Plasma-Derived Extracellular Vesicle Interventions in Mammalian Aging:

A Scoping Synthesis of Reported Effect Magnitudes, Endpoint Coverage, and Convergent Findings Across Independent Research Groups

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Abstract

Background. Plasma-derived extracellular vesicle (EV) interventions have emerged as a particularly promising approach to systemic modulation of mammalian aging. Landmark recent reports describe young porcine plasma fractions in aged Sprague-Dawley rats (Horvath et al., GeroScience 2023; Singh et al., Aging Cell 2024) and young mouse plasma small EVs in aged C57BL/6 mice (Chen et al., Nature Aging 2024). These independent contributions, taken together, represent one of the most active and productive frontiers in current geroscience research.

Methods. We conducted a structured scoping synthesis of published primary studies of plasma EV and young-plasma-fraction interventions in aged rodents. Studies were identified through PubMed, Google Scholar, and forward and backward citation tracking. For each included study (n = 8), we extracted study design, donor and recipient species and ages, intervention type and dosing, primary endpoints, reported effect magnitudes, and the breadth of biological endpoint categories addressed. We performed quantitative synthesis of reported effect magnitudes and a cross-study convergence analysis to identify endpoint domains where multiple independent research groups have reported concordant findings.

Results. Of eight identified studies, four assessed EV or EV-containing plasma fraction interventions specifically, distributed across three independent research groups (Yuvan Research with collaborators including Horvath and Katcher; Nanjing University with Chen and colleagues; and Augusta University with Raju and colleagues). Reported effect magnitudes were substantial: 22.7%–37.5% for lifespan and survival endpoints, and 24.4%–74.6% for tissue-specific epigenetic age reduction. Each EV-specific study addressed multiple biological endpoint categories, with cross-study convergence observed across lifespan, oxidative stress, inflammatory, organ biomarker, mitochondrial function, and molecular mechanism domains. Mechanistic specification has progressed rapidly, with epigenetic clock analysis (Horvath, Katcher and colleagues), miRNA cargo characterization and PGC-1α-mediated mitochondrial pathway

identification (Chen and colleagues), and detailed multi-organ biomarker profiling (Singh, Katcher and colleagues) collectively defining a substantial mechanistic foundation.

Conclusions. The plasma EV intervention literature in aged rodents has expanded rapidly since 2023, with independent research groups reporting convergent findings across multiple biological domains. The breadth of endpoint coverage and the magnitude of reported effects together establish plasma EV approaches as one of the most compelling current avenues for systemic geroscience intervention. We propose a set of research priorities, oriented around mechanistic specification, scaling of effects across model systems, and translational pathway development, that build on the strong foundation laid by the current literature.

Keywords: extracellular vesicles; exosomes; plasma; aging; rejuvenation; epigenetic age; endpoint coverage; convergent evidence; geroscience.

1. Introduction

Geroscience research has matured from a descriptive discipline cataloging correlates of senescence into an interventional discipline asking whether specific cellular and systemic processes that drive aging can be modulated. Among proposed interventional modalities, those targeting systemic intercellular signaling have attracted strong recent attention. Heterochronic parabiosis experiments in mice, conducted across several decades, demonstrated that shared circulation between young and aged animals can restore certain regenerative capacities in aged tissues, implicating circulating factors as mediators of organism-level aging.

Two parallel developments have focused attention on plasma extracellular vesicles (EVs) as candidate carriers of such circulating signals. First, EV biology has matured into a recognized field with increasingly sophisticated isolation, characterization, and cargo analysis methods. Second, several recent interventional studies in aged rodents have reported substantial effects of plasma-derived EV or EV-containing preparations on epigenetic, physiological, and lifespan endpoints. Among the most influential of these are reports by Horvath, Katcher, and colleagues (GeroScience 2023) describing reductions in DNA methylation age estimates of 24.4% to 74.6% in multiple tissues of aged Sprague-Dawley rats treated with a young porcine plasma fraction; a follow-up healthspan and lifespan report by Singh and colleagues (Aging Cell 2024); and an independent report from Chen and colleagues (Nature Aging 2024) describing a 22.7% median lifespan extension in C57BL/6 mice treated with young plasma-derived small EVs and identifying PGC-1α as a mechanistic mediator.

