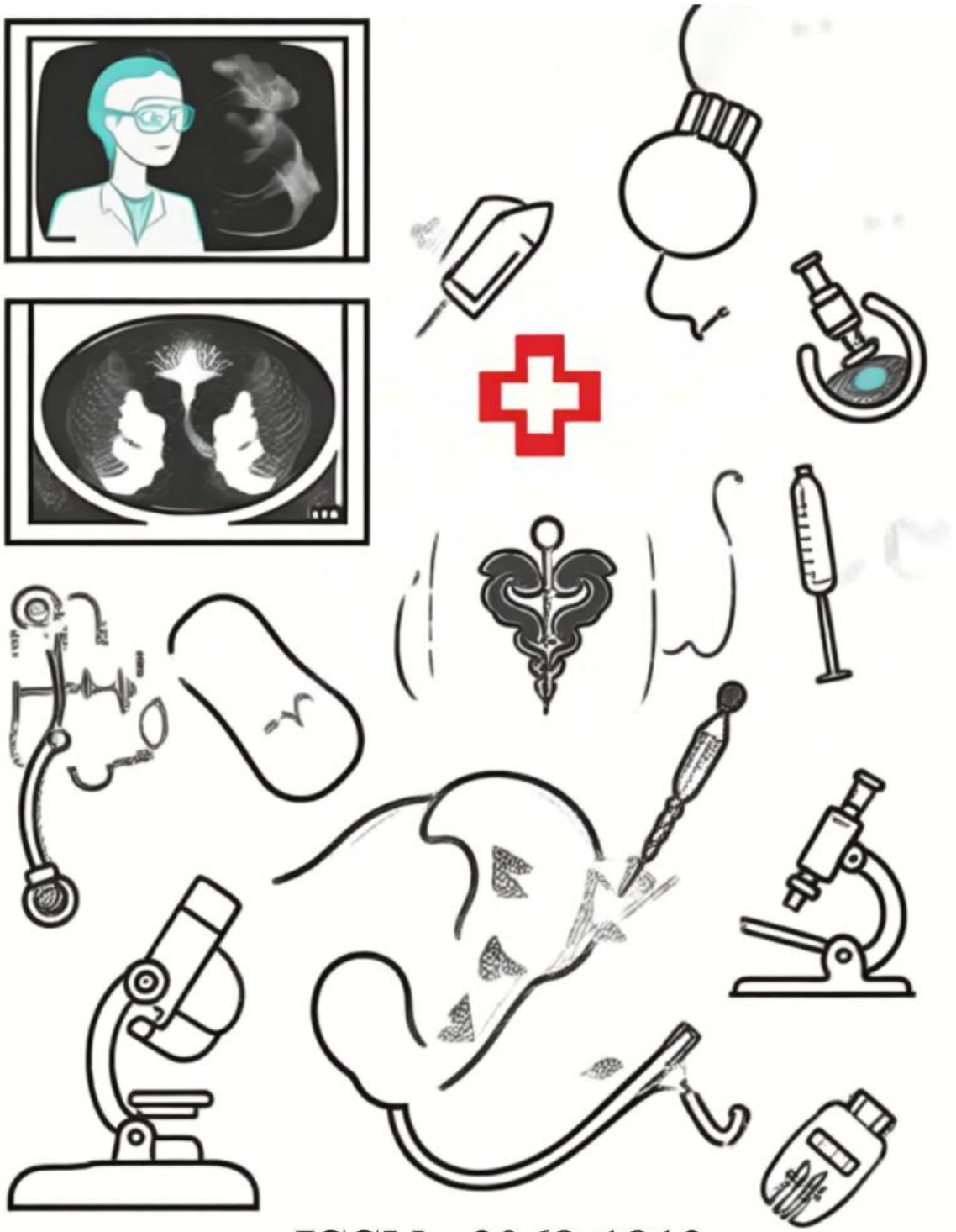
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Targeting mTORC1 and AMPK Signaling: Potential Therapeutic Approaches for Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive disease characterized by increasing incidence and mortality. The underlying mechanisms of IPF remain poorly understood, contributing to the limited availability of effective treatments. Current therapies mainly slow disease progression but fail to provide a cure. Consequently, increasing attention has been directed toward modulating signaling pathways such as mammalian target of rapamycin complex 1(mTORC1) and Adenosine monophosphate–activated protein kinase (AMPK), both of which are key regulators of metabolic reprogramming in IPF. This review summarizes recent advances in therapeutic strategies that target cellular metabolism by modulating mTORC1 and AMPK.

Keywords: Idiopathic Pulmonary Fibrosis; AMPK; mTORC1; Metabolic Reprogramming

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a prototypical interstitial lung disease (ILD) characterized by a progressive respiratory decline of unknown onset, with a median survival of 3–5 years after diagnosis in the absence of treatment (Lederer & Martinez, 2018). Since 2000, the age-standardized mortality rate has ranged from 0.5--12 per 100,000 persons annually, imposing a substantial socioeconomic burden comparable to that of malignancies such as pancreatic or prostate cancer (Ferlay et al., 2015; Zheng et al., 2022). Another study reported that IPF-related mortality has increased across Europe, with more than 17,000 deaths annually between 2013 and 2018 (Gonnelli et al., 2024).

Although the exact etiology of IPF remains idiopathic, several risk factors have been identified that contribute to disease susceptibility and progression. Advanced age (typically over 60 years) is a primary risk factor, with aging-related cellular senescence and telomere shortening playing key roles (Zaman & Lee, 2018). Males are disproportionately affected, potentially due to hormonal or

genetic influences (Kalafatis et al., 2019). Cigarette smoking is the strongest environmental risk factor, causing chronic epithelial injury and promoting fibrosis through oxidative stress and inflammation (Oh et al., 2012). Genetic predispositions, such as polymorphisms in the MUC5B promoter gene or mutations in telomere-related genes (e.g., TERT, TERC), increase familial risk and are found in up to 30% of cases (Park et al., 2021). Occupational and environmental exposures, including metal dust, wood dust, air pollution, and agricultural work, have also been linked to increased incidence, likely via repetitive microinjuries to the lung epithelium (Sack & Raghu, 2019). Additionally, comorbidities such as gastroesophageal reflux disease (GERD) may exacerbate fibrosis through microaspiration (Mei et al., 2022). The major risk factors contributing to IPF pathogenesis are summarized in Figure 1.

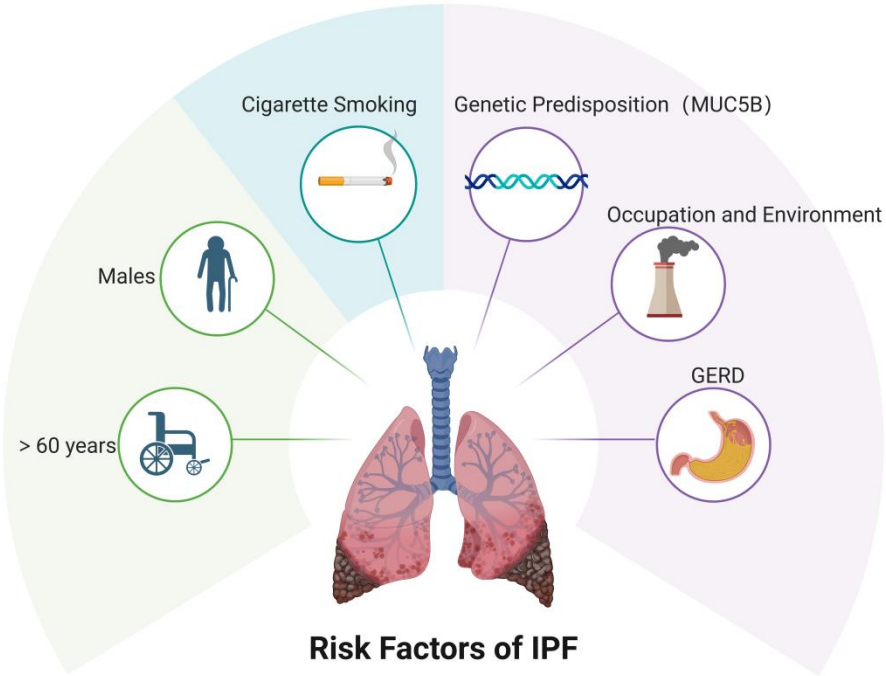


Figure 1.This diagram centers on the lungs and illustrates the primary risk factors for IPF

The main pathological features of IPF include diffuse alveolitis, extracellular matrix deposition, and fibroblast proliferation. These processes lead to characteristic histopathological findings, such as honeycomb cysts, fibroblastic foci, and hyperplastic epithelial cells, which reflect recurrent remodeling of the interstitium, distal airways, and alveolar spaces following abnormal injury and repair.

Current standard antifibrotic therapies are limited to pirfenidone and nintedanib. Pirfenidone has been shown to modulate the activity of transforming growth factor-β1 (TGF-β1) and tumor necrosis factor-α (TNF-α) while suppressing collagen synthesis and fibroblast proliferation. Nintedanib acts as a tyrosine kinase inhibitor, targeting the kinase activity of platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor receptors (Wollin et al., 2014). A recent randomized controlled trial demonstrated that pirfenidone- and nintedanib-

treated groups presented no significant differences in overall survival or hospitalization at the 24-month follow-up (Kim et al., 2024). However, frequent acute exacerbations, continued disease progression, and adverse events—such as photosensitivity, nausea, diarrhea, and liver dysfunction—often lead to treatment discontinuation (Takehara et al., 2022). Moreover, although these drugs slow disease progression, they neither halt nor reverse the course of IPF (Noble et al., 2016; Richeldi et al., 2014).

Accurate HRCT pattern classification—usual interstitial pneumonia (UIP), probable UIP, indeterminate UIP, or an alternative diagnosis—directly shapes the diagnostic pathway and the need for surgical/cryobiopsy. Misclassification delays antifibrotic initiation and confounds trial eligibility. Epidemiology indicates a rising global incidence with regional heterogeneity, whereas common comorbidities (e.g., GERD, OSA, metabolic syndrome) modulate trajectories and may intersect with the metabolic rewiring discussed below (Hutchinson et al., 2015; Raghu et al., 2018, 2022).

Therefore, metabolic reprogramming may offer a novel perspective on the mechanisms and treatment of IPF. The increased expression of glycolytic- and glutaminolytic-related enzymes and proteins in lung fibroblasts indicates enhanced glycolysis (Andrianifahanana et al., 2016) and glutaminolysis (Nigdelioglu et al., 2016; Selvarajah et al., 2019) as hallmarks of fibrotic metabolism. In IPF, both fibrotic and nonfibrotic regions show increased 18F-FDG uptake on PET–CT, reflecting enhanced glycolysis (Groves et al., 2009). Moreover, antifibrotic agents reduce this uptake in a bleomycin-induced murine model (Bondue et al., 2019). During fibrogenesis, metabolic reprogramming contributes to collagen synthesis as well as fibroblast proliferation and differentiation.

