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# Genetic, metabolic and hippocampal myelin contributions to episodic memory ageing

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# Genetic, metabolic and hippocampal myelin contributions to episodic memory ageing

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## Abstract

There is ongoing controversy about the role of the apolipoprotein-E (APOE) genotype in modulating cognitive trajectories in healthy ageing and Alzheimer's disease. We investigated associations between APOE genotype, cardiometabolic and inflammatory profiles, lifestyle, and hippocampal microstructure with late-life episodic memory trajectories in a community-dwelling, mid-to-old-age cohort. The genotyped sample (n=5325) with follow-up spanning over 20 years included nested cognitive (n=1378) and neuroimaging subsamples (n=301). We first tested whether the APOE ε4 allele was associated with systemic physiological profiles across adulthood, followed by assessment of APOE associations with cognitive ageing trajectories and their relationships with health profiles and MRI markers of hippocampal myelination. APOE ε4 carrier status was associated with an adverse lipid-related metabolic profile across adulthood. In late-life, APOE ε4 was selectively associated with steeper age-related episodic memory decline across cognitive domains examined, with effects emerging in the eighth decade of life and evident already among heterozygous carriers. Individual metabolic, inflammatory, cardiovascular, and lifestyle markers did not account for this APOE ε4-related memory effect. When considered jointly within their respective domains, adverse metabolic burden was associated with poorer episodic memory performance and reduced odds of memory maintenance, whereas a favorable lifestyle profile was associated with better episodic memory function, independently of APOE genotype. The association between hippocampal myelin content and steepness of episodic memory trajectories was stronger in APOE ε4 carriers, while hippocampal volume showed only a trend. These findings indicate that APOE ε4 is primarily linked to episodic memory decline dynamics, with hippocampal myelin marking trajectory differences, whereas peripheral metabolic burden and lifestyle relates to memory performance level.

# Introduction

Cognitive performance follows highly variable trajectories across the lifespan[1–4]. Among the cognitive domains affected by ageing, episodic memory[5] is especially susceptible to ageing-related pathology including cerebral small vessel disease, neurodegenerative disorders and late-life depression[2,3,6]. Despite considerable progress in the field, the pre-morbid processes that determine the timing and severity of episodic memory decline across adult life remain poorly characterized[7].

One established factor implicated in these processes is the APOE ε4 allele, the strongest common genetic risk factor for sporadic late-onset Alzheimer's disease[8,9], which has also been linked to accelerated cognitive ageing and impaired episodic memory function[10,11]. Its effects on episodic memory in community-dwelling populations remain incompletely defined, particularly with respect to domain specificity and the role of zygosity[11–15].

The mechanisms underlying this association are similarly unresolved. APOE is the brain's principal cholesterol transporter, mediating cholesterol transfer from astrocytes to neurons in a process that becomes critical as the brain matures. The ε4 isoform is less efficient at this function, resulting in impaired cholesterol delivery to neurons. Beyond this central role in lipid transport and metabolic regulation, APOE has also been implicated in vascular and inflammatory processes[16–18], raising the possibility that APOE-related vulnerability manifests in systemic physiological profiles well before memory symptoms emerge. Given that blood-based and other relevant markers are routinely accessible in clinical assessments, an unresolved but important question is whether such measures, individually or in combination, account for meaningful variation in episodic memory across adulthood.

Understanding how APOE ε4-related episodic memory vulnerability is expressed at the neural level is equally critical. Neuroimaging findings in this area have been inconsistent - some studies report age-dependent differences in hippocampal volume[19], while others point to white matter microstructural pathology, with effects largely restricted to homozygous carriers and little evidence of differences in heterozygotes[20]. Myelin-sensitive MRI markers of hippocampal tissue properties offer a complementary window onto the neural substrates of memory decline in ageing, a perspective made particularly pertinent by emerging evidence linking APOE-related lipid dysregulation to altered myelin biology[21–23]. Whether hippocampal myelination contributes to inter-individual differences in ageing-associated episodic memory decline, and whether such relationships differ by APOE-ε4 carrier status, remains largely underinvestigated.

The present study addressed these questions using a multi-level design in a large community-based cohort. We first examined how APOE ε4 carrier status relates to cardiometabolic and inflammatory profiles monitored over two decades of mid- to late adulthood. We then characterized associations between APOE ε4 and cognitive trajectories across domains to identify which domain is most affected. Finally, we assessed whether systemic markers or hippocampal myelination account for meaningful variation in cognitive trajectories and whether these relationships differ by genotype. Together, this approach was designed to clarify how APOE genotype, systemic physiology, and hippocampal myelination jointly contribute to ageing-related episodic memory decline in the general population.

# Results

## 1. Sample characteristics

Analyses were conducted in four nested subsamples derived from the CoLaus | PsyCoLaus epidemiological study[24,25]: i. **genotyped full cohort** (N=5,325; ≥ 35 years; female: 52.7%), and three sub-samples focusing on later life (≥ 65 years); ii. **cognitive analysis subsample** with at least one cognitive assessment and systemic health measurements (N = 1,378; baseline age 61.73 ± 6.1 years; female: 58.3%); **repeat longitudinal subsample** with longitudinal cognition (N = 746; baseline age 62.78 ± 5.1 years; female: 59.4%), and a **neuroimaging subsample** including brain MRI (N = 301; baseline age 61.53 ± 4.8 years; female: 54.8%) (details in Supplementary Table 1). Analytical subsamples differed from non-selected genotyped participants primarily in age, consistent with their later-life assessment structure, but showed limited imbalance in APOE genotype and other core baseline characteristics (Supplementary Table 2).

## 2. APOE and systemic health profile

We tested whether APOE ε4 carrier status was associated with longitudinal health profiles across metabolic, inflammatory, cardiovascular, and lifestyle domains, using all available observations across follow-up in the genotyped cohort covering midlife to older age (ε4 carriers: 22.4%; ε2+/ε4: 12.2%; ε3/ε3: 65.4%). APOE ε4 carriers showed a less favorable metabolic profile, dominated by lipid-related measures (Figure 1). The strongest main effect was observed for LDL cholesterol (β = 0.25, 95% CI [0.17, 0.32]), followed by total cholesterol (β = 0.22, 95% CI [0.16, 0.28]) and apolipoprotein B (β = 0.15, 95% CI [0.09, 0.19]). ε2 carriers (ε2+/ε4− vs. rest) showed opposing associations with these lipid markers (Supplementary Figure 1). Apolipoprotein B levels were higher in ε4 carriers, particularly among women (APOE-ε4 × sex: β = 0.07, 95% CI [0.03, 0.10]). APOE ε4 modified age-related metabolic trajectories, with modest but significant APOE ε4 × age interactions observed across several markers, including LDL cholesterol, total cholesterol, triglycerides, glucose, and HbA1c (β range: −0.05 to −0.09), indicating change of ε4-related effects at older ages.