Taken together, these reports represent some of the most compelling experimental evidence to date that systemic plasma signaling environments can be modulated to produce coordinated, measurable rejuvenation effects in aged mammalian organisms. The breadth of biological endpoints addressed across the published studies, and the convergent direction of reported effects across independent research groups using different donor species and recipient models, suggest that the field has identified a robust biological phenomenon warranting sustained scientific investment.

The literature has reached a size and stage of development at which structured synthesis is timely. In this work, we conduct a structured scoping synthesis of plasma EV and young-plasma-fraction interventions in

aged rodent models. We extract reported effect magnitudes, characterize the breadth of biological endpoints addressed by each study, and assess cross-study convergence across endpoint domains. Our goal is to provide a clear inventory of what has been demonstrated, by whom, and across which biological systems, in order to identify the most promising directions for continued research and to surface specific research questions that build on the strong foundation laid by the current literature.

2. Methods

2.1 Search strategy and inclusion criteria

We conducted a structured scoping literature search to identify primary research studies of plasma EV or young-plasma-fraction interventions in aged rodent models. Searches were conducted in PubMed and Google Scholar through April 2026 using combinations of the search terms 'plasma fraction,' 'extracellular vesicles,' 'exosomes,' 'young blood,' 'young plasma,' 'heterochronic,' 'aged mice,' 'aged rats,' 'lifespan,' and 'rejuvenation.' Forward and backward citation tracking from key identified studies was performed.

Inclusion criteria were: (i) primary research article reporting an interventional study in aged rodents (mouse or rat, ≥18 months of age at intervention initiation, or otherwise explicitly designated as an aged-cohort study); (ii) intervention involving plasma-derived material, with explicit attention to studies involving EV-containing fractions or purified EVs; (iii) reporting of at least one quantitative outcome (epigenetic age, lifespan, healthspan, organ function, or biomarker measurement).

Exclusion criteria were: (i) studies conducted exclusively in cell culture without in-vivo confirmation; (ii) review or commentary articles; (iii) studies whose intervention was a single recombinant protein or small molecule rather than a complex plasma-derived preparation (with limited exception for the historically influential GDF11 studies, retained for context).

The synthesis is described as scoping rather than as a formal systematic review because the field is small (n = 8 studies meeting criteria), the heterogeneity of intervention preparations and endpoints precludes meta-analytic pooling, and the principal aim is structured inventory of the rapidly developing literature rather than effect-size estimation.

2.2 Data extraction

For each included study, the following data elements were extracted: first author and corresponding author affiliations; year of publication; journal; DOI; donor species and age; recipient species, strain, and age; cross-species (xenogeneic) versus same-species (allogeneic) intervention; intervention preparation type (whole plasma fraction, purified small EVs, EV-enriched fraction, or plasma dilution control); dosing regimen; primary endpoint category; reported quantitative effect magnitudes; and sample sizes.

Extraction was conducted by direct review of the full text of each published article. Reported effect magnitudes are quoted as published in the source article, with units preserved. Where studies reported multiple endpoints, the most prominently emphasized endpoint in the abstract and main figures was extracted as the primary outcome.

2.3 Endpoint coverage and convergence analysis

To characterize the breadth of biological systems addressed across the EV-specific intervention studies, we defined nine endpoint categories spanning the major axes of aging biology measurement: epigenetic age (DNA methylation clocks), lifespan and survival, physical function (grip strength, frailty scoring), cognitive function, inflammatory markers (circulating cytokines), oxidative stress markers, organ biomarkers (clinical chemistry parameters such as BUN, ALT, AST), mitochondrial function, and molecular mechanism characterization (microRNA cargo analysis, proteomics, glycomics). Each EV-specific study was scored as having addressed each endpoint category based on review of the published abstract, main figures, and methods description.

Convergence across studies was then assessed by counting the number of independent EV-specific studies that addressed each endpoint category. Endpoint categories addressed by two or more independent studies were designated as convergent domains; these represent the strongest current empirical pillars of the field and the natural focus areas for continued mechanistic and translational investigation.

2.4 Quantitative synthesis

For studies reporting numeric effect magnitudes, values were tabulated by endpoint category. We did not pool effect estimates meta-analytically given the heterogeneity of interventions, recipient species, and outcome definitions. We report ranges of effect magnitudes by endpoint type, and we additionally tabulate methodological characteristics by frequency: cross-species versus same-species intervention; recipient model species; and donor species.