Adenosine monophosphate–activated protein kinase (AMPK) (Steinberg & Hardie, 2023) and the mammalian target of rapamycin complex 1(mTORC1) (Kim & Guan, 2015) function as master regulators and signal transducers of cellular metabolism and are closely associated with energy homeostasis, cell growth, autophagy, and apoptosis. Emerging experimental evidence indicates that this axis plays a pivotal role in various cancers and nonneoplastic diseases, including IPF. The interactions and regulatory networks among AMPK, mTORC1, and other signaling pathways reveal potential therapeutic targets. Increasing evidence suggests that the antidiabetic drug metformin and the lipid-lowering agent ezetimibe are promising candidates for repurposing in IPF.

2. Detailed Exploration of mTORC1 and AMPK as Central Regulators

AMPK, which is composed of three subunits, is regulated by the intracellular AMP/ATP ratio and functions as a cellular energy sensor by activating catabolic pathways to maintain energy homeostasis. When energy levels decrease, AMPK becomes phosphorylated, thereby stimulating ATP production. AMPK activation not only regulates energy balance through glucose and lipid metabolism but also exerts protective effects in IPF by reducing inflammation, epithelial–mesenchymal transition (EMT), oxidative stress, and extracellular matrix (ECM) production while inhibiting fibroblast activation and promoting fibroblast apoptosis (Yang et al., 2024). For

example, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), an AMPK activator, enhances p-AMPK expression and reduces α-SMA levels in TGF-β–treated primary lung fibroblasts (Rangarajan et al., 2018).

Several studies have demonstrated the associations among pulmonary fibrosis, agent-induced AMPK phosphorylation, and downstream biomarkers. Alpha-mangostin (α-MG), a compound extracted from mangosteen fruit, increased the p-AMPK/AMPK ratio, inhibited Smad2/3 phosphorylation and NOX4 protein expression, and consequently reduced α-SMA and collagen I levels in the lung tissue of a bleomycin-induced murine model (Li et al., 2019). Similarly, mogrol and bryodulоglucinol modulate AMPK/NOX4 signaling to reduce reactive oxygen species (ROS) production and attenuate fibrosis (Ding et al., 2022; B. Liu et al., 2021). With respect to Smad2/3, one study reported that cereblon-induced Smad3 activation promoted fibrosis by suppressing AMPK activity (Kang et al., 2021).

Mammalian target of rapamycin (mTOR), a downstream effector of AMPK, is a serine/threonine kinase belonging to the phosphatidylinositol 3-kinase (PI3K)-related family. It has been reported to mediate TGF-β1–induced profibrotic responses by promoting fibroblast proliferation (Saxton & Sabatini, 2017). mTOR complex 1 (mTORC1), which contains mTOR, is involved in multiple cellular processes, including metabolism, protein synthesis, autophagy, and cell proliferation and growth. Woodcock et al. reported that TGF-β1 activated mTORC1 and its downstream effector 4E-binding protein 1 (4E-BP1) (Woodcock et al., 2019). The subsequent activation of mTORC1 and 4E-BP1 induces the synthesis of activating transcription factor 4 (ATF4), which enhances the de novo serine–glycine biosynthetic pathway to meet increased collagen production demands (Selvarajah et al., 2019). Moreover, mTORC1 and ATF4 play central roles in TGF-β1–induced metabolic reprogramming. Rapamycin, an allosteric inhibitor of mTORC, was unable to suppress ATF4 activation. In contrast, Rapalink-1, which specifically inhibits the mTORC1 kinase domain, effectively prevents ATF4 activation and collagen accumulation (O'Leary et al., 2020).

These data place the 4E-BP1–ATF4 axis at the center of collagen anabolism: ATF4-driven serine–glycine/one-carbon metabolism supplies glycine for procollagen, whereas selective 4E-BP1 control of translation explains why rapamycin underperforms ATP-competitive mTORC1 inhibitors against matrix accumulation (Kang et al., 2013a; O'Leary et al., 2020; Selvarajah et al., 2019; Woodcock et al., 2019).

The interplay between AMPK and mTORC1 was partially elucidated in a previous study (Y. C. Kim & Guan, 2015). On the one hand, when the AMP/ATP ratio is elevated, AMPK becomes phosphorylated and activates tuberous sclerosis complex 2 (TSC2), which subsequently regulates Ras homolog enriched in the brain (Rheb), a potent activator of mTORC1. Rheb, in turn, activates mTORC1. On the other hand, AMPK directly regulates mTORC1 by phosphorylating RAPTOR, a key component of the complex (Gwinn et al., 2008).

Mechanistically, AMPK imposes dual brakes on mTORC1 via TSC2 and RAPTOR and couples energy stress to autophagy through ULK1. This forms a tractable 'push–pull' model in which AMPK agonism restores collagen turnover, whereas ATP-competitive mTORC1 blockade

suppresses ATF4-dependent translation—providing rational synergy (Gwinn et al., 2008; Hardie, 2011; Zhao & Klionsky, 2011).

Independent of AMPK activation, the PI3K–AKT–mTOR pathway lies downstream of receptor tyrosine kinases (RTKs) and has previously been proposed as an important therapeutic target in non-small cell lung cancer (NSCLC) (Zeng et al., 2025). The inhibition of mTOR through this pathway may also provide new therapeutic strategies against pulmonary fibrosis. A previous study demonstrated that omipalisib, a pan-PI3K and dual mTOR inhibitor, reduced AKT phosphorylation in IPF lung slices, thereby attenuating fibroblast proliferation and TGF-β1–induced collagen production (Mercer et al., 2016). A randomized, placebo-controlled trial confirmed the pharmacological effects of short-term oral omipalisib administration in IPF patients and further demonstrated limited adverse events with notable tolerability (Lukey et al., 2019). However, another study from the same period reported that mTOR did not depend primarily on upstream PI3K–AKT signaling for its fibrogenic effects, challenging earlier mechanistic assumptions (Woodcock et al., 2019). In support of this view, during TGF-β1 signaling, maximal phosphorylation of mTORC1 substrates occurs approximately 10 hours before peak AKT phosphorylation. Moreover, inhibition of PI3K or AKT alone did not affect downstream mTORC1 activity. Furthermore, 4E-BP1, but not p70S6K, was identified as the key downstream effector of mTORC1 that is responsible for promoting collagen synthesis. Conclusive evidence has shown that rapamycin, an allosteric inhibitor that selectively attenuates the phosphorylation of p70S6K and 4E-BP1 (Ser65), has no effect on TGF-β1–induced collagen deposition. In contrast, ATP-competitive mTOR inhibitors profoundly suppressed fibrosis by completely blocking 4E-BP1 phosphorylation at Thr37/46 and Ser65 (Kang et al., 2013b).

In summary, simultaneous activation of AMPK, suppression of mTORC1, and modulation of the AMPK/mTORC1 axis represent feasible strategies for agents to exert antifibrotic effects.

3. Emerging Therapeutic Strategies

3.1. Effects of Metformin in IPF Treatment

The first-line antidiabetic drug metformin exerts pleiotropic pharmacological effects and has been shown to reverse established fibrosis in IPF lungs as well as in models of bleomycin- or TGF-β1–induced lung injury.

Metformin was previously shown to attenuate TGF-β–induced lung fibrosis in vitro, as evidenced by immunofluorescence staining of α-smooth muscle actin (α-SMA) and concomitant decreases in phosphorylated SMAD2/3, STAT3, AKT, and ERK1/2 (L. Li et al., 2015). Although metformin downregulated TGF-β downstream signaling and associated biomarkers, this effect was abolished in the presence of an AMPK inhibitor. Thus, metformin attenuates TGF-β–induced fibrosis in an AMPK-dependent manner. NADPH oxidase 4 (NOX4), an isoform of the NOX family, has been identified as a modulator of TGF-β1/SMAD signaling through the regulation of intracellular reactive oxygen species (ROS) levels. Elevated NOX4 expression has been observed in myofibroblasts from IPF patients. Despite substantial NOX4 expression, bleomycin induced increased SMAD2/3 phosphorylation and ROS production. Metformin treatment, similar to

NOX4 knockdown or AMPK activation–mediated NOX4 suppression, significantly counteracted these effects (Sato et al., 2016). This study explicitly demonstrated that the inhibition of NOX4-induced ROS production and p-SMAD expression is a key component of the antifibrotic mechanism of metformin.

Another study revealed that bleomycin treatment resulted in increased inflammatory cell infiltration, alveolar remodeling, and fibrotic deposition, as evidenced by H&E staining. However, low- and medium-dose metformin pretreatment had minimal effects on extracellular matrix deposition, whereas only the highest dose significantly suppressed fibrotic pathology (Gamad et al., 2018). Moreover, unlike lower doses, high-dose metformin (500 mg/kg/day) markedly mitigated bleomycin-induced weight loss in rats. Both medium- and high-dose metformin reduced inflammatory cell infiltration. The dose-dependent effects of metformin on weight loss and inflammatory cell infiltration are summarized in Figure 2. Further studies are needed to clarify the optimal dosing regimen and initiation time of metformin treatment.