In the inflammatory domain, APOE-ε4 carriers showed lower C-reactive protein levels (β = −0.24, 95% CI [−0.32, −0.17]). An APOE ε4 × age interaction was observed for TNF-α (β = −0.06, 95% CI [−0.03, −0.08]), whereas interleukin-1β and interleukin-6 showed no evidence of APOE ε4 main or interaction effects.

For aggregate cardiovascular risk, the APOE ε4-related difference was greater in men than in women, reflected by a significant APOE ε4 × sex interaction for composite cardiovascular risk (SCORE2: β = 0.07, 95% CI [0.04, 0.10]; Supplementary Figure 2). No consistent APOE ε4 associations were observed for systolic or diastolic blood pressure, and no APOE ε4 × age interactions were detected for other cardiovascular risk markers. Lifestyle variables showed no evidence of association with APOE ε4 carrier status.

To assess whether these interactions could reflect age-related ascertainment or collider bias, we tested APOE ε4 carrier status against participant age and found no significant association. Across later-life subsamples and variables with more restricted wave availability, the direction of APOE ε4 associations was broadly consistent, with attenuation of effect sizes and reduced detection of interaction effects - as expected, given smaller sample sizes, restricted age ranges, and subsample selection (Supplementary Figure 3–8).

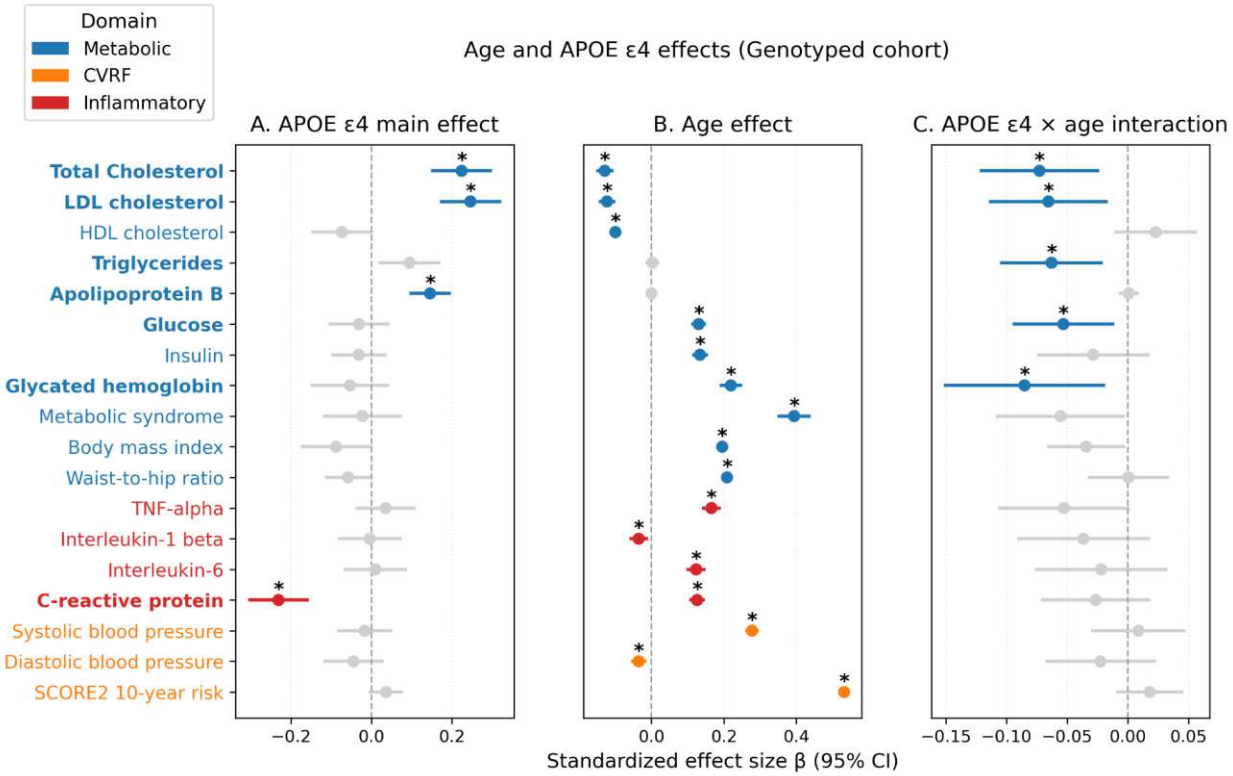



**Figure 1. Age and APOE ε4 associations with metabolic, cardiovascular, and inflammatory factors.**
A. APOE-ε4 carrier vs non-carrier differences at the reference age (intercept effects). B. Main age effects. C. APOE-ε4×age interaction effects on age-related change (slope effects). Forest plots display standardized effect sizes (β) with 95% confidence intervals. Asterisks (*) indicate significant associations (pFDRcorr < 0.05, per panel). Bold factor labels mark significant APOE-ε4-related effects, either main or interaction effects. Non-significant estimates are shown in grey.

## 3. Age and APOE genotype shape cognitive trajectories

Following characterisation of systemic health profiles by APOE genotype, we examined associations between age and APOE genotype with cognitive performance trajectories. Age was associated with worse performance across all studied cognitive domains (Supplementary Table 3) except processing speed, as measured by the Victoria Stroop task (Figure 2). The strongest age-related association was observed for episodic memory (Free and Cued Selective Reminding Test (FCSRT); $\beta = -0.33$), followed by executive function ($\beta > 0.22$) and global functioning ($|\beta| \geq 0.15$). ε4 carrier status was not associated with cognitive performance at the reference age. In contrast, APOE ε4 modified age-related trajectories for episodic memory, with ε4 carriers showing steeper age-related decline ($\beta = -0.31$, $p = 0.007$, 5% FDR threshold: $p \leq 0.007$). This association

remained significant when baseline age and time since the first cognitive assessment were modelled separately, supporting steeper within-person episodic-memory decline in ε4 carriers. Complementary post-hoc analysis showed that this association remained unchanged when homozygous carriers were excluded from the sample. APOE ε2 showed no evidence of main or age-interaction effects across cognitive domains (all pFDR > 0.05).