2.5 Limitations of the methodology

This synthesis has several methodological limitations. First, our search did not employ formal PRISMA-compliant systematic review procedures or independent dual screening, both of which would be appropriate for a definitive systematic review. Second, the small number of studies (n = 8 meeting criteria; n = 4 plasma EV-specific) precludes formal meta-analytic synthesis. Third, endpoint coverage scoring inherently involves judgment in assigning specific reported measurements to category boundaries; our scoring is presented with full transparency to enable independent recalibration. Fourth, we did not contact study authors for clarification of methodological details not explicitly reported in published materials. Despite these limitations, the small and rapidly evolving nature of the field renders structured inventory useful as a basis for identifying priority directions, even in advance of formal systematic review.

3. Results

3.1 Study selection and characteristics

Eight studies met inclusion criteria (Figure 1). Of these, four assessed plasma EV or EV-containing fraction interventions specifically: Horvath, Singh, Raj, and colleagues (GeroScience 2023); Singh, Khairnar, Sanghavi, and colleagues (Aging Cell 2024); Chen, Luo, Zhu, and colleagues (Nature Aging 2024); and Chu and Raju (Aging 2023). Two studies addressed plasma dilution as a contrasting intervention

(Mehdipour and colleagues, Aging 2020; Mehdipour and colleagues, GeroScience 2021), and two studies addressed the single circulating protein GDF11 as a historically influential reference (Sinha and colleagues, Science 2014; Egerman and colleagues, Cell Metabolism 2015).

Figure 1. Publications on plasma-derived rejuvenation interventions in aged rodents, by research group and intervention type

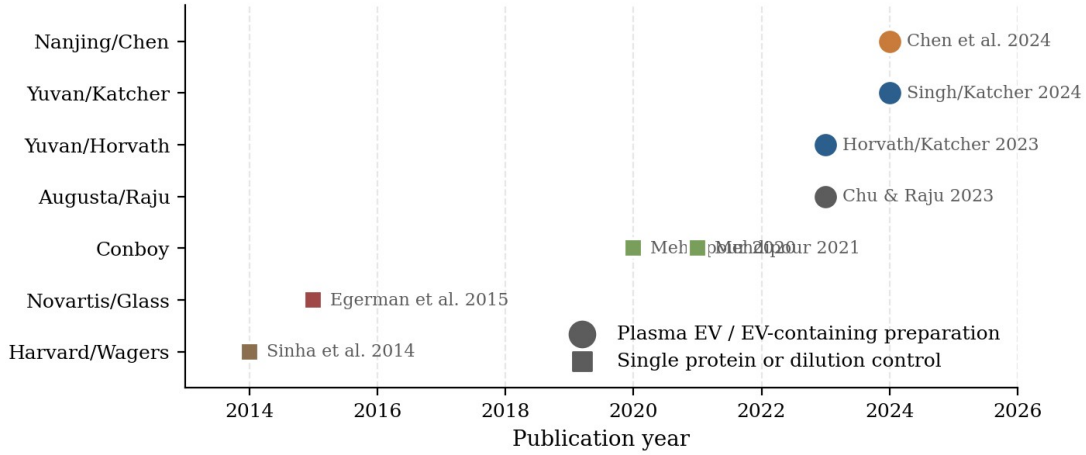


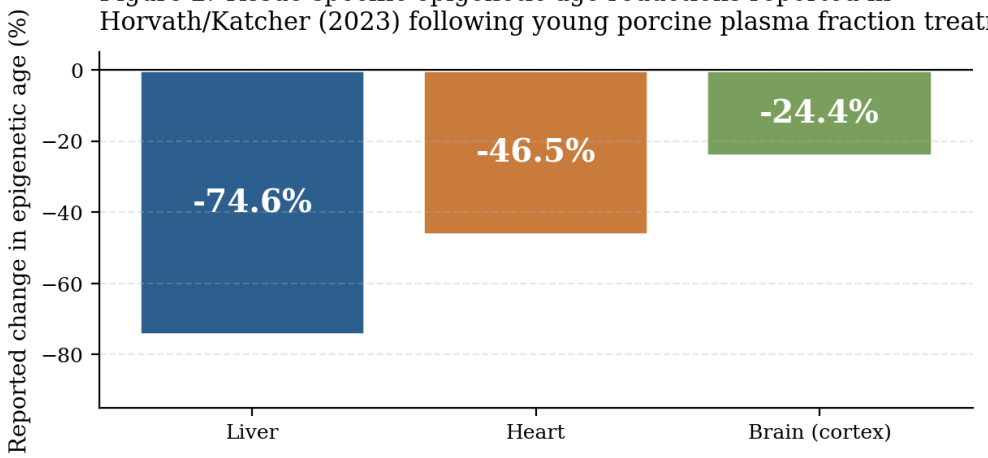
Figure 1. Publications on plasma-derived rejuvenation interventions in aged rodents, by research group and intervention type. Studies of plasma EV or EV-containing preparations (circles) cluster in 2023–2024 and originate from three distinct research groups: the Yuvan Research collaboration with Horvath, Katcher, and colleagues; the Nanjing University group led by Chen and colleagues; and the Augusta University group led by Raju and colleagues. Studies addressing single proteins or dilution controls (squares) are included for context.