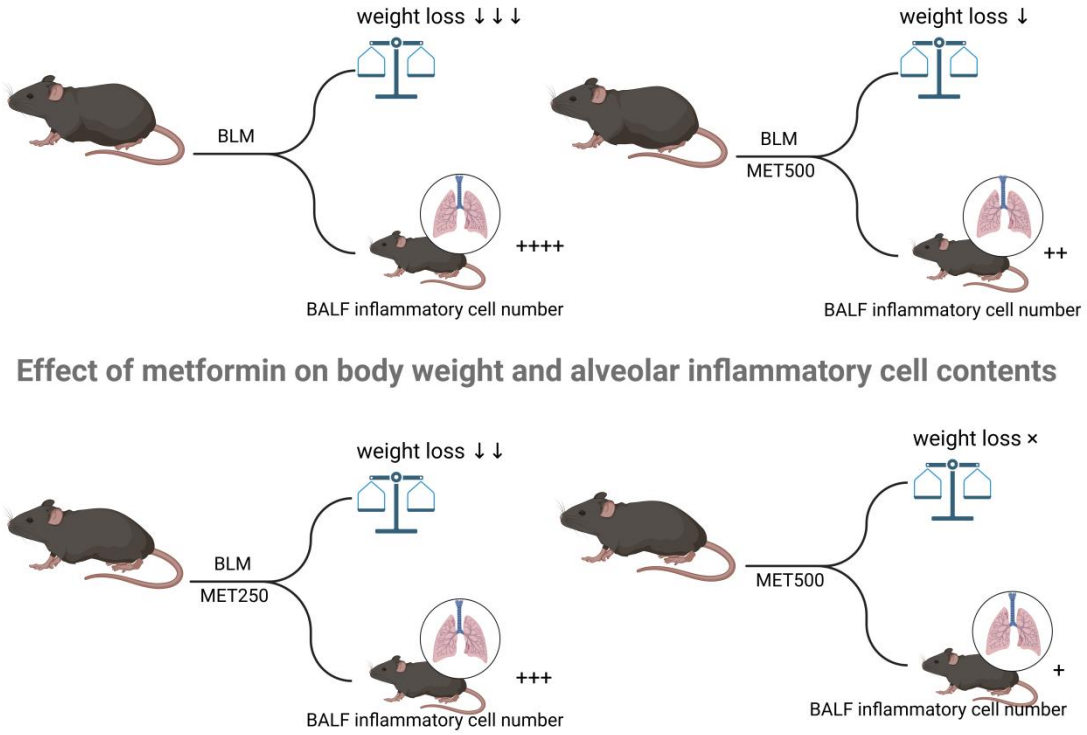


Figure 2. Dose-Dependent Effects of Metformin on Bleomycin-Induced Weight Loss and BALF Inflammatory Cell Infiltration in Rats.

Rangarajan et al. demonstrated that autophagy was partly dependent on AMPK activation and contributed to the regulation of collagen accumulation. When autophagy is inhibited by chloroquine in TGF-β1–treated fibroblasts, collagen turnover within autophagosomes increases (Rangarajan et al., 2018). Silencing the well-recognized upstream regulator AMPK consequently enhances extracellular matrix (ECM) deposition. In addition, AMPK activation reversed resistance to apoptosis by promoting mitochondrial biogenesis. In summary, AMPK-induced

autophagy and the restoration of apoptosis play important roles in fibroblast regulation, although downstream signaling events require further elucidation.

Micrometer-thick precision-cut lung slices (PCLS), derived from fibrotic regions of IPF patient lung tissue, serve as an ex vivo culture system. Compared with conventional cell culture systems, PCLS closely mimics the complex architecture of the respiratory system and provides more flexible, well-ventilated spaces. Another original research study replicated the effects of metformin in PCLS models (Kheirollahi et al., 2019). After 5 days of metformin treatment, significant improvements in lung structure and reduced collagen deposition were observed via hematoxylin and eosin staining, Masson's trichrome staining, and COL1A1 immunostaining. Three-dimensional reconstruction and flow cytometry–based quantification revealed an increased abundance of lipid droplets and lipid-containing cells. Further investigation via genetic labeling revealed that metformin promoted myogenic-to-lipogenic conversion of cells, an effect not observed with pirfenidone or nintedanib. However, this lipogenic differentiation is dependent on the BMP2 and PPARγ signaling pathways and is largely independent of AMPK, which is closely associated with ECM regulation.

Integrating across models, metformin engages at least three axes: (i) NOX4–ROS–SMAD dampening; (ii) AMPK–ULK1–autophagy restoration with reversal of apoptosis resistance; and (iii) BMP2–PPARγ-driven myogenic–to-lipogenic conversion in human PCLs, largely AMPK light. These programs explain both the reduction in the ECM and the reprogramming of the cell state (Kheirollahi et al., 2019; Rangarajan et al., 2018; Sato et al., 2016).

Fibroblast proliferation is considered one of the prominent features of pulmonary fibrosis. Forkhead box M1 (FOXM1), a member of the transcription factor family, is a key regulator of fibroblast activation and fibrotic progression (Penke et al., n.d.). Xuan Gu et al. further clarified the relationships among AMPK, FOXM1, and fibroblasts. In bleomycin-induced pulmonary fibrosis in mice, metformin treatment suppressed the expression of FOXM1 and Cyclin D1, a marker of the proliferative phenotype (Gu et al., 2021). In contrast, treatment with the AMPK inhibitor compound C led to AMPK deactivation and increased FOXM1 expression. Therefore, it was concluded that metformin-induced AMPK activation suppresses pathological fibroblast proliferation by downregulating FOXM1.

Recently, another AMPK downstream signaling pathway has been partially elucidated. Bone morphogenetic protein 9 (BMP9) promotes fibroblast activation through activin receptor-like kinase 1 (ALK1) and Smad1/5 signaling (Wang et al., 2021). Metformin promoted AMPK activation, suppressed BMP9 signaling, and subsequently downregulated ALK1 and Smad1/5, thereby reducing fibroblast proliferation and differentiation in vitro (Chen et al., 2022).

Elevated S100A4 expression—formerly regarded as a marker of fibroblast presence—has been reported in the bronchoalveolar lavage fluid (BALF) of IPF patients and in fibroblasts from bleomycin-induced rats, suggesting that S100A4 contributes to IPF pathogenesis (Gu et al., 2021; Lee et al., 2020). A recent study by Huimin Ji et al. elucidated how metformin attenuates fibrosis through the AMPK–STAT3–S100A4 axis, with STAT3 being a member of the STAT family activated by TGF-β1 (Ji et al., 2023). They first confirmed that metformin-mediated antifibrotic

effects in vivo were accompanied by reduced S100A4 protein levels and decreased STAT3 phosphorylation. Both pharmacological inhibition of STAT3 phosphorylation by the small-molecule inhibitor stattic and AMPK activation by metformin suppressed S100A4 expression and ultimately reduced α-SMA deposition.

Moreover, a meta-analysis demonstrated that metformin significantly reduced inflammation, fibrosis, and fibrosis-associated biomarkers (Wu et al., 2022). Furthermore, compared with the control diet, metformin significantly reduced mortality.

Future clinical studies should compare the side-effect profiles of metformin with those of pirfenidone and nintedanib and address potential safety concerns. The most common side effects are gastrointestinal (GIT) disturbances, including diarrhea, nausea, and abdominal pain, which are dose dependent and generally transient. These effects can be minimized by gradually increasing the metformin dosage (Akhter & Uppal, 2020; Feng et al., 2022). Rarely, metformin may cause lactic acidosis (MALA), a serious condition that can result in cardiovascular or renal failure, particularly in patients with hepatic or renal impairment (Brackett, 2010). The long-term use of vitamin B12 has been associated with vitamin B12 deficiency, although its clinical significance remains unclear (Aroda et al., 2016). In addition, the relatively low cost of metformin may make it a more sustainable option for patients than the considerably more expensive pirfenidone and nintedanib (Teague et al., 2022).

Clinical translation should prioritize lung tissue exposure mapping, stratification by metabolic comorbidity, and combination with pirfenidone or nintedanib. In human data, the results are mixed: a national claims-based cohort of IPF patients with T2D reported an association between metformin use and lower mortality/hospitalization (Teague et al., 2022), whereas a post hoc analysis of three phase III pirfenidone trials revealed no effect on clinically relevant outcomes (Spagnolo et al., 2018). Embedding pharmacodynamic biomarkers—LC3-II in PCLS, circulating long-chain acyl-carnitines/metabolomic signatures, and quantitative HRCT metrics (CALIPER/DTA)—can reduce the risk in phase II/III trials (Humphries et al., 2017; Kheirollahi et al., 2019; Maldonado et al., 2014; Rindlisbacher et al., 2018).

3.2. Ezetimibe in IPF Treatment

Ezetimibe, a drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypercholesterolemia, acts by inhibiting the intestinal cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1) (Garcia-Calvo et al., 2005).

Lee YS et al. further demonstrated that ezetimibe inhibited adipogenesis primarily by increasing AMPK activation and subsequently suppressing mTORC1 signaling, thereby halting cell proliferation and exerting antiobesity effects (Lee et al., 2020).

A recent article published in the European Respiratory Journal highlighted the therapeutic potential of the old drug ezetimibe for IPF, drawing extensively on findings from three major studies(Lee et al., 2024). Ezetimibe counteracted TGF-β1–induced COL1A1 expression in human and murine lung fibroblasts (hLFs/mLFs) in a dose- and time-dependent manner, with 20 μM treatment for 24 hours restoring COL1A1 and ACTA2 levels to near baseline. mRNA sequencing further revealed that ezetimibe reduced the expression of TGF-β1–induced myofibroblast markers

and increased the expression of autophagy-related genes. Gene set enrichment analysis revealed downregulation of fibrosis-associated genes and upregulation of autophagy-related genes. Using fluorescent protein–tagged LC3 transgenic mLFs, researchers reported increased LC3 conversion, accumulation of free GFP fragments, and increased numbers of autophagosomes and autolysosomes, indicating increased autophagic flux. Serum response factor (SRF) was subsequently identified as an autophagic substrate that is degraded through ezetimibe-induced autophagy. The study also demonstrated reduced phosphorylation of P70S6K and RPS6, downstream targets of the mTORC1 axis. mTORC1 activity was shown to be regulated by lysosomal cholesterol, whereas ezetimibe redistributed intracellular cholesterol without altering total cellular cholesterol levels. Additionally, a second study effectively replicated the in vitro findings in vivo, yielding consistent results. A third study suggested that ezetimibe, either as monotherapy or in combination with pirfenidone, may improve overall survival and reduce all-cause mortality in IPF patients. Ezetimibe also showed potential as a standalone therapy to improve lung function, with better FVC and DLCO outcomes than pirfenidone alone. Collectively, ezetimibe inhibits myofibroblast differentiation by targeting the mTORC1–autophagy axis and regulating cholesterol distribution. In IPF patients, it reduces mortality and slows the decline in lung function.

Mechanistic nuance: ezetimibe alters lysosomal cholesterol distribution without lowering total cholesterol, thereby tuning lysosomal mTORC1 signaling and permitting SRF degradation via increased autophagic flux—distinct from statins. These findings are consistent with those of fundamental studies on NPC1L1 targeting and lysosomal cholesterol–mTORC1 coupling (Castellano et al., 2017; Eid et al., 2017; Garcia-Calvo et al., 2005; Shin et al., 2022; Weinglass et al., 2008).

Notably, ezetimibe has a favorable safety profile and is characterized by mild and transient gastrointestinal side effects and rare serious adverse events. It is well tolerated and does not significantly increase the risk of major adverse events (Olmastroni et al., 2024).

