Cureus
Part of SPRINGER NATURE

Open Access Review Article

From Alveoli to Mitochondria: Respiratory and Aerobic Reserve as Therapeutic Targets in Longevity Medicine

Review began 10/23/2026
Review ended 11/01/2026
Published 11/11/2026

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DOI: 10.7759/cureus.119481

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Abstract

Longevity medicine seeks to extend both lifespan and healthspan, the years in which people can climb stairs, recover from illness, and live independently. Respiratory function and aerobic capacity contribute to these goals through different components of oxygen transport, yet their prognostic associations are often conflated with evidence that improving a measurement reverses aging. In this narrative review, we examine respiratory and aerobic reserve as complementary therapeutic targets, integrating pulmonary physiology, human aging biology, and intervention studies. We define reserve as the margin between a person's capacity and the demands of a given activity, not as another biological age score. Aging can narrow that margin at any step of oxygen transport, from ventilatory mechanics and the alveolar epithelium to the pulmonary microvasculature, cardiac delivery, and skeletal muscle mitochondria. Because these steps need not decline together and one can partly compensate for another, normal spirometry can coexist with poor fitness, whereas impaired lungs can coexist with preserved exercise performance. The strongest evidence still belongs to established interventions, such as aerobic and resistance training, pulmonary rehabilitation, smoking cessation, and selected disease-specific treatments, which have been shown to preserve function, reduce disability, or improve survival in defined populations, often without normalizing lung function. Emerging senolytics, nicotinamide adenine dinucleotide precursors, mitophagy interventions, metformin, mechanistic target of rapamycin inhibitors, and photobiomodulation have mostly been tested in small, short human trials with variable evidence. Recent trials also challenge the assumption that gerotherapeutics necessarily enhance exercise adaptation: in older adults, metformin blunted the mitochondrial response to aerobic training, and weekly sirolimus did not augment training gains. We therefore treat molecular target engagement, physiological improvement, daily function, clinical healthspan outcomes, and lifespan as separate links in the chain of evidence, and we emphasize indication-specific benefit versus harm. Three questions should guide future research: whether the hidden physiological cost of compensating for lung impairment predicts outcomes independently of preserved peak oxygen uptake, whether treating one limitation unmasks another, and whether gerotherapeutic-exercise combinations improve function beyond exercise alone. Integrating pulmonary assessment with directly measured exercise capacity and patient-centered outcomes offers a genuine strategy for evaluating longevity interventions while avoiding unsupported claims of lung rejuvenation.

Categories: Sports Medicine, Integrative/Complementary Medicine, Pulmonology
Keywords: cardiorespiratory fitness, exercise adaptation, gerotherapeutics, healthspan, longevity medicine, mitochondrial function

Introduction And Background

Healthy longevity describes, broadly, the preservation of function across an extended lifespan. Although simple to state, this goal depends on multiple physiological systems and requires the preservation of function at cellular, organ, and whole-person levels.

From a clinical pulmonology perspective, preserving function means maintaining independence and participation: the ability to climb stairs, walk outside the home, tolerate a respiratory infection, or resume activity after hospitalization. These tasks require coordinated ventilation, pulmonary gas transfer, cardiovascular oxygen delivery, and peripheral oxygen utilization. Aging or disease can reduce any of these capacities, while treatment may preserve useful function without normalizing every resting measurement. Longevity medicine therefore needs an account of how physiological improvement translates into independence, resilience, and survival rather than relying exclusively on molecular markers or an estimated biological age.

Both pulmonary function and cardiorespiratory fitness have strong prognostic associations. Lower forced expiratory volume in one second (FEV_1) predicted mortality over 29 years in the Buffalo Health Study, while a meta-analysis of fitness cohorts found a relative risk of all-cause mortality of 0.87 per additional metabolic equivalent [1-3]. Clinical guidance accordingly recognizes fitness as a useful physiological vital sign. These

findings establish relevance to risk assessment; yet they do not determine whether increasing FEV_1 or peak oxygen uptake (VO_2peak) causes a proportional gain in life expectancy, nor which intervention should be used to achieve that change.

A central clinical question is which limitations remain modifiable and whether treating them preserves activities that a person values. A respiratory intervention may reduce the effort required for a task; conditioning may increase the capacity available to perform it; resistance training may address a strength constraint that oxygen uptake alone does not capture. Trials preventing mobility disability provide direct healthspan evidence even when survival is not their principal endpoint [4,5]. Conversely, changes in a mitochondrial metabolite or an aging-associated molecular signature may be biologically informative without demonstrating functional benefit. The quanTifiEd immuNe-aging dySregulation index (TENSE), for example, summarizes immune aging-associated patterns in pathway enrichment data [6]. Connecting such molecular descriptions to measured respiratory and aerobic reserve could strengthen the evaluation of gerotherapeutic effects, but associations with functional decline, disability, and survival require clinical validation.

Studies centered on pulmonary aging, cardiorespiratory fitness, or molecular geroscience provide complementary accounts of structural decline, prognosis, and potential therapeutic targets. The translational issue that remains less clearly addressed across the literature is how to identify a modifiable limitation along the oxygen pathway and connect its treatment to gains in everyday function. Furthermore, senescence-related changes in oxygen transport, from pulmonary mechanics and alveolar-capillary gas transfer to cardiovascular delivery and skeletal muscle oxidative metabolism, may progress unevenly during aging.