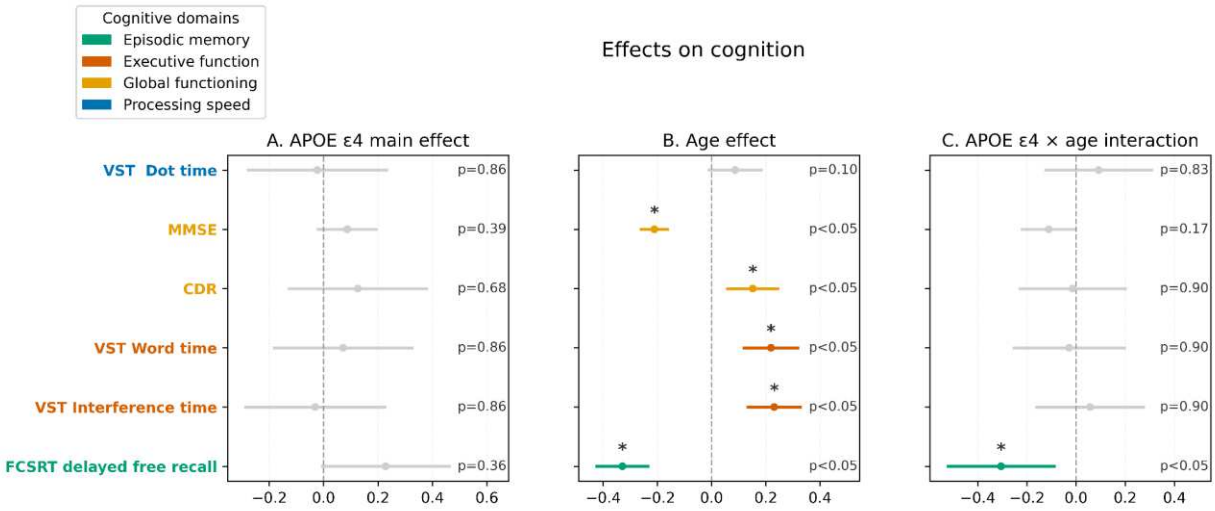



**Figure 2. Age and APOE-ε4 effects on cognitive performance across domains. A.** APOE-ε4 carrier vs non-carrier differences at the reference age (intercept effects). **B.** Main age effects. **C.** APOE-ε4×age interaction effects on age-related change (slope effects). Points show β and horizontal lines 95% CIs from longitudinal mixed-effects models. Colors denote cognitive domain, light grey points indicate non-significant effects, and asterisks indicate FDR-corrected significance.

## 4. APOE-ε4 carriers show steeper episodic memory decline

Given the selective age-dependent association of APOE ε4 with episodic memory, we investigated FCSRT delayed free recall trajectories in greater detail − this measure is hereafter referred to as episodic memory (EM). In the cognitive sample the mean episodic memory score at the first visit was 11.7±2.5 (range 0–16). Among participants with repeated measurements (N=747) with a mean follow-up interval of 4.7±0.95 years, the average score change (last minus first visit) was of -0.38±2.6 points, indicating significant inter-individual variability around the average decline.

More years of education was associated with higher episodic memory performance (β = 0.13 points per year of education, Figure 3) and women showed higher episodic memory than men after adjustment for education (β≈1.5 points). Episodic memory declined with age (β = -0.08 points/year). APOE ε4 carriers showed steeper age-related decline than non-carriers -0.14 vs. -0.08 points/year, corresponding to approximately 75% greater annual decline, with group differences most apparent from the early seventies onward.

Given the association between APOE ε4 and systemic metabolic and inflammatory measures, we examined whether systemic physiological or lifestyle factors explained or modified APOE ε4

related differences in episodic memory decline. Adjustment for these variables did not attenuate the APOE ε4×age interaction, and no significant APOE × systemic measure or APOE × lifestyle interactions were observed. Complementary mediation analyses using domain-level principal components and individual systemic physiological and lifestyle markers showed no evidence of significant indirect effects on the APOE ε4–episodic memory slope association.

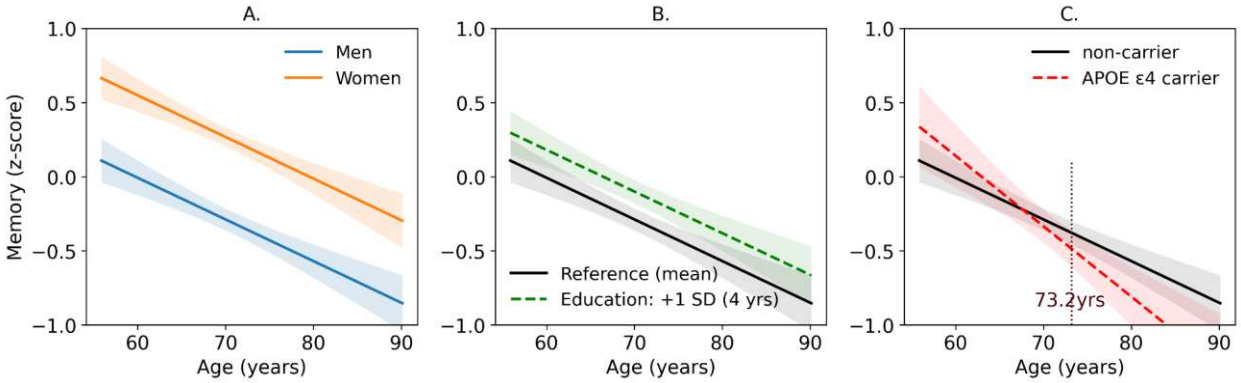



**Figure 3. Demographic and APOE4 effects on episodic memory trajectories. A.** Mixed-effects model predictions of standardized memory across age by sex. **B.** model predictions across age at mean vs +1 standard deviation (SD) education. **C.** model predictions across age by APOE-ε4 carrier status; the marked age indicates when the pointwise 95% CI for the model-estimated group difference first excludes zero. Bands show 95% CIs.

## 5. Effects on episodic memory performance and trajectories

Beyond the estimated group-level age-related decline, individual episodic memory trajectories showed substantial heterogeneity (Figure 4. A-B). Participants were classified according to within-subject episodic memory change, revealing that approximately 56% were decliners and 44% maintainers or improvers. We then examined whether domain-level systemic health and lifestyle profiles accounted for this inter-individual variability, summarizing measures from metabolic, cardiovascular, inflammatory and lifestyle domains into subject-level composite scores using principal component analysis (PCA).

**Profiles associated with episodic memory improver status**

Among aggregated measures, higher metabolic principal component (PC1), reflecting an adverse metabolic profile based on the component loadings shown in Figure 4.E, was associated with lower odds of episodic memory maintenance (OR per SD = 0.77, 95% CI 0.63–0.94; pFDR < 0.05), whereas lifestyle, inflammatory, and cardiovascular profiles were not associated with trajectory class. This association remained after accounting for APOE genotype, and APOE ε4 and -ε2 carrier frequencies did not differ across trajectory classes (Wald $\chi^2$, both pFDR > 0.05).

**Profiles associated with overall episodic memory performance**

We then examined whether the same domain-level composites were associated with mean episodic memory performance. A higher lifestyle PC1 reflecting better physical function, sleep quality and physical activity together with cohort-specific alcohol-consumption patterns (loadings shown in Figure 4.F) was associated with higher mean episodic memory (β = 0.11, 95% CI 0.02–0.21; pFDR < 0.05), whereas a higher metabolic PC1 was associated with lower mean episodic

memory (β = −0.16, 95% CI −0.25 to −0.08; pFDR < 0.05). No clear associations were observed for other cardiovascular or inflammatory profiles (PCs).