3.3. AMPK-mTOR in IPF

The AMPK–SMAD/NOX4/FOXM1/BMP9/STAT3 pathways targeted by metformin are largely independent of mTOR. A previous study demonstrated that Smad3 knockdown attenuated mTORC1-mediated phosphorylation of p70S6K and 4E-BP1 while also reducing COL1A1 mRNA levels (Woodcock et al., 2019). On the basis of these findings, a pathway model in which Smad3 activation directly promotes early COL1A1 mRNA transcription while influencing 4E-BP1 through mTORC1 activation was proposed. This dual regulation further enhances COL1A1 expression and ultimately collagen synthesis (Verrecchia et al., 2001). Since AMPK activation inhibits mTOR through multiple routes—including the AMPK–Smad3–mTOR, AMPK–TSC–mTOR, and AMPK–RAPTOR–mTOR pathways—the AMPK–mTOR axis should be considered an important regulatory pathway.

The lipopolysaccharide (LPS)-induced cellular pulmonary fibrosis model is a promising system for studying IPF mechanisms and therapeutics, as LPS acts as an autophagy inhibitor that

promotes fibroblast proliferation through the mTOR pathway (Xie et al., 2019). Metformin was found to attenuate PFKFB3-catalyzed glycolysis following AMPK phosphorylation and mTORC1 inhibition, thereby reducing collagen production in LPS-induced lung fibroblasts, although this specific effect has not yet been validated in animal models (Tang et al., 2021). Given the extensive studies on the AMPK–mTOR pathway in relation to metformin, further efforts are needed to validate this signaling pathway and establish additional well-substantiated pathways. With respect to ezetimibe, previous studies have demonstrated that its effects on fibroblast autophagy are dependent mainly on lysosomal cholesterol distribution–regulated mTORC1 modulation. In contrast, ezetimibe-mediated regulation of the AMPK–mTOR pathway has been proposed to counteract adipogenesis and reduce lipogenesis. Therefore, no evidence currently supports an antifibrotic role of ezetimibe through the AMPK–mTORC1 pathway.

Other antifibrotic drugs also target the AMPK/mTOR pathway. M2 macrophages, which are derived from alveolar macrophages, secrete profibrotic mediators that promote fibrosis. Nobiletin (NOB), a flavonoid isolated from citrus peels, has been shown to protect the liver from damage and ameliorate lung fibrosis (Dusabimana et al., 2019). One study demonstrated that NOB activated AMPK phosphorylation and inhibited mTOR, thereby enhancing autophagy. As a result, increased autophagy reduces M2 macrophage polarization and alleviates pulmonary fibrosis (Cheng et al., 2024). Furthermore, fenbendazole (FBZ), a benzimidazole compound used to treat parasitic infections and suppress cancer cell proliferation, is noteworthy for its mild side effects and durable efficacy (DUAN et al., 2013). Previous studies have shown that, in fibroblasts, FBZ activated AMPK and suppressed mTOR, thereby reprogramming glycolysis and the glycolytic capacity. This process, in turn, inhibits fibroblast proliferation and differentiation (Wang et al., 2022). The integrated AMPK–mTORC1 signaling network and its pharmacological modulators are schematically illustrated in Figure 3.

Taken together, these findings indicate that mTORC1 activity is elevated, whereas AMPK is deactivated in the lung tissue of IPF patients (Rangarajan et al., 2018). Only a few studies have investigated how drugs or reagents influence mTOR through AMPK and whether their mechanisms rely on AMPK activation, direct mTOR inhibition, or both. Moreover, no evidence has yet clarified which specific AMPK–mTOR pathway exerts the most potent antifibrotic effect. In addition, further studies are needed to explore the potential side effects associated with prolonged AMPK activation and/or mTOR inhibition and to determine whether long-term modulation of mTOR or other AMPK downstream pathways alone would result in fewer adverse effects than multipathway interventions. Furthermore, whether there is a connection between Smad3 downstream of AMPK and PFKFB3 downstream of mTORC1 and whether Smad3 is involved in mTORC1-associated autophagy remain unknown. Finally, comparisons between antifibrotic agents targeting AMPK and/or mTOR require further validation through meta-analyses, randomized controlled trials, and cohort studies. For example, ezetimibe induces autophagy via lysosomal cholesterol–mediated modulation of mTORC1, whereas metformin induces autophagy via AMPK activation. Future research should therefore compare the therapeutic efficacy of these two drugs and evaluate their long-term effects.

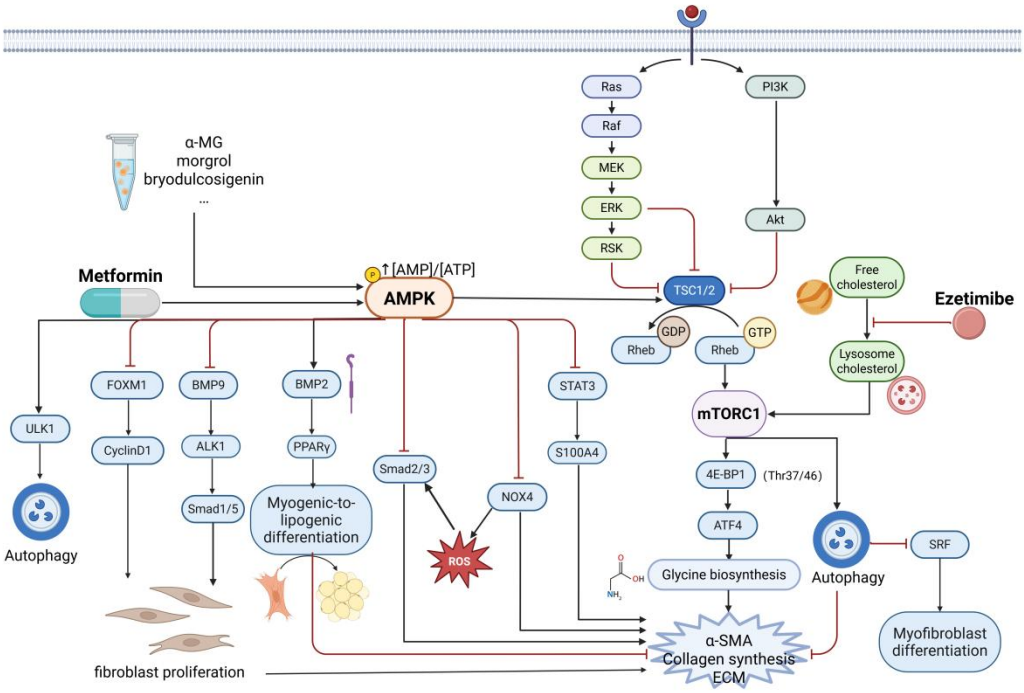


Figure 3. Schematic Overview of AMPK-mTORC1 Signaling Axis in Pulmonary Fibrosis and Pharmacological Modulators.

4. Strategic Targeting of the AMPK–mTORC1 Axis: Comparative Evaluation and Therapeutic Prioritization

The evidence above suggests that AMPK activation and mTORC1 inhibition exert their anti-fibrotic effects through interconnected but mechanistically different pathways. These interventions are not isolated pharmacological approaches, but rather can be viewed as complementary strategies targeting different regulatory levels of the AMPK-mTORC1 axis. AMPK activators, including metformin and several natural compounds, primarily restore cellular energy balance and enhance autophagic flux, thereby inhibiting fibroblast proliferation and extracellular matrix accumulation. In contrast, ATP-competitive mTORC1 inhibitors more directly inhibit collagen biosynthesis by blocking the 4E-BP1-ATF4 translational program, acting on the synthetic core of fibrosis formation. Ezetimibe represents a different mechanism, promoting the autophagic degradation of pro-fibrotic mediators by modulating lysosomal cholesterol-dependent mTORC1 activation without globally activating AMPK. From a translational medicine perspective, AMPK activation currently has the broadest experimental support, particularly in models that partially reverse established fibrosis. Direct inhibition of mTORC1 has strong mechanistic potency, but long-term safety needs careful evaluation, as sustained inhibition of mTOR may interfere with epithelial regeneration and host defense. Repositioned drugs such as metformin and ezetimibe benefit from their established human safety profiles, supporting their priority consideration in combination strategies. In summary, the development of effective treatments for idiopathic pulmonary fibrosis (IPF) may not depend on the inhibition of a single node, but rather on the strategic modulation of the AMPK-mTORC1 axis

to achieve a balance between restoring metabolism and inhibiting the synthesis of pathological proteins.

5. Challenges in Translating Preclinical Findings to Clinical Applications

To better simulate human IPF, complementary models are needed. Silica and radiation injury yield more persistent lesions than bleomycin does, whereas telomerase-deficient mice recapitulate aging-related susceptibility. Human organoids and precision-cut lung slices (PCLS) preserve epithelial–mesenchymal interactions and allow the quantification of autophagy and ECM remodeling under defined metabolic cues. Importantly, translational feasibility is underscored by pan-PI3K/mTOR inhibitors such as omipalisib, where preclinical antifibrotic efficacy has been bridged into early-phase clinical trials (Lukey et al., 2019; Mercer et al., 2016).

First, primary fibroblast cultures from healthy donors or IPF patients exhibit variability in growth and gene expression. Thus, the use of more practical and stable fibroblast lines is limited. A recent study proposed WI-38 cells, a human embryonic lung fibroblast line, as a reliable and consistent model for investigating fibroblast biology in lung fibrosis(Vásquez-Pacheco et al., 2024). This study compared WI-38 cells with primary IPF fibroblasts by inducing myofibroblast differentiation with TGF-β1 and lipofibroblast transition with metformin, followed by phenotypic and transcriptomic analyses using fibroblast-specific markers to validate and replicate research on the antifibrotic effects of metformin. Moreover, although the bleomycin-induced lung injury mouse model is the most commonly used model for studying lung fibrosis, it tends to heal spontaneously over time. In future studies, more stable models that closely mimic the pathology of IPF or patient-derived fibroblasts will be essential.

In addition, further studies are needed to explore the effects of metformin (MET) on downstream AMPK mechanisms and additional antifibrotic actions, although previous research has clarified some aspects of AMPK downstream signaling.

A key challenge in transitioning to clinical trials is optimizing the drug dosage, as metformin (MET) must be effectively delivered to the lungs for IPF treatment. Previous in vitro studies have shown that low doses of MET have minimal effects on reducing collagen deposition and lung structural deformation. Preclinical studies have used higher doses to achieve adequate lung concentrations, highlighting the need for tailored dosing strategies in clinical practice. IPF patients also exhibit individual variability in disease progression, family history, imaging features, comorbidities, and other relevant factors. A cohort analysis demonstrated that MET therapy was superior to pirfenidone and nintedanib in reducing all-cause mortality and hospitalization among IPF patients with diabetes (Teague et al., 2022). Future efficacy studies of MET should incorporate a broader range of comorbidities, allowing MET to be prioritized over traditional medications in IPF patients with specific coexisting conditions.