In our review, we present respiratory and aerobic reserve as an organizing concept by relating available capacity to the demands of a specified activity. Both respiratory and aerobic reserve are presented as complementary therapeutic targets for healthy longevity in aging adults with and without chronic respiratory disease. The central question is which interventions preserve or improve reserve and whether these effects translate into sustained mobility, greater independence, reduced disability, or longer survival. We aim to synthesize mechanisms of reserve loss, critically evaluate established interventions and emerging gerotherapeutics, and propose a conceptual clinical framework for interpreting their effects, with particular attention to tissue-specific effects, interactions with exercise adaptation, and treatment-related harms.

Review

Scope and evidence selection of the narrative review

Targeted (not exhaustive) PubMed, publisher, and reference-linked searches were completed through August 31, 2026, consistent with the narrative design. Searches addressed pulmonary aging and lung-function trajectories; cardiorespiratory fitness, oxygen transport, and mortality; exercise, mobility disability, and rehabilitation; epithelial and muscle mitochondrial biology; cellular senescence; and selected gerotherapeutics and exercise interactions. Human longitudinal cohorts informed prognosis, randomized trials were prioritized for therapeutic effects, and experimental studies supplied mechanistic context. Selection favored studies connecting a specified biological compartment to a functional or clinical endpoint. Bibliographic identifiers were checked, and accessible full texts were examined for primary endpoints, comparator groups, population restrictions, and adverse event interpretation.

Reserve relative to activity and stress

Aerobic capacity describes the upper performance available during an adequately performed exercise (ergospirometry) test. Aerobic reserve, as used here, describes the margin between that capacity and the oxygen requirement of a specified task. Respiratory reserve is related but distinct: it concerns ventilatory and gas-transfer capacity relative to the demands placed on the respiratory system. Neither is a single organ-specific aging clock. The same maximal oxygen uptake can support different functional margins when body mass, task efficiency, muscle strength, or environmental demands differ [7,8].

Directly measured VO_2peak during cardiopulmonary exercise testing (CPET) integrates the oxygen pathway but does not measure all dimensions of independence. Walking, chair rising, and carrying objects also depend on strength, balance, pain, cognition, and opportunity. The six-minute walk test assesses self-paced functional exercise capacity and is influenced by symptoms, pacing, and test conditions. Although it can elicit oxygen uptake comparable to CPET in chronic respiratory disease, walking distance is not interchangeable with directly measured VO_2peak [9]. Exercise capacity, daily activity, and disability are connected outcomes that require different measurements.

The oxygen cascade explains why an apparently adequate lung can coexist with poor aerobic performance. Whole-body oxygen uptake (VO_2) depends on cardiac output (Q) and the arterial-mixed venous oxygen content difference ($CaO_2 - CvO_2$), according to the well-known Fick equation. Hemoglobin concentration and saturation dominate arterial oxygen content, so a normal arterial oxygen tension alone does not establish adequate delivery [7,8].

At each step, different measurements identify different constraints. Spirometry and lung volumes characterize expiratory flow and mechanics; diffusing capacity for carbon monoxide (DLCO) and exertional oxygenation interrogate transfer; cardiac assessment and blood count address delivery; CPET and muscle testing examine integrated performance and peripheral function (Figure *1A*). Apart from established approaches to preserve or improve function, several emerging strategies aim to preserve epithelial, vascular, and mitochondrial function during aging (Figure *1B*). Experimental studies implicate PTEN-induced kinase 1 (PINK1)-dependent mitochondrial quality control in protecting aging alveolar epithelial cells from dysfunction, identifying a potential pulmonary target [10]. In older adults, high-intensity interval training improved skeletal muscle mitochondrial respiration and aerobic capacity, demonstrating that peripheral oxidative capacity remains modifiable [11]. Emerging cellular interventions require human studies showing that their biological effects translate into sustained physical function and independence.

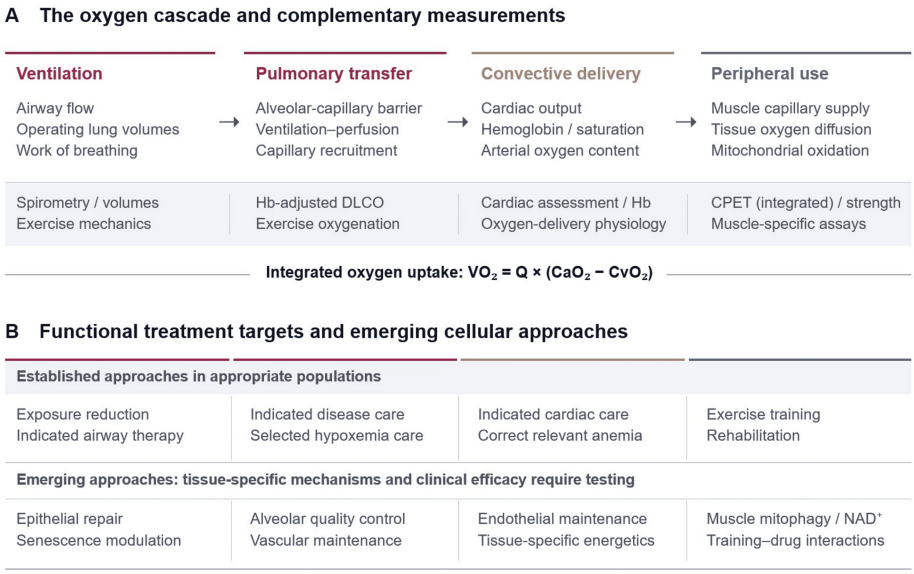


FIGURE 1: The oxygen cascade and tissue-specific therapeutic opportunities.