These associations were independent of APOE genotype, with no evidence of main or interaction effects (all pFDR > 0.30). Together, these findings indicate that systemic metabolic and lifestyle profiles relate to episodic memory level and trajectory class, but not to the rate of memory decline, which was selectively associated with APOE ε4.

**Interpretation of domain profiles**

To contextualize these findings, we examined the variables contributing most strongly to metabolic and lifestyle PC1. Higher metabolic PC1 scores, which were associated with lower episodic memory performance and lower odds of memory maintenance, reflected higher BMI, waist-to-hip ratio, metabolic syndrome, insulin, glucose and triglyceride levels, together with lower HDL cholesterol. Lifestyle PC1 reflected peak handgrip strength, alcohol consumption, better sleep quality and physical activity.

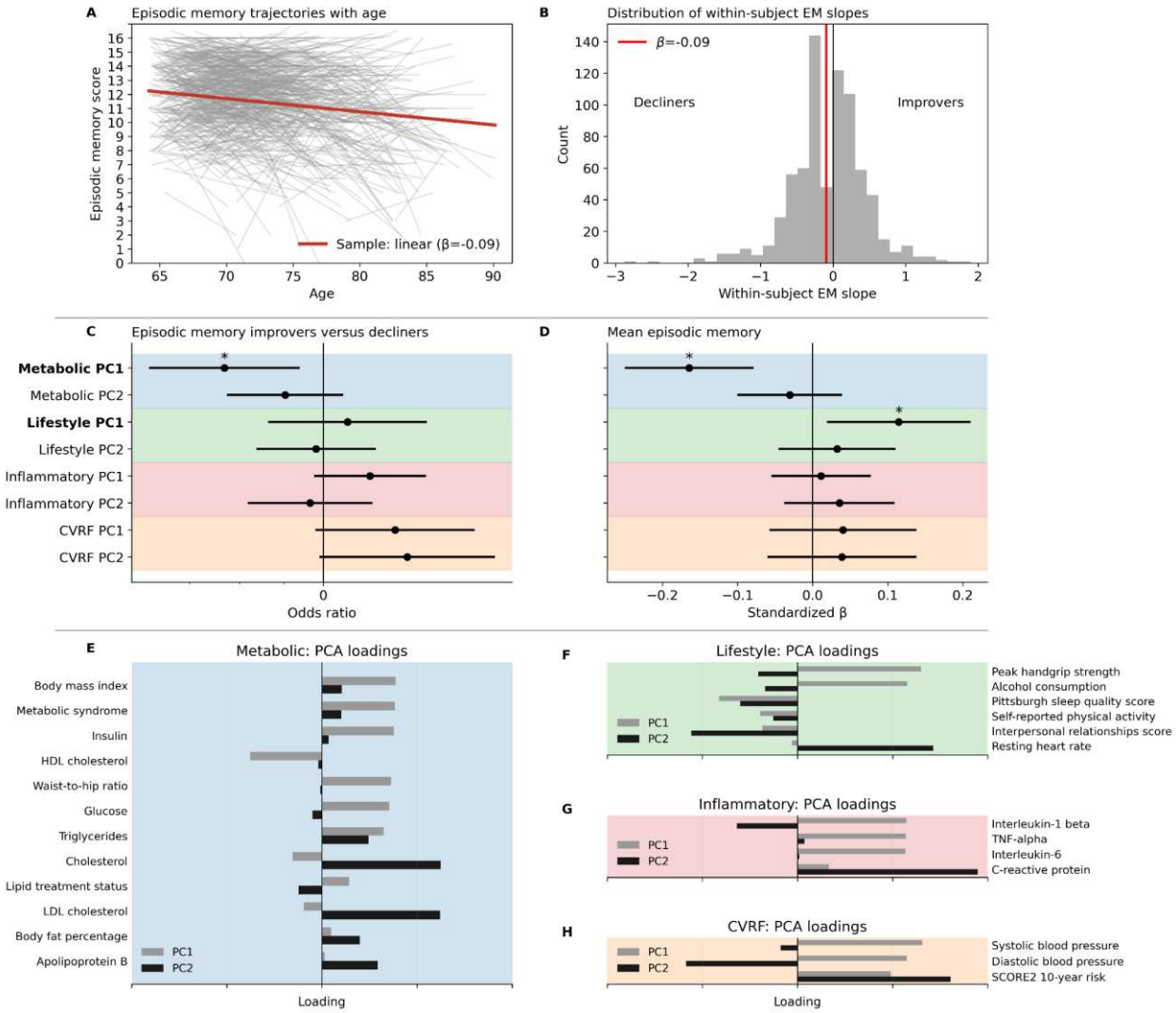



**Figure 4. Episodic memory trajectories, individual slopes, predictor associations, and domain-level PCA structure. A.** Individual episodic memory (EM) trajectories plotted against age (grey lines), overlaid with the sample-level linear fit (red). **B.** Distribution of

within-subject EM slopes derived from ordinary least squares, with vertical lines marking zero change (black) and the sample-average slope (red). **C.** Forest plot of odds ratios (log scale) for EM improvers versus decliners (negative slope). **D.** Forest plot of standardized β coefficients for mean EM. Horizontal bars indicate 95% confidence intervals; asterisks denote *pFDR* < 0.05. Predictors are grouped by domain (Metabolic, Lifestyle, Inflammatory, CVRF). **E–H.** Principal component analysis (PCA) loadings for each domain, showing variable contributions to PC1 and PC2. The proportion of variance explained by each principal component is reported in Supplementary Table 5.

## 6. Hippocampal myelination and episodic memory trajectory

To investigate neural correlates of episodic memory trajectories, we analyzed hippocampal microstructural markers in the neuroimaging subsample (N = 301). Higher hippocampal MTsat, indicative of myelin content, was associated with higher odds of being classified as a memory maintainer/improver (OR = 1.44–1.45, pFDR < 0.01), with a positive MTsat × APOE ε4 interaction indicating a stronger association in ε4 carriers (OR = 2.00, pFDR < 0.05). Consistent with these findings, higher hippocampal MTsat was also associated with a less negative episodic memory slope (β = 0.07, pFDR < 0.05), while APOE-ε4 carrier status modified this association (MTsat×APOE ε4 interaction: β = 0.17, pFDR < 0.01), indicating a stronger MTsat–slope relationship in ε4 carriers. Model-based predictions showed a comparatively small MTsat–memory slope association in non-carriers and a substantially stronger association in APOE ε4 carriers (Figure 5). These MTsat-memory associations persisted after additional adjustment for metabolic and lifestyle covariates, and neither metabolic nor lifestyle composite scores were associated with hippocampal MTsat, either as main effects or in interaction with APOE ε4.