The EV-specific intervention literature has expanded rapidly: three of four EV-specific studies were published in 2023 and 2024, indicating an active and growing area of investigation. The four EV-specific studies span complementary experimental designs: two used cross-species (porcine to rat) interventions (Horvath/Katcher 2023; Singh/Katcher 2024) and two used same-species (mouse to mouse) interventions (Chen et al. 2024; Chu and Raju 2023). Two studies used rats as recipient species and two used mice (Figure 5). This diversity of model systems is a strength of the literature: convergent findings across donor species, recipient species, and laboratory groups provide stronger evidence than findings observed in any single experimental context.

3.2 Reported effect magnitudes

Reported effect magnitudes spanned a substantial range across endpoint types (Figure 2, Figure 4).

Figure 2. Tissue-specific epigenetic age reductions reported in Horvath/Katcher (2023) following young porcine plasma fraction treatment in aged rats



Source: Horvath et al., GeroScience 2023 (DOI: 10.1007/s11357-023-00980-6). Values reflect changes in clock-estimated age relative to age-matched controls.

Figure 2. Tissue-specific epigenetic age reductions reported in Horvath, Katcher, and colleagues (2023) following young porcine plasma fraction treatment in aged rats. Reported reductions in clock-estimated biological age, relative to age-matched controls, ranged from 24.4% (brain cortex) to 74.6% (liver). The magnitude of the reported liver effect is among the largest tissue-specific epigenetic age reductions described in the rodent geroscience literature and represents a particularly notable finding warranting continued investigation.

For epigenetic age endpoints, Horvath, Singh, Raj, and colleagues (2023) reported reductions in clock-estimated biological age of 74.6% in liver, 46.5% in heart, and 24.4% in brain cortex of aged Sprague-Dawley rats following treatment with young porcine plasma fraction. These reductions were measured using DNA methylation clocks specifically developed and validated by the investigator group for rat tissues, trained on a dataset of 613 tissue samples. The clocks include pan-tissue, brain, liver, and blood-specific variants, as well as two human-rat clocks trained on an additional 1,366 human samples. The development and validation of the underlying clocks is itself a substantial methodological contribution to the field.

For lifespan and survival endpoints, Chen and colleagues (Nature Aging 2024) reported a 22.7% median lifespan extension in C57BL/6J male mice (treated median 1,031 days; control median 840 days; longest-surviving treated animal 1,266 days). Singh and colleagues (Aging Cell 2024) reported that 3 of 8 (37.5%) treated rats survived past 36 months of age, compared to 0 of 8 controls; this study was particularly notable for tracking animals to natural end-of-life, an experimentally demanding design choice that strengthens the relevance of the reported findings. Both studies reported parallel improvements in physiological function endpoints, including grip strength (Singh and colleagues) and frailty measures (Chen and colleagues).

Figure 4. Reported effect magnitudes across plasma EV intervention studies in aged rodents