DLCO: diffusing capacity of the lungs for carbon monoxide; Hb: hemoglobin; CPET: cardiopulmonary exercise test; VO_2: oxygen uptake; Q: cardiac output; CaO_2: arterial oxygen content; CvO_2: venous oxygen content; NAD+: nicotinamide adenine dinucleotide.

Image created by the authors using Microsoft PowerPoint (Microsoft Corp., Redmond, WA, United States).

The functional importance of reserve depends on demand. A reduction in capacity may be largely unnoticed during low-demand activities but become consequential during stairs, carrying loads, or recovery from illness. Declining capacity with age narrows the reserve available for everyday activities, bringing tasks such as stair climbing closer to an individual's functional limit (Figure *2A*). Acute illness may transiently lower available capacity, while subsequent inactivity can delay recovery (Figure *2B*). Starting reserve is one possible contributor to alternate recovery trajectories; illness severity, comorbidity, treatment, and rehabilitation also affect recovery. Trials demonstrating that physical activity reduces mobility disability in older adults support the clinical value of preserving functional capacity [4,5].

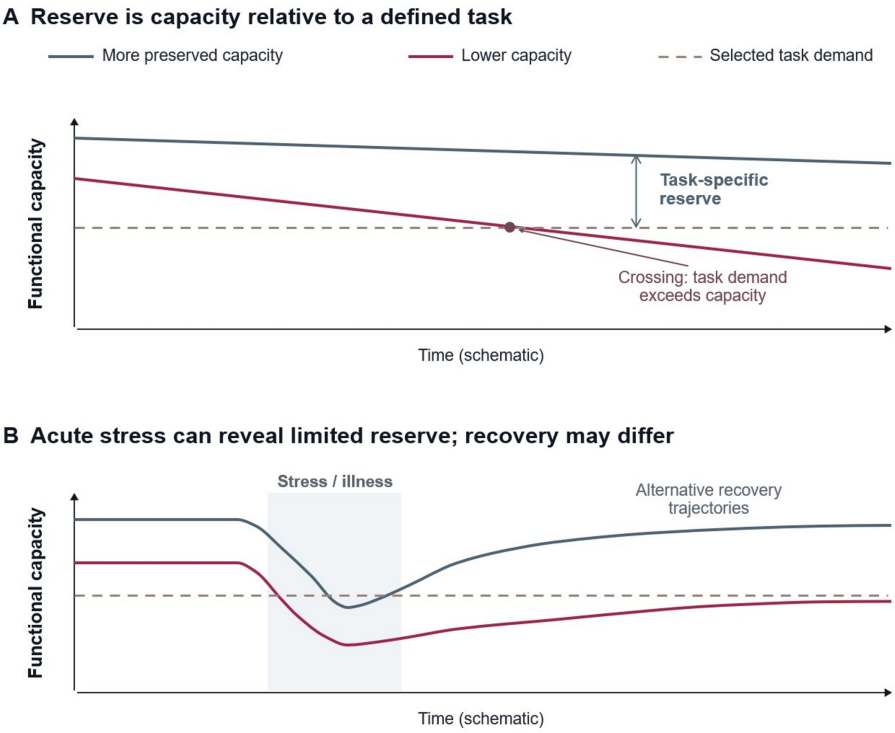


FIGURE 2: Task-relative functional reserve and potential implications for healthspan.

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Pulmonary maintenance and the limits of normal aging

Normal aging alters elastic recoil, chest wall mechanics, respiratory muscle performance, and the distribution of ventilation. Airway closure and changes in operating lung volumes can become more important when demand rises. Healthy age-related airspace enlargement should be distinguished from emphysematous destruction. Likewise, exercise limitation caused by breathing mechanics should be demonstrated rather than inferred from chronological age [12,13].

Gas transfer introduces another vulnerability. DLCO reflects both alveolar-capillary membrane conductance and uptake by hemoglobin in perfused capillaries, conventionally described by the Roughton-Forster relationship [14]. Lower DLCO can arise not only through reduced effective surface area, altered membrane properties, or reduced capillary blood volume but also through anemia or testing conditions. Hemoglobin adjustment, inspired volume, and test quality must therefore be considered before labeling a result as pulmonary aging [15]. Importantly, preserved spirometry does not exclude a diffusion or pulmonary vascular limitation during exertion.

At the cellular level, alveolar type II epithelial cells maintain surfactant and participate in epithelial repair. Human idiopathic pulmonary fibrosis (IPF) tissue and complementary models have linked impaired PINK1-dependent mitochondrial quality control to epithelial dysfunction and susceptibility to fibrosis [10]. This identifies a plausible maintenance pathway and a potential disease target. Its contribution to ordinary age-related lung function decline and the ability of a therapy to restore healthy human alveolar function remain separate questions.

A 2026 single-cell atlas of human lung aging reported heterogeneous changes among epithelial and endothelial populations, including altered surfactant-expressing alveolar cells, capillary differentiation, and transcriptional entropy. Conventional senescence signatures did not show a uniform age-associated increase [16]. Such findings argue for specifying cell identity and functional consequence when interpreting aging biology. A systemic senescence marker cannot be assumed to measure every relevant pulmonary compartment.