Moreover, a retrospective analysis revealed no effect of MET on the prognosis of IPF patients, which conflicts with findings from clinical trials (Spagnolo et al., 2018). Unfortunately, the study had several limitations, including a small sample size, the exclusion of late-stage patients and those with comorbidities, inconsistent durations of MET use (with some patients using it for only

a few days), and uncertainty regarding treatment adherence and potential drug interactions. In summary, future observational or experimental studies on MET for IPF should include larger, more comprehensive patient cohorts to ensure that findings are generalizable to the broader IPF population. Standardizing the duration of MET treatment, monitoring adherence to MET regimens under real-world conditions, and examining potential interactions with other commonly used medications in IPF patients will be crucial for understanding its long-term effects.

With respect to ezetimibe, studies on its antifibrotic efficacy are limited. The aforementioned research suggests that ezetimibe may act through the mTORC1–autophagy axis; however, its exact molecular targets and pathways remain incompletely understood. Since AMPK is involved in autophagy regulation, further investigation is needed to determine whether ezetimibe activates AMPK to influence autophagic degradation. Given that ezetimibe reduces lysosomal cholesterol content, future studies should examine how lysosomal cholesterol levels affect fibroblast differentiation, autophagic activity, and extracellular matrix (ECM) remodeling. The effects of ezetimibe on the SRF-mediated transcription of profibrotic genes, myofibroblast activation, and ECM accumulation also remain unclear. A detailed analysis of whether SRF cooperates with other pathways in response to ezetimibe treatment could help identify new antifibrotic mechanisms. Moreover, preclinical studies should include more animal models with established fibrosis, and clinical trials should monitor biomarkers of autophagy (such as LC3-II), cholesterol metabolism, and SRF activity in IPF patients. Metformin in combination with simvastatin has previously been studied in glioma progression via metabolic modulation, although through mechanisms distinct from antifibrosis (Qiao et al., 2024). Nevertheless, it is possible to treat IPF with multidrug combinations or by adding new agents to classical antifibrotic therapies. For example, a recent study demonstrated that metformin enhances the antifibrotic effects of pirfenidone, potentially through mechanisms involving oxidative stress reduction and NOX4 inhibition(Liu et al., 2024). These findings have greatly broadened the understanding of novel therapeutic strategies for IPF.

6. Conclusions

In summary, mounting evidence suggests that the AMPK-mTORC1 signaling axis is a core regulatory node in metabolic reprogramming in idiopathic pulmonary fibrosis. Dysregulation of this axis leads to persistent fibroblast activation, enhanced collagen biosynthesis, and impaired autophagy turnover.

Therapeutic strategies that restore AMPK activity, selectively inhibit mTORC1-dependent translation, or modulate lysosomal nutrient sensing offer mechanistically evidence-based approaches to halting fibrosis progression. Among current drug candidates, approved drugs such as metformin and ezetimibe offer practical opportunities for translation due to their established safety profiles, while selective mTORC1 inhibitors highlight the importance of targeting collagen synthesis at the level of translational control.

Future advancements in the treatment of idiopathic pulmonary fibrosis (IPF) may require fine-tuning of the AMPK-mTORC1 axis rather than broad metabolic inhibition, focusing on long-term

tolerability, pathway-specific biomarkers, and rational combination therapy strategies. Continuing to integrate mechanistic insights with translational research is crucial for developing more effective and sustainable treatments for IPF.

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Advances in Low-Concentration Atropine and Optical Interventions for Myopia Control

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Abstract

Myopia has become a global public health challenge, with its prevalence reaching epidemic proportions in recent decades, particularly in East Asian countries. This comprehensive review synthesizes recent evidence from clinical studies and meta-analyses to examine the efficacy and safety of low-concentration atropine and optical interventions for controlling myopia progression in children and adolescents. We show that low-concentration atropine (specifically 0.01%, 0.025%, and 0.05%) effectively slows myopia progression with a favorable safety profile. Furthermore, we evaluate optical interventions including orthokeratology (Ortho-K), Defocus Incorporated Multiple Segments (DIMS) spectacles, and peripheral progressive addition lenses. Emerging evidence suggests that combination therapy, integrating low-concentration atropine with an optical intervention, may yield superior effects compared to either modality alone. This review also discusses key issues such as treatment personalization, long-term adherence, and future research directions, providing evidence-based insights for clinicians managing childhood myopia.

Keywords: Myopia Control; Low-Concentration Atropine; Orthokeratology; Defocus Incorporated Multiple Segments (DIMS); Combination Therapy

1. Introduction

The global prevalence of myopia has increased at an alarming rate, with projections indicating that nearly half the world's population will be affected by 2050 (Holden et al., 2016). This trend poses a significant public health challenge, as higher levels of myopia substantially increase the

lifetime risk of sight-threatening ocular pathologies such as myopic maculopathy, retinal detachment, glaucoma, and cataract (Flitcroft, 2012). The economic and social burdens associated with managing myopia and its complications are considerable, driving intense research into effective methods to control its progression, especially during childhood.

Current understanding attributes the myopia epidemic to complex gene-environment interactions, with prolonged near work and limited time outdoors identified as key modifiable risk factors (Holden et al., 2016). This has prompted the development of interventional strategies aiming to slow axial elongation, the primary anatomical correlate of myopia progression. Among these, pharmacological intervention with low-concentration atropine eye drops and optical interventions using specially designed contact lenses or spectacles have emerged as the most extensively studied and clinically adopted approaches (Yam et al., 2019; Lam et al., 2020).

The purpose of this review is to synthesize the current evidence regarding the use of low-concentration atropine and various optical interventions for myopia control in children and adolescents. We evaluate their respective efficacy, safety profiles, and proposed mechanisms of action. Furthermore, we explore the growing evidence base for combination therapy, which integrates these modalities. Finally, we highlight prevailing challenges, gaps in knowledge, and future directions for research and clinical practice in this rapidly evolving field.

2. Main Content

2.1. Low-Concentration Atropine

2.1.1. Efficacy of Different Concentrations

The concentration-dependent efficacy of atropine is well-established. Landmark studies like ATOM1 and ATOM2 demonstrated that while 1% atropine was highly effective, it caused significant side effects like photophobia and near blur; lower concentrations, particularly 0.01%, offered a better risk-benefit balance (Chia et al., 2016; Chua et al., 2006). The subsequent LAMP study provided a clearer hierarchy: 0.05% atropine was most effective in reducing spherical equivalent (SE) progression and axial elongation over three years, followed by 0.025% and 0.01%, all superior to placebo (Yam et al., 2019; Yam et al., 2022; Yam et al., 2020). Emerging evidence suggests dosing frequency matters; twice-daily administration of 0.01% atropine may enhance efficacy compared to once-daily, especially in younger children (Xu et al., 2025).

Table 1. Efficacy of Different Atropine Concentrations in Key Clinical Trials

Concentration	Study	Follow-up	SE Progression (D), Mean ± SD	Axial Elongation (mm), Mean ± SD	Side Effect Grade
1%	ATOM1 (Chua et al., 2006)	2 years	-0.28 ± 0.92	0.02 ± 0.35	Significant

0.5%	ATOM2 (Chia et al., 2016)	2 years	-0.30 ± 0.60	0.27 ± 0.25	Moderate
0.1%	ATOM2 (Chia et al., 2016)	2 years	-0.38 ± 0.60	0.28 ± 0.28	Moderate
0.05%	LAMP Year 1(Yam et al., 2019)	1 year	-0.27 ± 0.61	0.20 ± 0.25	Mild
	LAMP Year2(Yam et al., 2020)	2 years	-0.55 ± 0.85	0.35 ± 0.33	Mild
	LAMP Year3 (Yam et al., 2022)	3 years	-0.78 ± 1.05	0.50 ± 0.43	Mild
0.025%	LAMP Year1(Yam et al., 2019)	1 year	-0.46 ± 0.63	0.29 ± 0.32	Mild
	LAMP Year2(Yam et al., 2020)	2 years	-0.85 ± 0.90	0.48 ± 0.38	Mild
	LAMP Year 3 (Yam et al., 2022)	3 years	-1.10 ± 1.12	0.68 ± 0.48	Mild
0.01%	ATOM2 (Chia et al., 2016)	2 years	-0.49 ± 0.63	0.41 ± 0.32	Very Mild
	LAMP Year1(Yam et al., 2019)	1 year	-0.59 ± 0.67	0.35 ± 0.29	Very Mild
	LAMP Year2(Yam et al., 2020)	2 years	-1.04 ± 0.97	0.59 ± 0.38	Very Mild
	LAMP Year3 (Yam et al., 2020)	3 years	-1.19 ± 1.15	0.75 ± 0.51	Very Mild
Placebo	LAMP Year1-3 (Yam et al., 2019; Yam et al., 2022; Yam et al., 2020)	1-3 years	-0.81 ~ -1.57*	0.41 ~ 0.82*	-

*Data approximated from the original study for comparison.

2.1.2. Mechanisms and Safety

The exact mechanism remains unclear but is believed to be primarily non-accommodative, involving direct action on muscarinic receptors (e.g., M1/M4) in the retina and sclera, influencing pathways like TGF-β and matrix metalloproteinases to inhibit scleral remodeling (Arumugam and

McBrien, 2012). Choroidal thickening and modulation of retinal dopamine signaling are also hypothesized contributors (Wu et al., 2019; Zhang and Wildsoet, 2015).

Safety is significantly improved at low concentrations. Common side effects like mild, transient photophobia and near vision blur are dose-dependent and generally well-tolerated at 0.01% (Chia et al., 2016). Allergic reactions are possible but uncommon. Systemic effects are rare. Rebound progression after cessation is a consideration but appears less pronounced with lower concentrations such as 0.01% and 0.05% (Lee et al., 2024).

2.2. Optical Interventions

2.2.1. Main Modalities and Efficacy

Optical interventions work by manipulating peripheral retinal defocus to provide a signal that slows eye growth.

(1) Orthokeratology (Ortho-K): Overnight wear of rigid gas-permeable lenses that temporarily reshape the cornea, providing clear daytime vision and a myopic defocus ring in the periphery. Meta-analyses show it slows axial elongation by approximately 45% on average (Sun et al., 2015a; Sun et al., 2015b).