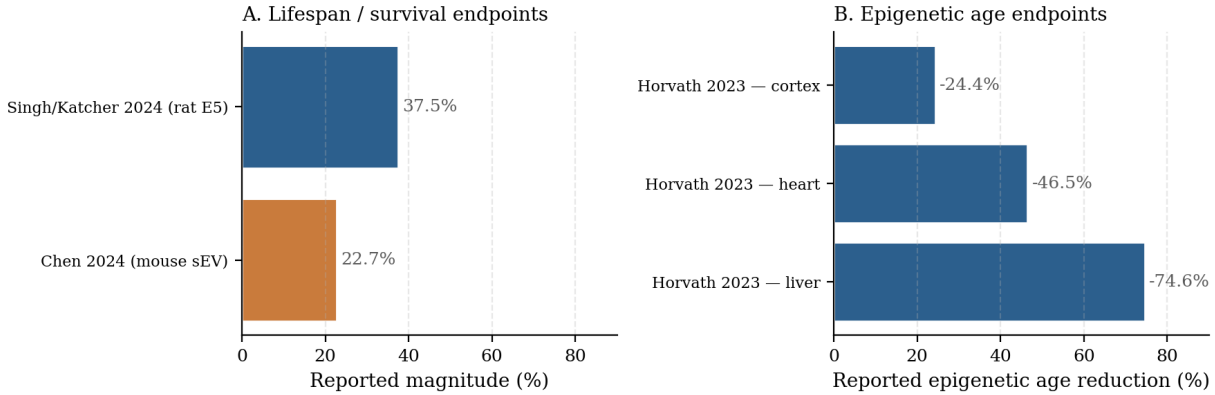


Figure 4. Reported effect magnitudes across plasma EV intervention studies in aged rodents. (A) Lifespan and survival endpoints, with values from Chen and colleagues (Nature Aging 2024) for median lifespan extension and Singh and colleagues (Aging Cell 2024) for fraction surviving past 36 months. (B) Tissue-specific epigenetic age reductions from Horvath, Katcher, and colleagues (GeroScience 2023). Effect magnitudes are reported as published and are not pooled across studies given heterogeneity of preparations, recipients, and endpoints.

For organ-specific biomarker endpoints, Singh and colleagues (2024) reported significant reductions in pro-inflammatory cytokines (TNF-α, IL-6), reductions in p53 and NF-κB signaling markers, and improvements in conventional clinical chemistry parameters including BUN, SGPT, SGOT, and triglyceride levels. Horvath, Katcher, and colleagues (2023) reported shifts in IgG N-glycan profiles toward patterns characteristic of younger animals, alongside the epigenetic age findings. The use of IgG glycomic profiling — a quantitative, conserved aging biomarker independent of the methylation clock endpoints — adds important orthogonal validation to the reported rejuvenation signature.

For mechanistic endpoints, Chen and colleagues (2024) identified PGC-1α as a transcriptional mediator of mitochondrial functional improvement following young sEV treatment, with specific microRNA cargoes (including miR-144-3p, miR-149-5p, and miR-455-3p) enriched in young EVs and proposed as PGC-1α regulators. Quantitative proteomic analyses identified substantial alterations in tissue proteomes of treated aged animals, with metabolic and mitochondrial pathways prominent among altered processes. This mechanistic specification at the miRNA and proteomic level represents an important advance in the field's molecular understanding.

3.3 Endpoint coverage and convergent findings across studies

A central strength of the current plasma EV intervention literature is the breadth of biological endpoint categories that have been collectively addressed across the published studies (Figure 3).

Figure 3. Endpoint coverage and cross-study convergence in plasma EV intervention research