The hallmarks of aging place mitochondrial dysfunction, impaired autophagy, senescence, and altered intercellular communication in a broader mechanistic framework [17]. Advanced chronological age is encountered in many fibrotic lung diseases. In fibrotic models, senescent cell clearance improved

pulmonary or physical function without necessarily reversing structural fibrosis [18]. Mitochondrial dysfunction can also produce senescence-associated secretory programs that differ from conventional inflammatory patterns [19]. These observations support tissue-specific intervention studies rather than treating all mitochondrial or inflammatory changes as equivalent therapeutic targets.

Peripheral plasticity and exercise adaptation

Longitudinal observations from the Baltimore Longitudinal Study of Aging show an accelerating decline in aerobic capacity at older ages [20]. Changes in cardiac performance, perfusion, oxygen extraction, muscle quality, and activity all contribute to this decline. Aging-related muscle dysfunction includes motor unit and contractile changes as well as oxidative metabolism [21]. Human cross-sectional studies associate lower muscle mitochondrial DNA abundance and adenosine triphosphate (ATP) production with age and aerobic capacity, but lifelong activity and other exposures complicate causal interpretation [22].

Exercise provides direct evidence that important components remain plastic. Repeated contractile activity activates pathways controlling mitochondrial protein synthesis, substrate use, and vascular adaptation [23]. In a 12-week human study, interval and combined training improved aerobic capacity in younger and older adults. Interval training increased muscle mitochondrial respiration in both age groups, whereas a significant increase in respiration after combined training was observed in younger participants. Resistance and combined training improved strength [11]. Thus, integrated functional gains need not reflect identical molecular responses across ages or exercise modes.

Endothelial regulation affects whether oxidative capacity can be supplied with oxygen [24]. The distribution of blood flow also matters: experimental human work demonstrates that respiratory muscle work can compromise leg blood flow during maximal exercise [25]. Reducing an excessive breathing burden may therefore improve performance through resource allocation as well as oxygenation. Peripheral conditioning can, in turn, reduce the ventilatory requirement at a standardized workload. The relevant treatment response is physiological and task-specific, not necessarily a larger resting FEV_1.

Chronic obstructive pulmonary disease (COPD) illustrates the reinforcing relationship between symptoms, low activity, exacerbations, nutritional impairment, and muscle dysfunction [26]. Exercise-related signaling provides another potential link. An acute human experiment in eight healthy men found that exercise and physiological interleukin-6 infusion attenuated endotoxin-induced tumor necrosis factor production [27]. This demonstrates context-dependent inflammatory responses, while the extent to which such signals preserve human alveolar maintenance during aging remains uncertain. Mechanistic explanations should therefore distinguish established oxygen transport from proposed interorgan mediation.

Divergence between pulmonary function and physical fitness

Paired measurements provide a stronger basis for discussing lung-fitness relationships than comparing unrelated mortality cohorts. In 2,314 Framingham participants with pulmonary testing and CPET, a one-liter lower FEV_1 corresponded to approximately 7.1% lower VO_2peak in the adjusted analysis; the FEV_1/forced vital capacity (FVC) ratio was not associated with VO_2peak [28]. Longitudinal observations from the Coronary Artery Risk Development in Young Adults study also linked higher treadmill performance and smaller fitness declines to less subsequent lung function decline [29]. These findings support joint assessment without establishing the limiting organ or an exercise-mediated regeneration pathway.

Developmental starting points require particular attention. COPD can arise through low early-adult lung function followed by a relatively ordinary decline, as well as through accelerated decline from a higher starting level [30]. Low early-adult lung function is also associated with earlier multimorbidity and mortality [31]. Accordingly, a low measurement does not identify a fast-aging rate. Fitness can similarly be low because of inactivity, body composition, anemia, medications, or inadequate test effort.

Pulmonary-aerobic discordance describes divergence between pulmonary measurements and integrated performance. Relatively preserved fitness despite impaired lung function may reflect compensation or residual capacity; poor fitness despite preserved spirometry may reflect a cardiovascular or peripheral constraint, or pulmonary dysfunction missed by spirometry. For therapeutic interpretation, the direction of change may be more informative than the size of a discrepancy. Fitness improvement with stable pulmonary function is beneficial even if the two measurements diverge further. Minimizing discordance is therefore not a defensible therapeutic goal. We analyze the measurements needed to distinguish physiology, molecular target engagement, and clinical benefit (Table *1*) and emphasize that the measures are complementary; none alone provides a validated global reserve score.

Measure	What it establishes	Limitation and context	Use in intervention studies
Spirometry, lung volumes, and DLCO	Airflow, ventilatory volume, and gas transfer	Resting values do not quantify exercise reserve; hemoglobin and test conditions affect DLCO.	Measure preservation or change in specified pulmonary domains
Direct CPET: absolute and mass-normalized VO_2peak	Integrated oxygen uptake under measured exercise conditions	Low uptake does not identify one defect; weight change alters the denominator.	Report L/min and mL/kg/min; document effort, gas exchange, and symptoms
Strength and body composition	Force generation and lean/fat tissue quantities	Lean mass is not muscle quality; strength gains need not increase VO_2peak.	Pair performance with tissue preservation, particularly during weight loss
Walking, gait speed, and daily function	Task performance and practical mobility	Walking distance is not maximal capacity; practice and testing conditions matter.	Standardize field tests; assess daily activities and disability separately
Molecular and epigenetic markers	Target engagement or a prognostic association	Biomarker improvement does not establish reserve, rejuvenation, or clinical benefit.	Use mechanistic endpoints alongside functional and clinical outcomes
Disability, hospitalization, and survival	Patient-centered healthspan or clinical events	These endpoints answer different questions; short trials may be underpowered for events.	Prespecify event definitions, follow-up, and harms

TABLE 1: Measurements and endpoints for evaluating respiratory and aerobic reserve.