(2) Defocus Incorporated Multiple Segments (DIMS) Spectacles: Spectacle lenses with a central correction zone surrounded by multiple micro-lenses creating constant peripheral myopic defocus. A 2-year randomized controlled trial (RCT) showed a 52% reduction in axial elongation compared to single-vision lenses (Lam et al., 2020).

(3) Peripheral Progressive Addition Lenses: Spectacles with added plus power in the lower/near segment to reduce accommodative lag. Evidence for efficacy is less consistent and generally suggests a more modest effect compared to Ortho-K or DIMS (Perea-Romero et al., 2025).

Table 2. Comparison of Major Optical Interventions for Myopia Control

Intervention	Primary Mechanism	Average Efficacy	Key Advantages	Key Limitations/Risks
Orthokeratology	Corneal reshaping, inducing peripheral myopic defocus	Approximately 45% reduction in axial elongation (Sun et al., 2015b)	No daytime optical device; high efficacy	Risk of microbial keratitis; requires expert fitting/compliance
DIMS Spectacles	Continuous peripheral myopic defocus via embedded lenslets	Approximately 52% reduction in axial elongation (Lam et al., 2020)	Non-invasive; excellent safety; easy wear	Potential minor peripheral visual disturbance; cost
Peripheral Progressive Lenses	Reduction of accommodative lag & peripheral defocus modulation	Variable, typically less than above (Perea-Romero et al., 2025)	Non-invasive; suitable for non-contact lens wearers	Weaker evidence base; need adaptation to progressive design

2.2.2. Limitations

Ortho-K carries a risk of microbial keratitis, emphasizing the critical need for strict hygiene and professional supervision (Bullimore and Brennan, 2019). Its efficacy and suitability can be influenced by corneal topography and patient age. Spectacle-based interventions, while very safe, depend heavily on consistent wear time for optimal effect, and their higher cost can be a barrier.

2.3. Combination Therapy

2.3.1. Rationale and Evidence

Combining low-concentration atropine (acting via biochemical pathways) with an optical intervention (acting via physical defocus signals) offers a multi-targeted approach, potentially yielding additive or synergistic effects (Tan et al., 2019; Zheng and Tan, 2022). Clinical studies support this: a randomized trial found Ortho-K combined with 0.01% atropine resulted in significantly less axial elongation at one month than either treatment alone (Tan et al., 2019). Similarly, combining atropine with DIMS spectacles showed enhanced efficacy, particularly in children with rapid baseline progression (Yam et al., 2025).

In addition to the synergistic clinical effects, emerging evidence suggests that the combination of low-concentration atropine and optical interventions may involve complementary molecular mechanisms. Atropine is believed to act on muscarinic receptors (particularly M1 and M4) in the retina and sclera, modulating downstream signaling pathways such as TGF-β and matrix metalloproteinases (MMPs), which are critical for scleral remodeling and axial elongation (Arumugam and McBrien, 2012). Optical interventions, such as DIMS and Ortho-K, induce peripheral myopic defocus, which may influence retinal dopamine release and choroidal thickness, both implicated in eye growth regulation (Zhang and Wildsoet, 2015). The convergence of pharmacological and optical signals may act on shared pathways—such as retinal pigment epithelium-derived signaling—or target distinct but complementary processes, leading to additive inhibition of myopia progression.

2.3.2. Clinical Considerations

Combination therapy is particularly suited for rapid progressors or those inadequately controlled on monotherapy. A pragmatic approach is to initiate one intervention (often optical) and add low-concentration atropine (typically starting with 0.01%) if progression remains concerning after 6-12 months. Individualized decision-making based on progression rate, age, ocular parameters, and adherence is paramount.

2.4. Comparison Between Low-Concentration Atropine and Repeated Low-Level Red-Light Therapy

Repeated low-level red-light (RLRL) therapy has recently emerged as a novel non-pharmacological intervention for myopia control. A multicenter randomized controlled trial by Jiang et al. (2022) demonstrated that RLRL therapy significantly reduced axial elongation and spherical equivalent progression over 12 months, with an efficacy comparable to 0.05% atropine. Unlike atropine, which requires daily eye drops and may cause photophobia or allergic reactions,

RLRL is administered in clinic-based sessions and has shown a favorable safety profile with no reported systemic adverse events.

However, the two interventions differ in mechanism, patient acceptability, and applicability. Atropine acts via biochemical modulation of scleral and retinal pathways, while RLRL is thought to stimulate choroidal thickening and retinal dopamine release through photobiomodulation. In terms of patient selection, atropine may be more suitable for children with good adherence to daily medication, whereas RLRL may benefit those who prefer non-pharmacological, clinic-supervised treatments. Combination of both modalities has not yet been systematically studied, but may offer additive effects in rapid progressors. Future studies should evaluate the safety and efficacy of combining RLRL with atropine or optical devices in pediatric populations. Future research should explore head-to-head comparisons in diverse ethnic groups and age ranges to refine treatment algorithms.

3. Discussion

The evidence synthesized confirms that both low-concentration atropine and specific optical interventions are effective for slowing childhood myopia progression. The choice between them, or the decision to combine them, hinges on a nuanced risk-benefit analysis tailored to the individual patient. Atropine offers a non-optical, systemic-acting approach but requires daily instillation and long-term commitment. Optical interventions like Ortho-K and DIMS provide an immediate visual correction benefit and act locally but have specific contra-indications (Ortho-K) or adherence dependencies (spectacles).

The promising results for combination therapy align with the multi-factorial nature of myopia pathogenesis, suggesting that concurrently targeting different physiological pathways (biochemical and optical) can be more effective. However, most combination studies have relatively short follow-up periods. Longer-term data are needed to confirm sustained efficacy, understand any interactive effects on safety (e.g., corneal health under Ortho-K with concurrent atropine), and establish optimal protocols for initiation and cessation.

A significant challenge remains the inability to reliably predict an individual's response to a given therapy. Future integration of genetic markers (Tedja et al., 2018), biometric data (e.g., baseline choroidal thickness), and environmental factors into predictive models is crucial for advancing personalized myopia management. Furthermore, most evidence derives from Asian populations; more research in other ethnic groups is warranted to ensure global applicability. Emerging therapies, such as repeated low-level red-light therapy which has shown significant efficacy in recent RCTs (Jiang et al., 2022), also warrant further long-term safety and efficacy evaluation.

The emergence of RLRL therapy adds a new dimension to myopia management. Its efficacy, combined with its non-invasive and non-pharmacological nature, makes it an attractive option for children who cannot tolerate atropine or fail to adhere to daily eye drop regimens. However, long-term safety data beyond one year remain limited, and its availability is currently restricted to specialized centers. Therefore, treatment selection should be guided by patient age, progression

rate, compliance potential, and access to follow-up care. Integrating RLRL with existing optical or pharmacological interventions may represent a future direction for personalized myopia control.

4. Conclusions

Low-concentration atropine and advanced optical interventions are cornerstone evidence-based strategies for controlling myopia progression in children. Their distinct mechanisms provide a rationale for combination therapy, which emerges as a potent option for managing rapid progression. Successful implementation requires individualized treatment plans, careful monitoring, and strong patient/parent education regarding adherence and safety. Future research should focus on long-term outcomes, predictive analytics, and refining combination protocols to optimize efficacy and safety, ultimately mitigating the future burden of high myopia. Personalized treatment strategies integrating genetic, biometric, and behavioral factors will be key to optimizing outcomes.

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Pathogenesis and Integrated Traditional Chinese and Western Medicine Treatment Strategies of Allergic Rhinitis Based on the "Spleen (Stomach)-Lung-Nose Axis" Theory

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Abstract

In recent years, the prevalence of allergic rhinitis (AR) in China has increased markedly, significantly impairing patients' quality of life and imposing a substantial socioeconomic burden. Against this background, some scholars have proposed the "Spleen(Stomach)-Lung-Nose Axis" theory based on the Huangdi Neijing, elucidating the close physiological and pathological interconnections among the spleen (stomach), lung, and nose. Guided by this theory, this study correlates the traditional Chinese medicine pathogenesis of AR with modern pathophysiological mechanisms and explores an integrated traditional Chinese and Western medicine therapeutic strategy. This strategy aims to synergize the advantages of both medical systems to provide a more comprehensive and effective treatment regimen for AR, with the goal of alleviating symptoms, improving quality of life, and ultimately reducing the socioeconomic burden.

Keywords: Spleen; Lung; Traditional Chinese Medicine; Rhinitis; Allergic Rhinitis

1. Introduction

Allergic rhinitis (AR) is one of the advantageous diseases for prevention and treatment intraditional Chinese medicine (TCM) (Wu et al., 2021). Epidemiological data show that the prevalence of AR in China has been continuously increasing in recent years. Its typical symptoms, such as nasal congestion, rhinorrhea, and sneezing, severely affect patients' quality of life and work efficiency, and increase the socioal-economic burden. Some patients may develop

complications such as nasal polyps and otitis media, further exacerbating the condition. Therefore, AR has become a hot topic in current research by both Chinese and Western medicine.

Pulmonary and Spleen Deficiency Syndrome is one of the typical patterns of AR (Yang, S. et al., 2012; Zhang et al., 2020), highlighting the central role of lung and spleen (stomach) functions in the pathogenesis and treatment of AR. Although the pathogenic mechanism of lung-spleen deficiency has not been fully elucidated, existing studies have confirmed a close association between pulmonary-spleen deficiency and the pathological process of AR. Based on the theory of the Huangdi Neijing, scholars have proposed the concept of the "Spleen (Stomach)-Lung-Nose Axis" (Liu et al., 2023). This article aims to systematically analyze the intrinsic connections between the pathophysiological mechanisms of AR and the "Spleen (Stomach)-Lung-Nose Axis" theory, thereby exploring integrated traditional Chinese and Western medicine strategies for prevention and treatment.