Hippocampal volume showed a positive trend with episodic memory slope (β = 0.07, pFDR = 0.056) but did not reach significance, and associations with mean episodic memory were not significant for either hippocampal MTsat or volume. Subfield analyses indicated regional specificity - higher MTsat in the subiculum was associated with a more positive memory slope (β = 0.07, pFDR < 0.05), with weaker or absent associations in cornu ammonis (CA) 1-3, CA4 and dentate gyrus (DG). APOE ε4 further strengthened the MTsat–slope association in CA1–3 and the subiculum, whereas evidence for modification in CA4/DG was not significant.

Complementary analyses of white matter tracts within the hippocampal formation were not significant, indicating that the ε4 moderation observed for hippocampal MTsat did not generalize to these tracts.

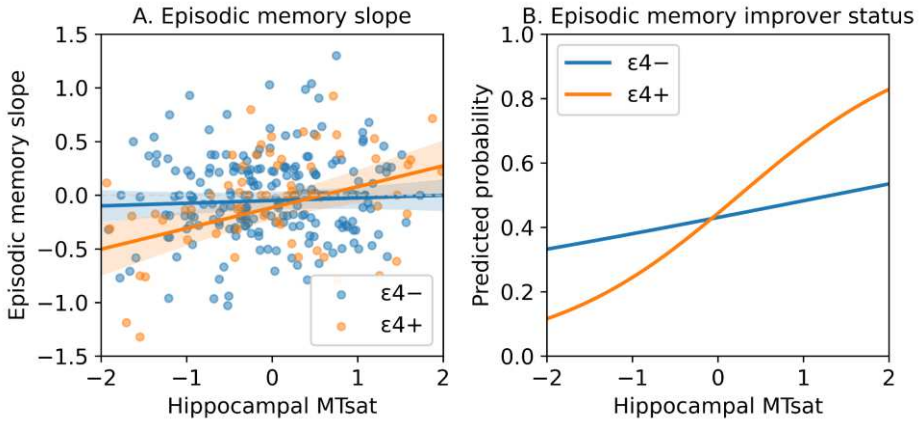



**Figure 5. APOE ε4 moderates the association between hippocampal myelin-sensitive MTsat and episodic memory slope. A.** Adjusted model predictions for hippocampal MTsat and episodic memory slope, separately for APOE ε4 carriers (orange) and non-carriers (blue). Higher slope values indicate more favorable memory trajectories over time. **B.** Adjusted predictions show the corresponding probability of belonging to the memory-improver group across hippocampal MTsat, stratified by APOE ε4 status. MTsat and episodic memory slope values are z-scored.

# Discussion

This population-based study examined how APOE alleles, cardiometabolic, vascular and inflammatory, and lifestyle factors relate to late-life episodic memory trajectories. Four principal findings emerged - APOE ε4 carrier status confirmed expected lipid-related metabolic differences, with associations varying by age; the APOE ε4 allele selectively predicted steeper age-related episodic memory decline; systemic metabolic and lifestyle profiles were associated with memory performance level and improver status; and hippocampal myelin content, was positively associated with episodic memory trajectory, with effects more pronounced in ε4 carriers.

Despite the well-established link between APOE ε4 and risk for Alzheimer's disease, its influence on domain-specific cognitive decline, its timing and its dependence on zygosity in the general population remain incompletely understood. The selective association of APOE ε4 with episodic memory change observed here aligns with meta-analytic evidence[11] and longitudinal data showing that memory decline is more robust than changes in executive function domains[10,12]. Population-based studies support this memory vulnerability, though modest broader associations across domains have also been reported in late-life cohorts[11,14,26]. Taken together, these findings support the view that APOE ε4 confers selective vulnerability in episodic memory rather than a broad multi-domain cognitive disadvantage.

APOE-ε4-related cognitive differences appear age-dependent, with associations in earlier adulthood remaining inconsistent but emerging more clearly from the late sixties onward[13,14,27,28]. Our findings indicate that ε4-related episodic memory vulnerability becomes apparent in the early seventies and progressively diverges with age. We found no evidence for sex moderation, in contrast to some prior reports[29,30], though power to detect higher-order interactions was limited.

A further unresolved question is whether APOE ε4-associated cognitive decline extends beyond homozygous carriers[10,12,14]. The association in our data was unchanged after exclusion of homozygotes, indicating that the effect is not driven by a small high-risk subgroup and is consistent with a contribution from heterozygous carriers, who represent nearly one quarter of the general population[31]. This may help reconcile prior inconsistencies, where null effects in heterozygotes have been reported[11,13,14], likely reflecting broader age ranges, shorter follow-up, or lower sensitivity of cognitive measures. We also did not find any associations between APOE ε2 and cognitive trajectories, consistent with prior reports[27,32].

Although APOE ε4 was associated with a systemic physiological profile broadly consistent with previous studies[33], particularly higher lipid-related metabolic markers, these associations were partly age-dependent, with several ε4-related metabolic differences attenuating at older ages. Inflammatory findings showed a different pattern: lower CRP levels and a negative APOE ε4 × age interaction for TNF-α pointed to a more favorable inflammatory-marker profile among ε4 carriers. Importantly, this set of systemic physiological markers (inflammatory, cardiometabolic, vascular) did not account for APOE ε4's association with episodic memory decline. Neither individual systemic markers nor their interactions with APOE ε4 explained the ε4 × age effect on episodic memory, in line with findings of Corley et al[26]. This suggests that the observed ε4-related decline was not explained by the measured peripheral physiological differences and may instead reflect partially distinct central nervous system mechanisms or systemic pathways not captured by the available markers. Patterns did emerge, however, when variables were captured jointly as domain-level composites: adverse metabolic burden driven primarily by higher adiposity- and lower lipid-related measures was associated with lower mean episodic memory and reduced odds of memory improvement, whereas a lifestyle composite reflecting better physical function, sleep quality, physical activity and cohort-specific alcohol-consumption patterns was associated with higher mean episodic memory. Critically, neither composite explained APOE ε4-related decline, arguing against a simple causal pathway in which genotype-related memory decline is mediated by systemic physiological burden. Instead, these findings suggest partially dissociable mechanisms, with APOE ε4 linked primarily to decline dynamics, and systemic health factors linked predominantly to memory level and broad resilience.