CPET: cardiopulmonary exercise testing; DLCO: diffusing capacity of the lungs for carbon monoxide; VO_2peak: peak oxygen uptake.

Established interventions and clinical healthspan

Trials measuring disability give longevity medicine a direct clinical anchor. The Lifestyle Interventions and Independence for Elders (LIFE) randomized trial enrolled 1,635 sedentary adults aged 70-89 years at risk of mobility disability. Major mobility disability, defined as the inability to complete a 400 m walk, occurred in 30.1% receiving structured physical activity versus 35.5% receiving health education over an average of 2.6 years (hazard ratio 0.82, 95% confidence interval 0.69-0.98) [4]. The Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) trial evaluated physical activity and nutritional counseling in older adults with physical frailty and sarcopenia. In its prespecified primary analysis of participants with Short Physical Performance Battery scores of 3-7, mobility disability occurred in 46.8% versus 52.7% of controls (hazard ratio 0.78, 95% confidence interval 0.67-0.92); participants with better baseline performance were analyzed separately [5]. These outcomes address independence more directly than a circulating aging marker. Neither trial establishes that the clinical effect is mediated exclusively by improved pulmonary function or VO_2peak.

Mortality evidence for fitness remains extensive but predominantly observational. A large treadmill referral cohort and an overview of cohort meta-analyses found consistent associations between higher fitness and lower mortality [32,33]. Change in fitness can also predict subsequent outcomes [34]. The Generation 100 trial, however, did not demonstrate a significant reduction in all-cause mortality from combined supervised exercise groups versus physical activity recommendations over five years in adults aged 70-77 years [35]. The comparator group was active and training exposure overlapped. Disability prevention, physiological improvement, and survival should each be judged against the comparator and population actually studied.

Resistance training and body composition influence the capacity to perform tasks even when oxygen delivery is adequate. In older adults with obesity undertaking weight loss, combined aerobic and resistance exercise improved physical function and limited lean-tissue loss more effectively than aerobic exercise alone [36]. Caloric restriction and aerobic exercise also produced additive improvements in weight-normalized VO_2peak in older patients with obesity and heart failure with preserved ejection fraction [37]. Weight loss can raise oxygen uptake expressed per kilogram without increasing absolute uptake. This may still make walking easier; the physiological mechanism and the clinical benefit should both be described accurately.

Smoking cessation combines preservation of pulmonary trajectories with randomized survival evidence. Sustained quitters in the Lung Health Study had approximately half the subsequent annual FEV_1 decline of continuing smokers; the randomized cessation program also reduced long-term all-cause mortality [38,39]. The survival benefit includes effects beyond the lung, including cardiovascular and cancer pathways. It cannot be assigned solely to a change in spirometry.

Pulmonary rehabilitation addresses performance despite persistent respiratory disease. Cochrane syntheses reported average six-minute walk improvements of approximately 44 m in COPD and 40 m in interstitial lung disease (ILD), together with relevant symptom or quality-of-life benefits [40,41]. Contemporary American Thoracic Society guidance supports rehabilitation in appropriate chronic respiratory disease populations [42]. A large post-hospital COPD cohort found lower one-year mortality associated with rehabilitation initiation, but residual selection and recovery differences remain possible [43]. Functional benefit is meaningful independently of whether a specific causal survival effect is established.

Treating a pulmonary longevity constraint without claiming rejuvenation

Disease treatment can change the effort required to achieve a task. In hyperinflated COPD, tiotropium reduced hyperinflation and improved fixed-work cycle endurance by approximately 21% over six weeks [44]. This is a mechanical and endurance effect, not automatically a VO_2peak effect. Lung volume reduction surgery produced survival benefit in selected patients with predominantly upper-lobe emphysema and low exercise capacity, while other profiles experienced harm [45]. Anatomy, baseline performance, and procedural risk jointly determine the value of intervention.

Oxygen treatment demonstrates the importance of indication. Trials supported survival benefit from longer-duration oxygen in severe chronic hypoxemic obstructive lung disease [46], whereas long-term oxygen did not improve death or first hospitalization in COPD with moderate resting or exertional desaturation [47]. These results provide no basis for treating normoxemic healthy adults to extend life. The therapeutic aim is correction of a demonstrated limitation in a population with relevant evidence.

In IPF, nintedanib and pirfenidone slow FVC decline, while pooled pirfenidone analyses support a mortality benefit with the limitations of pooled and relatively infrequent events [48-50]. Preserving function in progressive disease has substantial clinical value without implying reversal of ordinary aging. In pulmonary hypertension associated with ILD, inhaled treprostinil improved walking distance over 16 weeks; the trial was not a definitive survival study [51]. Supervised training improved VO_2peak and hemodynamic measurements in stable pulmonary arterial or inoperable chronic thromboembolic pulmonary hypertension [52]. These examples show why the therapeutic target may be circulation or peripheral conditioning despite preserved expiratory flows. We compare established interventions by their functional effects, clinical endpoints, and applicability (Table *2*).