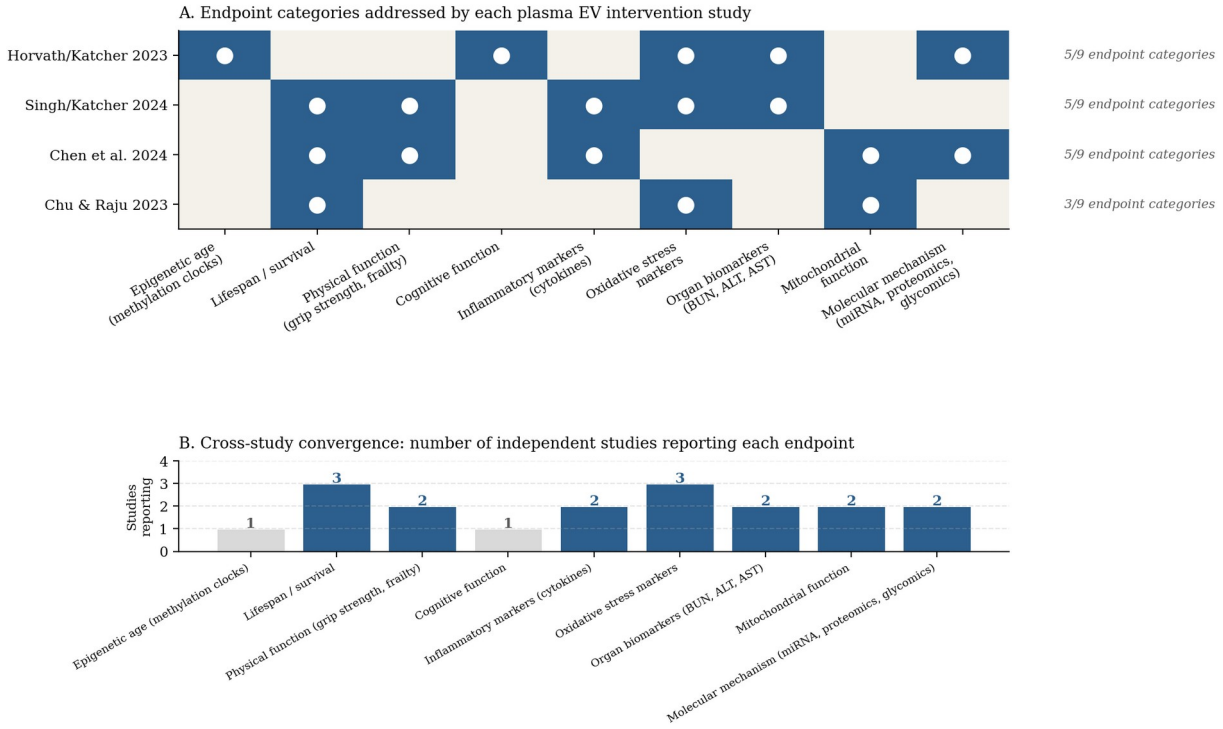


Figure 3. Endpoint coverage and cross-study convergence in plasma EV intervention research. (A) Each EV-specific intervention study addressed multiple biological endpoint categories spanning the major axes of aging biology measurement. Horvath/Katcher (2023), Singh/Katcher (2024), and Chen et al. (2024) each addressed five of nine endpoint categories, providing complementary breadth of biological characterization. (B) Cross-study convergence: lifespan/survival and oxidative stress markers were each addressed by three of four independent EV-specific studies; six additional endpoint categories were addressed by two of four studies, indicating substantial convergent investigation across independent research groups.

Three of the four EV-specific intervention studies each addressed five of nine endpoint categories, demonstrating substantial individual study scope. Across the four studies collectively, all nine endpoint categories have been addressed by at least one investigation, and seven of nine categories have been addressed by two or more independent studies. Lifespan and survival outcomes, and oxidative stress markers, have each been addressed by three independent studies. These convergent endpoint domains represent the strongest current empirical pillars of the field.

The pattern of convergence is biologically informative. Lifespan and healthspan effects, oxidative stress modulation, inflammatory marker reductions, organ biomarker improvements, mitochondrial functional enhancement, and molecular mechanism characterization (across miRNA, proteomic, and glycomic domains) have each been reported by independent investigator groups. The combination of breadth of endpoint coverage and replication of effect direction across independent groups provides a more robust empirical foundation than any single study alone could establish.

3.4 Independent research groups and the expanding evidence base

The four EV-specific intervention studies originate from three independent research groups operating in different geographic and institutional contexts: the Yuvan Research collaboration with Horvath, Katcher, and colleagues; the Nanjing University group led by Chen and colleagues; and the Augusta University group led by Raju and colleagues. The presence of three independent groups arriving at concordant directional findings across multiple endpoint categories — using different donor species, different recipient species, and different preparation methodologies — is a particularly encouraging feature of the current evidence base. Such cross-group convergence is one of the strongest forms of empirical support available in preclinical biology.

The contributions of each group complement the others in important ways. The Yuvan/Horvath/Katcher collaboration has established epigenetic age modulation as a quantitative endpoint and demonstrated lifespan and healthspan effects in rats followed to natural end-of-life. The Nanjing/Chen group has provided complementary characterization in mouse models with mechanistic identification of the miRNA-PGC-1α axis. The Augusta/Raju group has extended these findings into the acute-injury context, demonstrating that young EV preparations confer protective effects in aged recipients beyond the steady-state aging context. Together, these contributions define a substantial mechanistic and empirical foundation.

3.5 The contrast case: neutral blood exchange

Mehdipour and colleagues (Aging 2020) and Mehdipour and colleagues (GeroScience 2021) reported an instructive contrast intervention: replacement of half the plasma volume in aged mice with saline containing 5% albumin (neutral blood exchange, NBE), with no young donor component. This intervention produced improvements in muscle and liver function (2020) and cognition with reduced neuroinflammation (2021), supporting the view that systemic signaling environments are dynamically modifiable through multiple complementary mechanisms.