Because APOE ε4-related memory divergence was not captured by systemic measures, we asked whether it might be reflected in hippocampal microstructural variation, given proposed links between APOE-related lipid biology, myelin regulation and memory. Higher hippocampal MTsat was associated with less negative episodic memory trajectories, particularly among APOE ε4 carriers, whereas MTsat was not associated with mean memory performance. This dissociation suggests that hippocampal microstructural variation relates more closely to memory trajectory rather than to performance level. The pattern was more evident for MTsat than for hippocampal volume, which showed only a trend-level association with memory slope, supporting the view that myelin-sensitive markers capture subtler variation relevant to memory ageing than gross volumetric measures. Notably, APOE ε4 was not itself associated with hippocampal myelin content, indicating that the key finding reflects a stronger microstructure-trajectory relationship in genetically vulnerable individuals rather than a simple genotype difference in hippocampal signal. One potential mechanism is APOE ε4-related disruption of cholesterol transport in oligodendrocytes, which has been linked experimentally to abnormal cholesterol accumulation, reduced myelination and poorer memory[21]. Separately, APOE ε4-related vulnerability may also involve other early non-amyloid alterations in medial temporal microstructure, including blood–brain barrier dysfunction[34], though the present data do not address this mechanism directly.

A principal strength of this study is the integration of multi-decade systemic, physiological, and lifestyle data with longitudinal cognitive testing in a population-based framework, further extended by quantitative neuroimaging that allowed investigation of hippocampal myelination beyond conventional morphometric markers.

**Limitations**

Several limitations warrant consideration. Analyses addressing systemic, cognitive, and neuroimaging questions were conducted in distinct nested subsamples; findings should therefore be interpreted as complementary across biological levels rather than as directly comparable effect estimates. The grouping of systemic factors into metabolic, inflammatory, and cardiovascular risk (CVRF label) domains was used for analytical clarity, although these domains overlap biologically and metabolic and inflammatory factors may themselves contribute to cardiovascular risk. Brain MRI was acquired at a single late-life time point, precluding assessment of longitudinal microstructural change and limiting causal inference regarding temporal relationships between hippocampal myelin and memory trajectories. The neuroimaging subsample differed modestly from the broader cohorts in education and cardiovascular risk (Supplementary Table 1 and 2), and APOE ε4-related systemic differences were weaker in this smaller MRI sample (Supplementary Figure 4), which may be considered when interpreting MRI-specific estimates. Selective survival and continued participation may also have influenced the stronger MTsat–memory trajectory association observed among APOE ε4 carriers, as carriers with poorer health or cognitive trajectories may have been underrepresented in the longitudinal neuroimaging sample. Finally, episodic memory slopes were derived from a limited number of observations per participant; while complementary modelling approaches yielded consistent patterns, slope estimates remain sensitive to measurement variability.

**Conclusion**

This study advances a multi-layered account of episodic memory ageing, the most age-sensitive cognitive domain in this cohort. APOE ε4 carriers showed steeper episodic memory decline, alongside a mixed, age-dependent systemic physiological signature. Metabolic and lifestyle profiles related primarily to memory performance level and resilience classification rather than decline rate. Hippocampal myelin-sensitive MTsat emerged as a neurobiological correlate of memory trajectories, with effects most pronounced among ε4 carriers. Together, these findings challenge single-cascade mechanistic models and instead support the view that distinct genetic, systemic and microstructural processes shape complementary dimensions of late-life cognitive heterogeneity in ageing.

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**Conflict of interest statement**

The authors declare no competing interests.

**Code availability**

The underlying code for this study is available in the github repository and can be accessed via this link (https://github.com/mihaly-lren/apoe).

**Data availability**

Due to participant confidentiality and applicable Swiss data-protection regulations, the individual-level CoLaus|PsyCoLaus dataset is not publicly accessible. Researchers who satisfy the requirements for access to confidential data may request de-identified data from the CoLaus Datacenter at CHUV in Lausanne, Switzerland. Details on the application and collaboration process are provided at https://www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

**Author contributions**

Conceptualisation (BD, MG), study design and methodology (BD, MG, CR, AB), MRI data acquisition (BD, MG, AL, FK, CR), Data processing (BD, FK, AL), Statistical analysis (BD, MG), data visualization (MG), interpretation of the results (BD, MG, CR, MGP, AB, ZK, JV, PM), first draft of the manuscript (BD, MG). All authors discussed the results and contributed to the writing or revision of the manuscript.. Funding acquisition (BD, FK, AL).

# Methods

## Study design and participants

The four analytical samples were derived from the CoLaus | PsyCoLaus population-based cohort[24] and differed in inclusion criteria (Figure 6). They were hierarchically nested, with each nested subsample drawn from the preceding broader one. To assess potential selection effects, representativeness of each subsample relative to the genotyped parent cohort was evaluated using age- and sex-adjusted regression models at follow-up wave 2, in which, inclusion in a given subsample was modelled as the predictor; adjusted mean or proportion differences with 95% confidence intervals and standardized mean differences were reported for each variable.
The CoLaus | PsyCoLaus study, including the BrainLaus imaging study, was approved by the Institutional Ethics Committee of the University of Lausanne (CER-VD; project number PB_2018-00038 (239/09)). All participants provided written informed consent.

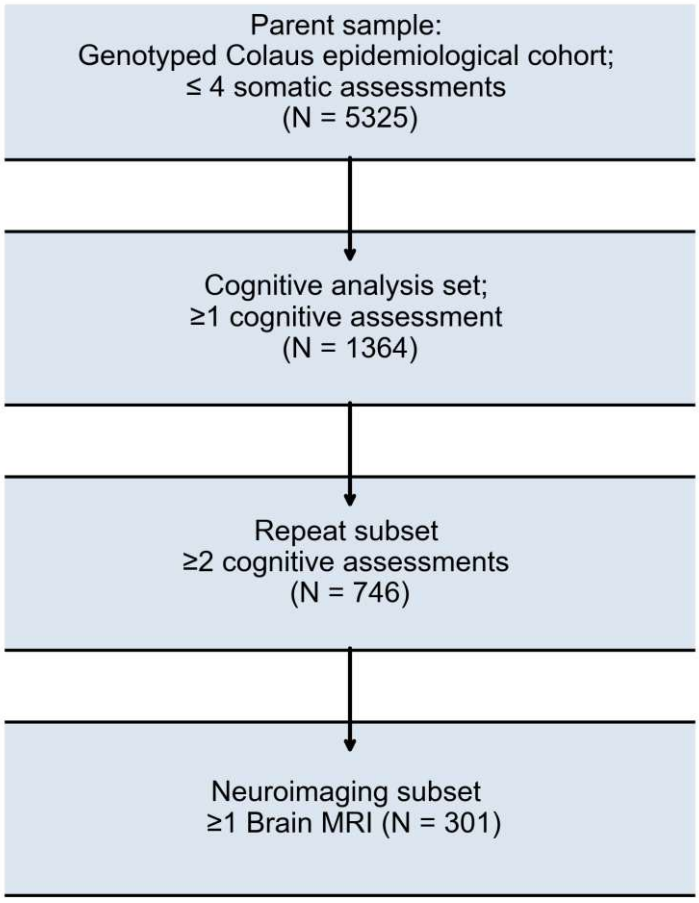



**Figure 6. Sample derivation and analytical subsamples.**
Flow diagram illustrating the derivation of analytical subsamples from the genotyped CoLaus epidemiological parent cohort based on predefined inclusion criteria (for example, ≥2 assessments), with corresponding sample sizes (N).