Intervention and population	Established benefit	Survival evidence	Applicability and caution
Smoking cessation and exposure avoidance	Cessation slows FEV_1 decline in smokers with obstruction.	Randomized cessation program reduced long-term mortality.	Trial population had obstruction; survival benefit is not proven to arise solely from preserved FEV_1.
Aerobic and resistance training in older adults	Aerobic capacity and strength improve; mitochondrial responses vary by modality and age.	Generation 100 randomized primary mortality comparison was null; cohort fitness associations remain prognostic.	Functional benefit does not specify added life-years or reversal of pulmonary aging.
Multicomponent activity in at-risk older adults	Reduced incident mobility disability in specified LIFE and SPRINTT populations.	These trials establish disability prevention, not lifespan extension.	Benefit depends on baseline function and selection; serious adverse events did not differ significantly.
Pulmonary rehabilitation in COPD or ILD	Walking performance and quality of life improve.	Post-discharge COPD survival association is observational; randomized ILD survival evidence remains uncertain	Walking benefit is distinct from maximal capacity or structural repair; delivery considers exertional desaturation.
Weight loss with exercise in older adults with obesity	Combined training improves function and limits lean-tissue loss versus aerobic training alone.	The cited trial did not establish survival benefit.	Lean and bone loss can persist; musculoskeletal injuries occurred. Report absolute and weight-normalized fitness.
Bronchodilation or LVRS in selected COPD	Bronchodilation improves fixed-work endurance; LVRS improves exercise capacity in selected emphysema.	LVRS benefit or harm varies with emphysema distribution and baseline capacity.	Short bronchodilator trial did not test survival; procedural risk and phenotype determine LVRS suitability.
Oxygen for chronic hypoxemic COPD	Increases available oxygen; effects depend on the severity and context of hypoxemia.	Randomized survival benefit in severe hypoxemia; no death/hospitalization benefit in moderate desaturation.	Disease-specific eligibility; no extrapolation to normoxemic healthy aging.
Antifibrotic treatment in IPF	Slows FVC decline rather than normalizing lung function.	Pooled pirfenidone trials support disease-specific mortality benefit.	Gastrointestinal effects; pirfenidone skin effects. Findings do not establish reversal of normal pulmonary aging.

TABLE 2: Established interventions: functional outcomes, survival evidence, and applicability.

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; LIFE: Lifestyle Interventions and Independence for Elders; LVRS: lung volume reduction surgery; SPRINTT: Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies; SPPB: Short Physical Performance Battery; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

Emerging gerotherapies and evidence limitations

Senolytics seek to reduce the maladaptive effects of persistent senescent cells, but the human pulmonary evidence is preliminary. An open-label dasatinib-quercetin pilot in 14 patients with IPF reported physical test improvements with unchanged pulmonary function [53]. A subsequent placebo-controlled pilot involving 12 participants supported feasibility, lacked clear functional separation, and reported more non-serious adverse events during treatment [54]. These results establish a reason for further investigation, not routine treatment of healthy adults or proof of survival benefit. Removing a pathological cellular population also differs from assuming that every senescence-associated process should be suppressed.

Nicotinamide adenine dinucleotide (NAD^+) precursors illustrate the distance between biochemical availability and physiological effect. Nicotinamide riboside (NR) increased NAD-related metabolites in human trials [55], while a study in 12 older men found no improvement in measured muscle mitochondrial bioenergetics despite metabolic and transcriptional changes [56]. Target engagement does not establish increased oxidative ATP production. Findings must also remain specific to the compound, formulation, tissue, and population studied.

Urolithin A has been investigated as a mitophagy-directed intervention, with early human evidence of mitochondrial-related biomarker changes [57]. In a randomized trial of 66 older adults, some muscle endurance outcomes improved, but between-group differences in the primary six-minute walk and maximal

ATP-production endpoints were not significant [58]. A 2026 synthesis of five small trials found low-certainty, statistically inconclusive evidence for walking improvement [59]. Short-term endurance or biomarker signals should be separated from durable independence, respiratory improvement, and lifespan extension.

Metformin promoted resolution of established bleomycin-induced fibrosis in mice [60], whereas a 2026 observational analysis of 2,226 patients with fibrotic ILD from the prospective Canadian Registry for Pulmonary Fibrosis (CARE-PF) found no significant association between baseline metformin use and slower FVC decline [61]. In older adults undertaking aerobic training, metformin impaired exercise-induced increases in muscle mitochondrial respiration; the attenuation of maximal oxygen uptake (VO_2max) improvement was a nonsignificant between-group trend [62]. These findings challenge extrapolation from a plausible mechanism to uniform preservation of pulmonary and aerobic capacity.

mTOR inhibition and the possibility of competing adaptations

Mechanistic target of rapamycin (mTOR) signaling links nutrient sensing, protein synthesis, and cellular maintenance, but its inhibition can have different consequences across tissues and time scales. In an acute human experiment, rapamycin blocked the early increase in muscle protein synthesis after resistance exercise [63]. An acute muscle response does not establish the long-term effect of intermittent dosing on strength, disability, or survival. Separate trials of the mTOR inhibitor RTB101 studied immune function in older adults. Antiviral gene expression increased and a second prespecified pooled phase 2b comparison showed fewer laboratory-confirmed infections, but the phase 3 trial did not reduce clinically symptomatic respiratory illness; the primary endpoints and populations differed [64]. These immune findings cannot substitute for evidence of improved exercise adaptation and illustrate the need to evaluate each compound against its own clinical endpoint.