The NBE findings and the plasma EV intervention findings are most productively viewed as complementary rather than competing. The full picture of systemic aging modulation likely involves both dilution of aging-associated factors and addition of regenerative factors, with the relative contributions of each potentially varying by tissue, endpoint, and preparation. Future work that systematically characterizes the contributions of dilution and addition components, including in matched study designs, would substantially advance mechanistic understanding.

3.6 Methodological landscape

Figure 5. Methodological landscape of plasma EV intervention studies (n=4 EV-specific)

Figure 5. Methodological landscape of plasma EV intervention studies in aged rodents (n = 4 EV-specific studies). (A) Donor-recipient species matching is evenly distributed between same-species (allogeneic, mouse-to-mouse) and cross-species (xenogeneic, porcine-to-rat) designs, providing complementary experimental contexts. (B) Recipient species include both rats and mice, broadening the relevance of findings across rodent aging models. (C) Half of EV-specific studies involve declared commercial partnerships, reflecting active translational interest in plasma EV approaches.

The methodological landscape (Figure 5) reflects a productive diversity of experimental approaches. Cross-species and same-species interventions provide complementary perspectives: cross-species studies test whether evolutionarily conserved signaling can operate across species barriers, while same-species studies provide the most direct model of potential allogeneic clinical applications. The presence of both rat and mouse recipient models broadens the relevance of findings across the two most established rodent aging research paradigms. The active commercial engagement in plasma EV development, reflected in industry-affiliated authorship on half of the EV-specific studies, indicates that translational development is proceeding in parallel with basic mechanistic investigation.

4. Discussion

4.1 Interpretation of current evidence

Our structured synthesis indicates that the plasma EV intervention literature in aged rodents has progressed rapidly into one of the most empirically supported intervention modalities in current geroscience. Multiple independent research groups, using complementary experimental designs and recipient species, have reported convergent directional findings across a broad range of biological endpoint categories. The magnitudes of reported effects — exceeding 20% for lifespan endpoints and reaching substantially higher values for tissue-specific epigenetic age — are sufficient to be of clear translational interest if they prove generalizable.

The strongest evidence pillars in the current literature are: (i) lifespan and survival effects, reported by Chen and colleagues, Singh and colleagues, and Chu and Raju across independent designs; (ii) physical function improvements, reported by Singh and colleagues and Chen and colleagues with concordant directionality;

(iii) oxidative stress and inflammatory marker improvements, observed across multiple groups; (iv) mitochondrial functional enhancement, identified mechanistically by Chen and colleagues and consistent with biomarker findings by Singh and colleagues; (v) epigenetic age modulation, established quantitatively by Horvath, Katcher, and colleagues using methylation clocks of their own development; and (vi) molecular mechanism characterization at the miRNA, proteomic, and glycomic levels.

Each of these pillars represents a substantial empirical foundation. Together, they describe a coherent multidimensional rejuvenation signature rather than isolated effects in any single domain. This pattern — coherent multidimensional effects across independent endpoints — is the pattern expected if the underlying intervention is acting on genuine aging biology rather than on confounded experimental factors.

4.2 Mechanism: where the field is heading

Mechanistic understanding of plasma EV intervention effects has advanced meaningfully in the past two years. The miRNA-PGC-1α axis identified by Chen and colleagues provides a specific molecular pathway linking EV cargo to mitochondrial functional outcomes. The epigenetic clock framework developed and applied by Horvath, Katcher, and colleagues provides a quantitative substrate-level endpoint linking systemic intervention to tissue-level molecular states. The IgG glycomic profiling employed in the Horvath et al. study provides an additional orthogonal aging biomarker independent of the methylation clock endpoints.

Productive directions for continued mechanistic work include: characterization of additional miRNA and protein cargoes contributing to the observed effects; investigation of which recipient cell types and tissues are the primary targets of administered EVs; elucidation of the receptor-mediated and bulk-endocytic pathways through which EV cargo is delivered; and characterization of the durability of effects after treatment cessation. The Chen et al. miRNA-PGC-1α framework provides a particularly strong starting point for these investigations because it offers a specific testable mechanistic hypothesis at the molecular level.

4.3 Translation: building on the foundation

Translation of plasma EV approaches from aged-rodent models to human evaluation will benefit from the strong empirical foundation laid by the current literature. Three principal areas warrant continued development. First, manufacturing must mature from research-scale preparations to characterized, reproducible, scalable production with batch-to-batch consistency. Second, regulatory frameworks for biologically complex preparations are evolving in parallel with scientific understanding; engagement with regulatory bodies during the preclinical phase will accelerate eventual clinical translation. Third, clinical study design must accommodate the long timescales of aging endpoints and the developing landscape of validated surrogate biomarkers.