## Systemic physiological and lifestyle measures

Systemic physiological and lifestyle measures were obtained as part of the standard CoLaus | PsyCoLaus assessment protocol, with detailed descriptions of variable collection and data handling provided by Firmann et al[24]. These included metabolic, cardiovascular, inflammatory, and lifestyle-related variables derived from clinical examinations, blood samples, anthropometric measurements, medication records, and structured questionnaires. Certain variables were not available at each wave and were therefore analyzed at the wave at which they were available; wave-specific availability is detailed in Supplementary Table 6.

## Genotyping and APOE categorisation

Participants were genotyped using the BB2 customised Affymetrix Axiom Biobank array[24]. As described in Hodel et al., 2021, imputation was performed using reference data from the Haplotype Reference Consortium and the combined 1000 Genomes Phase 3 and UK10K panels. Standard quality control procedures were applied, excluding variants with low minor allele frequency (<1%), poor imputation quality (INFO < 0.8), or evidence of deviation from Hardy–Weinberg equilibrium ($P < 1 \times 10^{-17}$)[35]. The resulting dataset comprised approximately 9 million single nucleotide variants (SNVs).

APOE genotype was determined using two SNVs, rs429358 and rs7412, extracted from individual-level genotyping[36,37]. As genotype data were unphased, allele combinations were assigned without regard to chromosomal phase. Genotypes were defined by combining the two alleles, and participants were classified as APOE ε4 carriers (ε4/ε4, ε3/ε4, ε2/ε4) or non-carriers (ε2/ε2, ε2/ε3, ε3/ε3). In a complementary analysis, the APOE genotype was dichotomized as ε2 carrier/ε4 non-carrier (ε2+ε4−) versus all remaining participants. 74 participants were excluded due to invalid or missing genotyping data resulting in sample size 5325 individuals with APOE categorisation. The individuals' resulting genotypes were cross-checked and found identical with that reported in Trofimova et al., 2023[38].

## Cognitive measures

Cognitive performance was assessed within the CoLaus | PsyCoLaus study using a standardized neuropsychological battery[25] as part of the psychiatric evaluation protocol and within the BrainLaus Brain imaging study. Cognitive tests were grouped into domains for descriptive purposes, including episodic memory, processing speed, executive function, and global cognitive functioning; see detailed definitions and test descriptions provided in Supplementary Table 3. Episodic memory, the primary outcome of interest, was assessed using the 20 minutes delayed free recall from the Free and Cued Selective Reminding Test (FCSRT).

## Brain imaging: acquisition and processing

Brain MRI data were acquired on a single 3T whole-body system (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany) using a 64-channel head coil, following a multi-parameter mapping protocol described previously [39]. Quantitative maps of magnetization transfer saturation (MTsat) were computed from the raw MR image using the hMRI toolbox[40,41], using dedicated signal equations[42]. MTsat data are markers of the myelination of brain tissue[43–45].

## Brain imaging: regional feature extraction

Regional measures were extracted using a multi-atlas parcellation approach based on maximum probability tissue labels from the MICCAI 2012 Multi-Atlas Labeling challenge (https://my.vanderbilt.edu/masi/about-us/resources-data), with labels as described in Yan et al., 2022[46] . Atlas labels were non-linearly registered to individual subject space using the geodesic shooting algorithm implemented in SPM12[47]. For each region, median MTsat values of quantitative MRI parameters and regional tissue volumes were computed. White matter tracts were delineated using the TractSeg framework[48], and tract-level median MTsat values were extracted following the procedure described in Trofimova et al., 2023[38].

Neuroimaging analyses focused on hippocampal regions, including whole hippocampus and subfields (CA1–3, CA4/dentate gyrus, and subiculum), using MTsat and volume measures. Complementary analyses were conducted for three white matter tracts within the hippocampal formation and related pathways (fornix, cingulate and uncinate fascicle), using tract-level quantitative MRI metrics, as per Trofimova et al., 2023.

## Statistical analysis

### a. APOE and systemic health profile

Statistical analyses were first conducted within the parent genotyped cohort of 5,325 participants with available information on age, sex, educational level, and APOE ε4 carrier status. For analytical purposes, systemic markers were grouped into metabolic, vascular and inflammatory domains, recognising that these categories are not biologically mutually exclusive. For each metabolic, cardiovascular (CVRF) and inflammatory marker, we fitted longitudinal linear mixed-effects models using age as the time axis and participant-specific random effects to account for repeated measurements across up to four follow-up waves. Models included fixed effects for age, sex, educational level, APOE ε4 carrier status, and interaction terms between APOE ε4 status and age and sex. Continuous outcomes were standardized prior to analysis to facilitate comparison of effect sizes across biomarkers. Random-intercept and random age-slope models were fitted, binary outcomes (e.g. metabolic syndrome) were analyzed using generalized estimating equations with a binomial link and exchangeable correlation structure. Variables were median imputed, with participant-level coverage exceeding 97% for all biomarkers except HbA1c (70%>).

For each outcome variable **Y**, models were specified as:

$$\mathbf{Y = Age + Sex + Education + APOE\varepsilon4 + (Age \times APOE\varepsilon4) + (Sex \times APOE\varepsilon4) + (1+Age|Participant),}$$

with age used as the time axis and participant-specific random intercepts and age slopes accounting for repeated measurements. FDR correction was applied separately across all tested factors within each effect family: age effects, APOE ε4 main effects, and APOE ε4 × age interactions.

The same above analysis was repeated for the different subsamples to assess consistency of results and selection bias (Supplementary Figures 2-7). Identical analyses were carried out for

APOE ε2 carriers (ε2+/ε4− vs. non-carriers), results shown in Supplementary Figure 1, for the genotyped sample.

### **b.** Age and APOE in cognition

Statistical analyses were conducted in participants with available cognitive data, age, sex, education and APOE genotype. For each cognitive outcome, we fitted longitudinal linear mixed-effects models with age as the time axis and participant-specific random effects to account for repeated measurements. Models included fixed effects for age, sex, education, time gap between cognitive measurements, APOE ε4 carrier status and an age×APOE ε4 interaction and random intercept and slope. Analogous models were fitted for APOE ε2. Cognitive outcomes were standardized to enable comparison of effect sizes across tests.

For each cognitive outcome, longitudinal models were specified as:

**Y = Age + Sex + Time gap + Education + APOEε4 + (Age×APOEε4) + (Sex×APOEε4) + (1+Age | Participant),**

where *Y* denotes the standardized cognitive outcome. Age × sex and age × education interaction terms were evaluated in secondary models to assess whether age-related cognitive change differed by sex or educational attainment.

In a sensitivity analysis, the age time axis was decomposed into age at the first cognitive assessment and time elapsed since that assessment to distinguish between-person age differences from within-person cognitive change.