2. Overview of the "Spleen (Stomach)-Lung-Nose Axis" Theory

The "Suwen Jingmai Bielun" states: "Drinking enters the stomach, disperses essence and qi, ascends to the spleen, where the spleen disperses essence, then ascends to the lungs, regulates the water pathways, and descends to the bladder, distributing water and essence throughout the five meridians." This passage elucidates the coordinated pathways of water metabolism involving the stomach, spleen, and lungs. The essence of food and drink is transported by the spleen and stomach to the lungs, where lung qi disperses and elevates, nourishing the nasal orifices. Professor Cheng proposed the existence of a "spleen (stomach)-lung-nose axis" linking the spleen, stomach, lungs, and nose. Although this theory originates from water metabolism, it is grounded in the visceral theory of the Huangdi Neijing and also encompasses core physiological processes such as qi movement. The Huangdi Neijing posits that the dynamic interaction among the spleen, stomach, lungs, and nose relies on qi movement: the spleen governs the ascent of clear qi, the stomach governs the descent of turbid qi, and the lungs oversee dispersion and descent. These three qi movements interdependently regulate water metabolism and the dispersion of clear yang. The function of the nasal orifices depends not only on lung qi dispersion but also on the ascending and descending actions of the spleen and stomach. Thus, the "spleen (stomach)-lung-nose axis" is a physiological axis involving multiple components such as water metabolism and qi movement. If the axis is coordinated, the nasal orifices are nourished; if unbalanced, pathogenic factors proliferate, leading to nasal diseases. For instance, spleen deficiency impairs transportation, leading to insufficient lung qi and the failure of clear yang to ascend, resulting in the nasal orifices losing warmth. Similarly, if stomach qi fails to descend, turbid yin rises and obstructs the nasal collaterals, causing nasal congestion and rhinorrhea, which may lead to nasal obstruction.

The "Suwen Yujizhenzang Lun" states, "The spleen is an isolated organ, located in the central and nourishing the periphery... If it fails, it leads to obstruction of the nine orifices." This "nine orifices" includes the nasal orifice, clearly indicating that spleen deficiency (insufficiency) can result in malnourishment of the nasal orifice, thereby providing theoretical support for the "spleen (stomach) -lung-nose axis" from a pathological perspective. Ying Lou, in his "Yixue Gangmu",

notes, “The nose is the orifice of the lung, and the Yangming stomach meridian encircles the nose and mouth. Therefore, when wind-cold invades the stomach meridian, nasal obstruction occurs; when spleen heat transfers to the lung, epistaxis and rhinorrhea occur.” This theory elucidates the influence of the spleen, stomach, and lung on the nasal orifice from both the aspects of external pathogen invasion and internal injury transmission, further corroborating the core role of this axis in maintaining the body's defense and internal homeostasis. From a pathological standpoint, it provides additional evidence for the “spleen (stomach)-lung-nose axis” theory.

3. Reflections on the Pathogenesis of Allergic Rhinitis Based on the “Spleen (Stomach)-Lung-Nose Axis” Theory

3.1. “Inherent Deficiency” and Increased Genetic Susceptibility to AR in Individuals

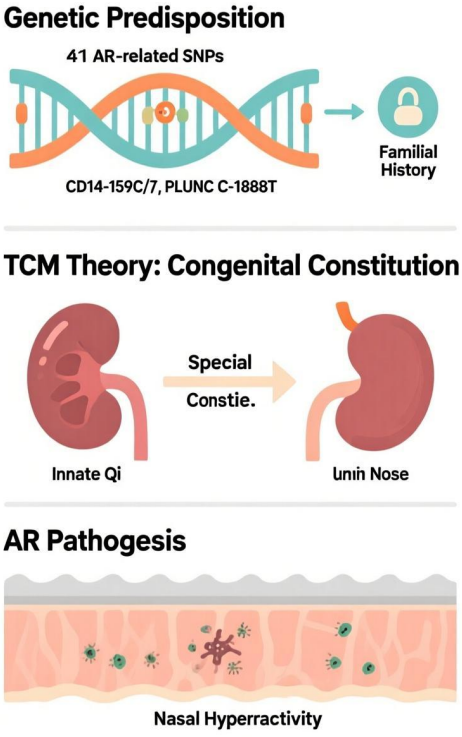
Based on the "Spleen (Stomach)-Lung-Nose Axis" theory, the stability of the axis system relies on the solid material foundation and coordinated physiological activities of the spleen, stomach, and lung, with this foundation largely derived from innate endowment. The evident genetic predisposition observed in the pathogenesis of AR can be regarded as a weak link in the innate homeostasis of the axis system. Modern pathophysiological studies have demonstrated (Subspecialty Group of Rhinology et al., 2022) that the pathogenic premise of AR lies in a sensitized state induced by certain allergens. This sensitized state frequently occurs in specific populations. Epidemiological surveys indicate that over 10% of AR patients have a family history of allergic diseases. Foreign studies have found (Choi et al., 2021) that AR is significantly influenced by genetic factors, with concordance rates as high as 45%–60% among monozygotic twins, which corroborates from a modern medical perspective the potential impact of innate factors on the defensive stability of the axis system.

Genetic studies have provided evidence for this: genome-wide association studies and HLA fine-tuning studies (Waage, J. et al., 2018) identified 41 risk loci for AR; research based on the CD14 gene (Shan et al., 2023) proposed that the dominant gene model (CC vs CT+TT) at the CD14-159C/T locus may increase susceptibility to AR. Researchers from Fudan University in Shanghai (Zhang et al., 2021) identified six key genes influencing the pathogenesis of allergic rhinitis through bioinformatics analysis: CD44, HLA-DPA1, HLA-DRB1, HLA-DRB5, MUC5B, and CD274. These findings reveal the micro-level basis of “innate endowment” at the genetic level, and their abnormalities may predispose the “spleen (stomach)-lung-nose axis” to fragility in subsequent development and environmental challenges.

Traditional Chinese Medicine theory posits that innate endowment originates from the father's essence and the mother's blood, residing in the kidneys as the root of primordial qi, which constitutes the foundation of life activities. The “Suwen Tian Nian” states, “With the mother as the base and the father as the shield,” emphasizing that the yin-yang balance of parents determines the strength and constitutional differences of offspring. The primordial qi in the kidneys, as the foundation of innate endowment, requires nourishment from the postnatal transformation of food essence by the spleen and stomach to activate lung function and fortify the exterior defenses. Congenital deficiency leads to insufficient primordial qi and kidney essence

depletion, resulting in inadequate nutrient supply for spleen and stomach transformation, thereby causing spleen deficiency.The spleen is responsible for the dysfunction of transportation and transformation. Spleen deficiency leads to an imbalance in the metabolism of qi and body fluids, thereby generating dampness and transforming it into phlegm. The accumulation of phlegm-dampness obstructs lung qi, resulting in lung invasion and nasal obstruction. This is the so-called "the spleen is the source of phlegm generation, and the lung is the container of phlegm." Additionally, the spleen is the mother of the lung, and when the mother is diseased, it affects the child. Spleen deficiency leads to lung deficiency, and insufficient lung qi fails to defend the exterior. Therefore, innate insufficiency can result in an unstable foundation of the "spleen (stomach)-lung-nose axis," weakening the axis function and increasing susceptibility to allergic rhinitis.

Research based on Professor Wang Qi's classification of nine constitutional types revealed that the Special Endowment Constitution, Qi-deficiency constitution and Yang-deficiency constitution (Zhang et al., 2024; Tian et al., 2023) are the primary TCM constitutional types in patients with allergic diseases. Existing studies (Wang et al., 2019) indicate that AR patients with Special Endowment Constitution may have a related family history. This suggests that the three constitutions caused by "inherent endowment deficiency" impairs the acquired spleen and stomach, thereby weakening the lung-defense system's ability to protect against external pathogens. Ultimately, this leads to dysfunction of the "spleen (stomach)-lung-nose axis," manifesting as heightened hypersensitivity of the nasal passages to external allergens (Figure 1). Therefore, endowment deficiency serves as the intrinsic initiating factor contributing to the imbalance of the "spleen (stomach)-lung-nose axis" and the increased susceptibility to AR in individuals.



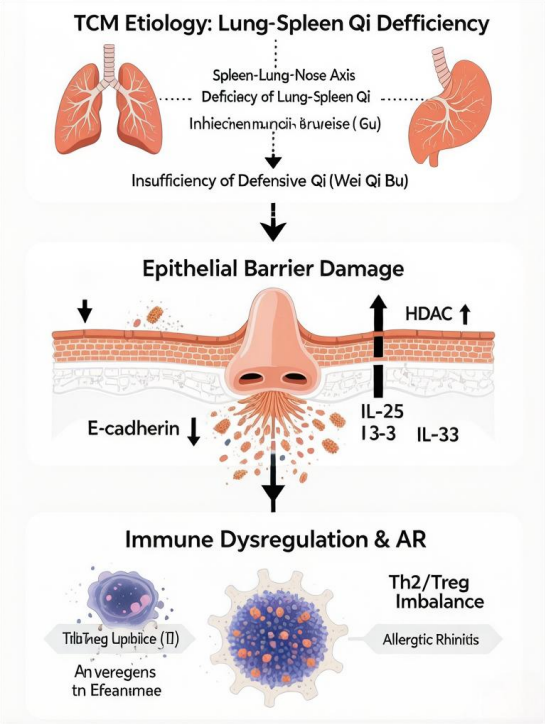


Figure 1.XXX **Figure 2.XX**

3.2. "Weiqi Insufficiency" and Damage to the Nasal Mucosal Epithelial Immune Barrier

The nasal mucosa serves as the primary barrier against AR, and impairment of its epithelial barrier function is one of the key pathological mechanisms of AR. Current research has revealed that downregulation of E-cadherin expression and activation of histone deacetylases (HDACs) are closely associated with damage to the nasal epithelial barrier (Lee et al., 2021; Duan et al., 2021) (Figure 2).

E-cadherin is a calcium-dependent intercellular adhesion transmembrane glycoprotein that plays a critical role in maintaining stable connections between epithelial tissue cells. In patients with allergic rhinitis, the expression and immunoreactivity of E-cadherin in nasal epithelium are reduced (Lee et al., 2016). Downregulation or loss of E-cadherin disrupts intercellular junctions, weakens the epithelial immune barrier, and diminishes its ability to block allergen penetration into the submucosa. This results in enhanced proteolytic degradation of airborne allergens and epithelial cell dysfunction. Additionally, the balance between cysteine proteases and antiproteases in the nasal mucosa is disrupted, leading to reduced secretion of E-cadherin within epithelial cells. Consequently, this triggers an amplified immune response, activates monocytes, and initiates a cascade of allergic reactions.

The activation of histone deacetylases (HDACs) is considered a key factor in triggering AR due to damage to the nasal mucosal epithelial barrier. When the nasal mucosal epithelial barrier is compromised, HDACs activate mucosal repair mechanisms and trigger protective inflammatory responses. Epithelial damage in the local skin and mucosal barrier can lead to the release of inflammatory factors such as interleukin-25 (IL-25) and interleukin-33 (IL-33), which induce allergic reactions in the nasal epithelium, promote the onset and progression of AR, and further compromise the integrity of the epithelial immune barrier (Lee et al., 2016; Bergougnan et al., 2020).