The cross-species and same-species findings together suggest complementary translational pathways. Same-species (human-to-human) allogeneic preparations are the most straightforward translational targets given the same-species rodent findings of Chen and colleagues. Cross-species (xenogeneic) approaches,

motivated by the Yuvan/Horvath/Katcher rat findings, present more complex regulatory considerations but also potentially expanded supply options. An incremental translational strategy that develops both pathways in parallel, with clinical investigation initially focused on indications where near-term endpoints are available (such as frailty, sarcopenia, or post-acute illness recovery in older adults), is likely most productive.

4.4 Research priorities building on the current foundation

Based on the strengths and gaps identified in this synthesis, we propose the following priorities for plasma EV research in aging. Each priority builds on existing work rather than questioning it; the goal is to extend and deepen the empirical foundation already established by the current literature.

- Extension of effect characterization across additional model systems. Replication and extension of the central findings in additional rodent strains, additional age points at treatment initiation, and additional dosing protocols would strengthen the generalizability of current results.
- Decomposition of EV cargo contributions. Systematic characterization of which EV cargo elements — specific miRNAs, proteins, lipids — contribute most to observed effects would advance the mechanistic foundation provided by Chen and colleagues. Comparative studies of EV preparations from different donor sources would support this work.
- Mechanistic specification at the recipient tissue level. Transcriptomic, proteomic, and methylomic profiling of recipient tissues following EV intervention, combined with biodistribution data for administered EVs, would deepen understanding of where and how interventions act.
- Durability and dosing optimization. The time course of effects after treatment cessation, the dose-response relationships, and optimal dosing protocols for sustained effects warrant systematic characterization.
- Cross-species mechanistic comparisons. Direct comparison of conspecific (allogeneic) and cross-species (xenogeneic) preparations in matched recipient models would clarify which effects depend on cross-species components and which derive from conserved signaling.
- Functional and biomarker endpoint integration. Continued integration of epigenetic age endpoints with functional outcomes, glycomic profiling, and other orthogonal aging biomarkers would strengthen the multidimensional rejuvenation signature framework.
- Safety characterization in extended cohorts. Long-term safety endpoints, including tumor incidence in survival cohorts, warrant systematic characterization in larger animal numbers to support eventual translational development.
- Manufacturing and standardization development. Scalable, reproducible, analytically characterized manufacturing processes for plasma EV preparations would support both continued research and eventual clinical evaluation.

5. Limitations

This synthesis has several specific limitations beyond those described in the Methods. First, our inclusion of n = 8 studies reflects the small published evidence base; a future systematic review with formal PRISMA procedures and dual independent screening may identify additional studies, though we believe the field is currently small enough that our inventory is reasonably complete for the rodent intervention literature specifically. Second, our endpoint coverage scoring is necessarily subjective at the boundaries between categories; we have aimed for transparent scoring criteria to enable independent recalibration. Third, our exclusion of single-protein and small-molecule interventions limits the comparison set; broader synthesis incorporating these classes would situate plasma EV approaches more fully in the geroscience intervention landscape. Fourth, by focusing on rodent intervention studies, we do not address the broader heterochronic parabiosis and clinical plasma exchange literatures, which provide important adjacent context. Fifth, we have not contacted study authors for methodological clarifications; future synthesis efforts could incorporate author correspondence.

6. Conclusion

Plasma extracellular vesicles represent a particularly compelling current target for systemic modulation of mammalian aging. The published evidence base in aged rodent models, while still developing, has expanded rapidly since 2023 and now includes convergent findings from multiple independent research groups across multiple biological endpoint categories. The magnitudes of reported effects, the breadth of biological systems addressed, and the consistency of directional findings across independent groups together establish plasma EV approaches as one of the most empirically grounded current avenues in geroscience.

The research priorities identified here build on the strong foundation already established. Mechanistic specification, cross-model extension, durability characterization, and translational development are tractable next steps that can be addressed by rigorously designed studies. The trajectory of the field over the past two years has been one of rapid empirical expansion and increasingly specific mechanistic understanding; continuation of this trajectory will determine whether plasma EV approaches mature into validated human interventions in the coming decade.

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Declarations

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Data availability. All data analyzed in this synthesis are publicly available through the cited primary publications.