False discovery rate (FDR) correction was applied across cognitive outcomes. Effect estimates are reported as β coefficients with 95% confidence intervals, shown separately for main APOE effects (intercept differences) and age×APOE interaction effects (slope differences).

Outcomes lacking sufficient repeat observations were analyzed cross-sectionally using linear regression with the same fixed-effect covariates. Cross-sectional analyses showed similar age associations, supporting the robustness of the age-related pattern obtained from the longitudinal analysis (Supplementary Figure 9).

In exploratory analyses, we examined whether systemic metabolic and inflammatory measures moderated age-related trajectories of episodic memory (EM; FCSRT delayed free recall). Longitudinal mixed-effects models were extended with main effects and interaction terms (Age×Factor and Age×APOE×Factor). Continuous moderators were standardized prior to analysis. Models retained the same covariates and random-effects structure as the primary analyses. Individual factors such as physical activity did not significantly moderate age-related decline in episodic memory after correction for multiple testing, but physical activity effect estimates suggested a trend towards attenuated decline with higher physical activity levels (Supplementary Figure 10).

### **c.** Episodic memory (within subject slopes and group analysis)

Participants with ≥2 episodic memory (EM) assessments were included. For each participant, a within-subject slope was estimated using ordinary least squares regression of EM on age. Trajectories were classified as **Decliners** (slope < 0) or **Improvers** (slope ≥ 0).

We tested whether APOE ε4 carrier status differed between trajectory groups using multivariable logistic regression, adjusting for age at first memory assessment, time-gap between assessments, sex, and education. Carrier status (ε4+ vs all others; complementary analysis: ε2+ε4- vs all others) was modelled as the binary outcome, with the trajectory group entered as the predictor and covariates included as additional regressors. Group differences were evaluated using a Wald $\chi^2$ test.

### **d.** Systemic health and episodic memory

To test whether episodic memory performance and trajectories were associated with systemic health, we summarized correlated measures within lifestyle, cardiovascular risk, metabolic and inflammatory domains using principal component analysis (PCA). Variables included in each domain are listed in Supplementary Table 6. PCA was used to derive orthogonal domain-level summary scores, reducing dimensionality, predictor redundancy and potential multicollinearity in downstream regression models. For each domain, historical measures available up to the first memory assessment were aggregated at the participant level using within-person averages. Variables were z-standardized before PCA, and the first two principal components were retained. Component-wise and cumulative explained variance for retained components are reported in Supplementary Table 5. Participant-level component scores were then extracted and z-standardized before inclusion in regression models, such that estimates reflect associations per 1-standard deviation higher component score.

**Episodic memory performance:** Average episodic memory performance was defined as the within-person mean across repeated episodic memory assessments and modelled as a continuous outcome using multivariable linear regression.

**Episodic memory slopes:** Episodic memory change was modelled as a continuous outcome using individual memory slopes. Slopes were estimated using participant-specific ordinary least squares regressions of episodic memory on age.

**Episodic memory improvers versus decliners:** We tested whether systemic health differentiated episodic memory improvers (slope ≥ 0) from decliners. Improver versus decliner status was modelled as a binary outcome using multivariable logistic regression.

For each outcome (performance, slope, improver status), the same core model included the first two principal component scores from each systemic health domain, APOE ε4 carrier status and covariates: age, sex, education and the time interval between memory assessments:

> **Outcome = Lifestyle PC1 + Lifestyle PC2 + Cardiovascular PC1 + Cardiovascular PC2 + Metabolic PC1 + Metabolic PC2 + Inflammatory PC1 + Inflammatory PC2 + APOEε4 + covariates.**

To assess genetic moderation, subsequent models included interaction terms between APOE ε4 carrier status and the domain components associated with the corresponding outcome in the core

model. Analogous models were fitted for APOE ε2 carrier status, defined as ε2+ε4− versus all others. For continuous outcome models, outcomes and continuous predictors were z-standardized, and heteroskedasticity-robust standard errors were used. Logistic regression effects are reported as odds ratios with 95% confidence intervals, and linear regression effects as standardized regression coefficients with 95% confidence intervals.

### **e.** Mediation analysis

To assess whether systemic health profiles statistically accounted for APOE ε4 associations with episodic memory change, we performed exploratory single-mediator analyses using the domain-level principal component scores described above. The first two components from each domain were tested separately as mediators. Individual systemic markers and lifestyle variables were examined in complementary exploratory analyses. For each mediator, we estimated the APOE ε4–mediator association, the mediator–episodic-memory slope association adjusted for APOE ε4, and the total, direct and indirect effects. Indirect effects were quantified as the product of paths (a × b), with 95% confidence intervals estimated using 10,000 bootstrap resamples. Models included age in the mediator model and sex, education and the interval between episodic-memory assessments in the outcome model; analyses used participants with complete data for the mediator tested.

### **f.** Neuroimaging and memory outcomes

We tested whether hippocampal myelin content and volume were associated with longitudinal episodic memory outcomes in the imaging subset (N = 301). Hippocampal MTsat and hippocampal volume were entered separately as predictors in regression models with three memory outcomes: within-subject episodic memory slope estimated by OLS, mean episodic memory across repeated measures, and improver status (positive vs negative slope). All continuous predictors were standardized. Linear models were adjusted for covariates: total intracranial volume (TIV), age, sex, education level, and the time interval between repeated cognitive assessments (time gap). For improver status, we used the same covariate set in logistic regression and reported odds ratios per SD increase.

To assess whether health profiles explained the MTsat–memory association, we additionally adjusted models for metabolic and lifestyle domain scores (PC1), entered as main effects. To test genetic moderation, we included APOE ε4 carrier status and an interaction term with each brain marker. Example model:

**Memory slope = Hippocampal MTsat + APOEε4 + (Hippocampal MTsat×APOEε4) + Metabolic + Lifestyle + covariates**

To localise hippocampal effects, we repeated the MTsat and volume models for three bilateral hippocampal subfields (CA1–3, CA4/DG, subiculum), computed as the sum of left and right measures.

To test whether associations extended to hippocampal-connected white matter, we repeated separate models in three tracts (fornix, uncinate fasciculus, cingulum), for measures volume and MTsat, using the same outcomes, covariates, and APOE interaction terms, for example:

**Memory slope = Cingulum MTsat + APOEε4 + (Fornix MTsat×APOEε4) + covariates**

As a complementary analysis, we tested whether lifestyle, metabolic and cardiovascular profiles explained hippocampal MTsat. We entered domain components (PC1 and PC2), APOE ε4 status and covariates simultaneously and used LASSO regularisation to identify predictors with non-zero coefficients.

**Hippocampal MTsat = Lifestyle (PC1, PC2) + Metabolic (PC1, PC2) + CVRF (PC1, PC2) + APOEε4 + covariates**

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