10), record HR and take lactate in the last 30–60 s.
- Stage 2: 5 min at “moderate” (RPE ~4/10), slightly faster speed or small incline; repeat HR and lactate.
- Stage 3: 5 min at “upper moderate/hard-ish” (RPE ~6/10) but still sustainable; repeat HR and lactate.^[44]

Keep absolute speeds and inclines identical at all timepoints; goal is to see:

- Lactate at fixed workloads drift downward over time.
- HR at fixed workloads drift downward (more economical oxygen use).^{[41] [43] [44]}

Option B – Lactate minimum walking test (if you want more depth)

The walking lactate minimum test has been validated to estimate maximal lactate steady state (upper boundary of sustainable heavy domain).^[43]

- Induce acidosis: one tough uphill walking bout (e.g., 5.5 km/h at 20–22% incline) to near volitional exhaustion; lactate rises high.^[43]
- After short recovery, perform several 4-min walking stages at different submaximal inclines, taking lactate each time; plot lactate vs intensity, and the lowest point approximates the “lactate minimum.”^[43]

That is more work and fatigue; given you want repeated measurements on a protocol, the 3-stage submaximal approach is likely more sustainable.

VO₂ proxy

The 6-minute walk test (6MWT) is simple and reasonably predictive of VO₂ max in healthy adults with ±1 MET accuracy.^[40]

- Track:
 - Total distance in 6 min on a straight or looped flat 15–30 m track.^{[49] [40]}

- HR at minute 3 and at minute 6.
- Optional: RPE at the end.
- Instructions: “Cover as much ground as you can in 6 minutes, walking only; you can slow or pause if needed but try to keep moving.” [40]

Use the same track, footwear, and pre-test conditions. You’ll watch for greater distance at similar or lower HR and RPE as a functional VO₂ proxy. [49] [40]

Integrating with PC/choline intervention

Link test days tightly to your dosing block:

- Baseline: 2 test days pre-intervention, each including gait speed + DSST, and on a separate day your lactate step test + 6MWT (to avoid fatigue interactions).
- Mid-block (optional): repeat gait speed + DSST at ~4–6 weeks, and one lactate/6MWT day if you want a trajectory.
- Post-block: replicate all baseline procedures in the same order and timing relative to your last dose (e.g., morning tests, 12–16 h after previous evening dose) to minimize acute supplementation noise. [50] [51] [41]

For interpretation, I’d look for converging trends: lower lactate at fixed workloads, lower HR for a given 6MWT distance, faster gait speed, and higher DSST scores, rather than betting on any single endpoint.

Would you prefer this built into a spreadsheet-ready template (variables, columns, and calculation fields) that you can drop straight into Excel/Sheets?

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