A 2026 randomized trial directly examined the combination of exercise and weekly sirolimus in 40 sedentary older adults over 13 weeks [65]. Sirolimus did not enhance the training response. The primary intention-to-treat chair-stand estimate favored placebo but remained statistically inconclusive (difference −2.13 repetitions, 95% confidence interval −4.61 to 0.34); complete-case and per-protocol sensitivity analyses favored placebo. Adverse event counts were numerically higher with sirolimus without a statistically established difference in event rate. The trial was small and exploratory, and it did not measure muscle mTOR activity or mitochondrial mechanisms directly.

Inspiratory muscle training (IMT) targets a potentially modifiable component of respiratory reserve by repeatedly loading the muscles of inspiration. In a six-week sham-controlled trial with 35 completers aged 50-79 years, high-resistance IMT increased treadmill exercise duration by approximately 12% and improved submaximal exercise economy, while VO_2peak and mobility remained unchanged [66]. Another trial in healthy older adults increased inspiratory strength and diaphragm thickness without improving walking performance, physical activity, or quality of life [67]. These findings suggest that respiratory muscle adaptation remains possible with aging, although its contribution to sustained everyday function requires further investigation.

Photobiomodulation (PBM), using red or near-infrared light, is being investigated as an adjunct to exercise and rehabilitation. A crossover trial in 12 patients with COPD reported improved walking performance after application to respiratory muscles, without significant changes in spirometry or respiratory muscle strength [68]. In 24 healthy men aged 60-80 years, however, the tested PBM protocol provided no additional gains in muscle mass, strength, or functional capacity alongside resistance training [69]. Its relevance to healthy aging remains exploratory, with effects on respiratory or peripheral muscles requiring distinction from direct effects on lung tissue.

Preserving respiratory and aerobic reserve with age involves supporting tissue maintenance while retaining the capacity to adapt to exercise. Drugs targeting cellular maintenance may also influence the energetic stress, protein turnover, and remodeling involved in training, making their interaction with exercise relevant to their clinical value. IMT offers a targeted approach to respiratory muscle conditioning, while PBM remains an investigational adjunct whose effects may depend on the tissue and treatment protocol. We bring these approaches together, linking their strongest human findings to their potential relevance for aging and the questions that remain about sustained functional benefit (Table 3).

Candidate and context	Strongest relevant human result	Applicability and harms	Unanswered clinical question
Dasatinib plus quercetin in IPF	Open-label function signal; small controlled pilot showed no meaningful functional separation.	More reported non-serious adverse events in controlled pilot; efficacy and long-term safety unresolved.	Can senolysis preserve pulmonary function or reduce disability in a defined phenotype?
NR in middle-aged/older adults	NAD-related metabolites increased; older men trial showed no muscle bioenergetic improvement.	Short-term tolerability in small samples does not establish long-term safety; compound-specific findings.	Does biochemical engagement produce durable CPET, mobility, or respiratory benefit?
Urolithin A in older adults	Muscle endurance and biomarker signals; primary walking and ATP outcomes not significant.	No adverse event difference in a small, short trial; generalizability remains limited.	Are integrated capacity or disability benefits reproducible beyond selected muscle tests?
Metformin during aerobic training in older adults	Impaired mitochondrial respiratory adaptation; VO_2max between-group attenuation was nonsignificant	Responses were heterogeneous; established diabetes indications are a separate question.	Can metabolic phenotype identify who benefits without impairing training adaptation?
Sirolimus during exercise in older adults	No demonstrated training enhancement; primary chair-stand comparison nonsignificant; sensitivity analyses favored placebo	Exploratory short trial; one possibly drug-related pneumonia. Definitive harm is not established.	Can mTOR modulation preserve adaptation while improving meaningful clinical outcomes?
Gerotherapeutic-exercise combinations	Metformin and sirolimus training trials caution against assumed additivity.	Results do not establish class-wide antagonism; interactions and safety require direct testing.	Which combinations improve mobility or clinical events beyond exercise alone?
IMT	A six-week sham-controlled trial improved treadmill endurance and exercise economy, without improving VO_2peak or mobility. Another trial improved inspiratory strength and diaphragm thickness without functional gains.	Direct human evidence in healthy midlife and older adults; targets respiratory muscle conditioning and potentially exercise tolerance.	Which older adults benefit most, and does adding IMT to whole-body exercise produce sustained improvements in daily activity or reduce disability?
PBM (red light therapy)	A small acute COPD trial improved walking performance without significant spirometric or respiratory muscle strength changes. The tested protocol added no benefit to resistance training in older men.	Investigational adjunct with protocol-specific findings; preservation of aging lung tissue remains unestablished.	Are benefits mediated through muscle or lung tissue, what dose reaches the relevant target, and can reproducible, sustained functional gains be achieved with acceptable long-term safety?

TABLE 3: Emerging gerotherapies: human functional evidence and unresolved clinical questions.

ATP: adenosine triphosphate; COPD: chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise testing; IMT: inspiratory muscle training; IPF: idiopathic pulmonary fibrosis; mTOR: mechanistic target of rapamycin; NAD: nicotinamide adenine dinucleotide; NR: nicotinamide riboside; VO_2max: maximal oxygen uptake; VO_2peak: peak oxygen uptake; PBM: photobiomodulation.

From a favorable biomarker to a patient benefit

A higher VO_2peak, more efficient breathing, or better gas transfer may increase the capacity available for everyday activity. For healthy aging, the significance lies in whether these gains help people climb stairs with less breathlessness, recover activity after illness, or maintain independence. Physiological measurements help explain how an intervention works; sustained function and clinical outcomes establish what it achieves. Even a strong association between a marker and survival does not establish that changing the marker through treatment will extend life [70].

Epigenetic measures, NAD-related metabolites, and mitochondrial signatures offer insight into biological responses that may precede detectable functional change. Their promise is considerable, but their clinical meaning remains specific to the outcome being studied. An epigenetic measure associated with aging-

related outcomes, for example, does not by itself demonstrate restored pulmonary function or a survival benefit from treatment [71]. Figure *3* summarizes the evidence needed to connect intervention, physiological effects, patient benefit, and survival (Figure *3A*); distinguishes target engagement from functional endpoints (Figure *3B*); and places effects and harms in clinical context (Figure *3C*).

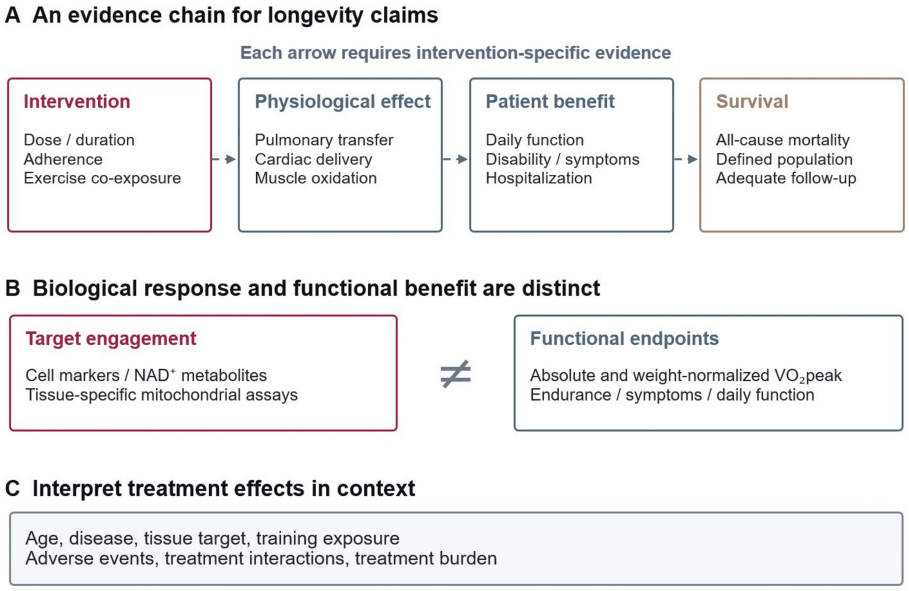


FIGURE 3: Evidentiary requirements for claims of benefit in longevity medicine.

NAD+: nicotinamide adenine dinucleotide; VO_2peak: peak oxygen uptake.

Image created by the authors using Microsoft PowerPoint (Microsoft Corp., Redmond, WA, United States).

Weight change illustrates how an apparently straightforward improvement can have several explanations. Weight-normalized VO_2peak may rise because body mass falls, even when absolute oxygen uptake remains unchanged; reporting both helps clarify the contribution of improved aerobic capacity [8]. Similarly, measurements at a matched workload can reveal whether breathing or oxygen delivery has become less demanding during the same activity. Consistent test conditions, adequate effort, and appropriate pulmonary reference equations make these changes easier to interpret and connect to the person's functional experience [8,72].

Research priorities and limitations

Three propositions, in our eyes, need to be prioritized for a future research agenda. First, preserved maximal performance may conceal the physiological cost of compensating for pulmonary impairment. CPET at matched external work, operating lung volumes, exertional oxygenation, and subsequent recovery outcomes could test whether this cost carries prognostic information beyond VO_2peak. Second, relieving one constraint may expose another: lung-directed treatment may reveal peripheral limitation, while improved conditioning may increase the exercise demand placed on an impaired lung. Serial physiological measurements can test whether the dominant limitation changes. Third, gerotherapy combinations should be compared with exercise alone using prespecified interaction hypotheses, functional primary endpoints, and systematic harm assessment.

We emphasize the limitation that our review spans different populations, test methods, and follow-up periods. Disease-specific treatment effects cannot be generalized to normal aging, and biochemical effects in one tissue need not predict another. Much of the mortality evidence is observational; gerotherapy trials are frequently small or short, with exploratory outcomes.

Conclusions

Respiratory and aerobic reserve provide complementary ways to consider the capacity needed for independence and recovery across aging. Pulmonary maintenance, oxygen delivery, skeletal muscle function, and task demand interact, so a low resting measurement or a favorable molecular marker cannot identify the entire therapeutic opportunity. Joint physiological assessment can help locate modifiable limitations while preserving the distinction between developmental history, disease, and aging.

Established interventions demonstrate that function, disability risk, and survival can improve in defined populations, often without normalization of every pulmonary measurement. Emerging gerotherapies require evaluation of tissue specificity, exercise interactions, durable patient benefit, and harm. Longevity medicine is strengthened when therapeutic claims follow the evidence from mechanism to physiological change and then to meaningful clinical outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

The authors acknowledge the use of GPT 5.6 Sol (OpenAI, San Francisco CA, USA) to improve the linguistic clarity and readability of the manuscript. All scientific ideas, conceptual development, critical interpretation of evidence, and formulation of conclusions are the work of the authors, who retain full responsibility for the scientific content of this manuscript.

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