In TCM theory, the Lung governs qi and manages respiration, while Wei-defensive qi has the function of resisting external pathogens. The Spleen is the source of qi and blood production, serving as the foundation for the generation of Wei-defensive qi. Statistics show that among patients with allergic rhinitis, those with yang deficiency and qi deficiency constitutions account for the highest proportion, both characterized by "insufficient Wei-defensive qi" as the core feature, suggesting that Lung-Spleen qi deficiency is an important pathogenesis of this disease (Wang et al., 2022). Among these, Spleen deficiency leading to Lung deficiency is the key link. The Spleen belongs to Earth and the Lung to Metal, with a mother-child organ relationship; Spleen Earth deficiency fails to nourish Lung Metal, known as "mother-organ disorder affecting the child." Simultaneously, the Spleen governs the transportation and transformation of water and grain essences. If Spleen deficiency impairs transportation and transformation, the source of qi and blood generation diminishes, reducing the essential substances transported upward to the Lungs. Consequently, Lung qi also becomes deficient, impairing its functions of diffusion and descending. Lung qi deficiency further affects the generation and distribution of Wei-defensive qi—although Wei-defensive qi originates from the Spleen, it relies on Lung qi diffusion to be distributed to the nasal orifices and body surface. Lung deficiency impairs diffusion, making it difficult for Wei-defensive qi to reach the nasal passages, thereby compromising the local

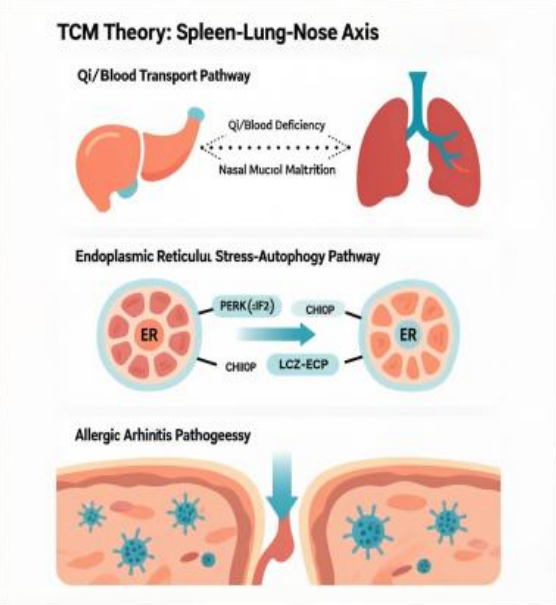
defensive barrier's integrity. The “insufficient Wei-defensive qi” resulting from Lung-Spleen qi deficiency not only manifests as decreased immune defense function (Th2/Treg imbalance) but is also directly associated with nasal epithelial barrier damage (downregulation of E-cadherin and activation of HDAC), ultimately leading to an imbalance in the “Spleen-Lung-Nose” axis stability, which constitutes the core internal cause of the pathogenesis of allergic rhinitis.

3.3. “Insufficient Generation of Qi and Blood, Abnormal Transport and Distribution” and the Effect of Endoplasmic Reticulum Stress-Autophagy Pathway in Nasal Mucosa

In cellular metabolism, the endoplasmic reticulum stress-autophagy pathway is closely associated with micro-level functions such as cellular nutrient regulation and tissue repair. Studies have shown (Zhu et al., 2024) that the PERK/eIF2α/CHOP signaling pathway not only induces cellular autophagy but may also be involved in the pathogenesis of AR. The endoplasmic reticulum stress-autophagy system plays a significant role in the pathogenesis of asthma by participating in antigen presentation, regulating immune-inflammatory response cells, and modulating the functions of airway constitutive cells. Asthma and AR are often referred to as “the same airway, the same disease,” suggesting that their mechanisms may be analogous in AR. Nedjic and his team (Nedjic et al., 2008), in their study of thymic epithelial cell autophagy, proposed that autophagy may contribute to immune diseases by regulating endogenous antigen presentation. Existing research (Yu et al., 2019) has confirmed that LC3 regulates the high expression of eosinophil cationic protein (ECP) in AR patients through specific signaling pathways. Therefore, cellular autophagy may play a critical role in the toxic effects and inflammatory severity of AR by modulating eosinophil activity.

The “Spleen (Stomach)-Lung-Nose” axis theory posits that robust function of the Lung and Spleen forms the foundation for the generation and distribution of qi and blood. The nasal orifice, as the terminal organ of this axis system, relies on the effective transmission and coordinated operation of this axis for its normal physiological functions. Spleen deficiency initially leads to a depletion in the source of qi and blood generation, which subsequently affects the upward distribution of qi and blood along the axis, ultimately resulting in a lack of nourishment to the nasal mucosa. As stated in Suwen (Plain Questions), Chapter Sixty-Two: “When qi and blood are disharmonious, yin and yang become counteractive; defensive qi is in turmoil within the defensive tier, while nutrient blood rebels within the meridians; qi and blood separate from their proper places, creating one vacuity and one repletion.” This reveals the importance of the exuberance and decline of qi and blood in the context of disease. An imbalance in the state of qi and blood movement within the axis directly leads to pathological changes in the terminal organ. The Spleen acts as the foundation of the axis, governing the ascent of the clear to transport essences; the Lung acts as the pivot of the axis, governing diffusion and descending to distribute qi and blood to the nasal orifice. If both the Lung and Spleen are deficient, it will trigger dysfunction of the axis: Spleen deficiency results in the failure of clear yang to ascend, weakening the starting point of the axis; Lung deficiency leads to a loss of diffusion function, obstructing transmission along the axis. The mutual reinforcement of insufficient qi and blood generation and disordered distribution deprives the nasal mucosa of nourishment, thereby triggering allergic rhinitis. Thus, it can be seen that the deficiency in qi and blood generation and the disturbance in

their distribution, caused by the dysfunction of the "Spleen (Stomach)-Lung-Nose" axis, may influence the progression of the disease by activating the endoplasmic reticulum stress-autophagy pathway in the nasal mucosa (Figure 3).



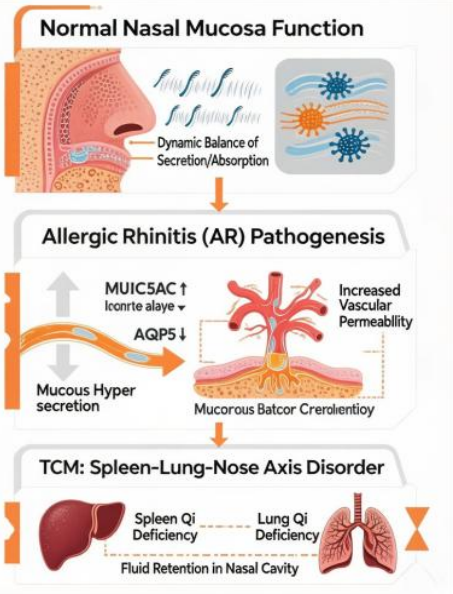


Figure 3 **Figure 4**

3.4. "Abnormal Transformation and Transportation of Water-Liquid, Stagnation and Accumulation of Water-Dampness" and Hypersecretion of Nasal Mucus and Increased Vascular Permeability

The nasal mucosal tissue produces abundant secretions that serve to defend against bacterial invasion and maintain the moisture balance of the respiratory tract. Additionally, the production and absorption of these fluids are regulated by a dynamic equilibrium. Modern medical research has confirmed that increased permeability of nasal microvessels and excessive mucus secretion are critical components in the pathogenesis of AR (Figure 4). The nasal mucosal epithelium contains ciliated epithelial cells, whose periodic coordinated ciliary movements provide the driving force for mucus transport. Excessive mucus can impair the ciliary transport function of the nasal mucosa, reduce respiratory mucosal function and allergen clearance, and exacerbate the chronic inflammatory process of AR. Mucin (MUC), the primary component of nasal mucus, is a highly glycosylated linear oligopeptide sequence. Studies have found that the imbalance of MUC5AC/AQP5 (Liu et al., 2020) leads to mucosal fluid metabolism disorders and hypersecretion of mucus. Simultaneously, increased permeability of microvessels in the nasal mucosa results in plasma component extravasation into surrounding tissues, causing local tissue edema, which further exacerbates mucus secretion. Inhibition of MUC5AC expression in patients with AR can significantly reduce mucus secretion and improve symptoms of allergic rhinitis (Zhao et al., 2024).

Nasal mucus is a type of body fluid, and its hypersecretion is a manifestation of abnormal fluid distribution. The "Spleen (Stomach)-Lung-Nose" axis theory is based on the metabolic pathway of body fluids, stating that "fluids enter the stomach, overflow the essence and qi, and ascend to

the spleen." The initial site of fluid metabolism is the spleen and stomach. When spleen qi is weak, its transportation and transformation functions are impaired, preventing the conversion of ingested nutrients into qi, blood, and body fluids, as well as the elimination of water retention from the body. Fluid retention in the nasal cavity leads to mucosal edema and increased vascular permeability, resulting in excessive mucus secretion. The lung, as the upper source of water, plays a crucial role in the dispersion and descent functions of fluid metabolism. When lung qi is weak, its dispersion function is diminished, failing to distribute fluids upward and outward, leading to localized fluid accumulation. Simultaneously, its descent function is also compromised, preventing the downward transport of fluids to excretory organs such as the bladder, thereby exacerbating fluid metabolism disorders. Therefore, an imbalance in the "Spleen (Stomach)-Lung-Nose" axis, whether in the spleen-stomach or lung, can result in localized fluid retention, manifested as excessive nasal mucus secretion and increased vascular permeability.

4. Reflections on the Integrated Traditional Chinese and Western Medicine Treatment Approach for Allergic Rhinitis Under the "Spleen (Stomach)-Lung-Nose Axis" Theory

Based on the "Spleen (Stomach)-Lung-Nose Axis" theory, the pathogenesis of AR can be explored, revealing certain commonalities between traditional Chinese and Western medicine in explaining the pathophysiological process of AR caused by lung-spleen qi deficiency. Therefore, this study proposes integrating the theories of both traditional Chinese and Western medicine, combining the strengths of both approaches, which holds practical significance for optimizing the current treatment regimen for AR of the lung-spleen qi deficiency type.

In Western medical treatment, the primary strategy is symptomatic management, with a focus on the "nasal" component of the "spleen (stomach)-lung-nose axis" to alleviate patient discomfort. Therapeutic approaches (Subspecialty Group of Rhinology et al., 2022; Papadopoulos et al., 2016) include the use of nasal corticosteroids (e.g., mometasone furoate), antihistamines (e.g., loratadine), and leukotriene receptor antagonists (e.g., montelukast). Additionally, allergen immunotherapy (AIT) is available, but its efficacy is limited in patients with multiple sensitizations and may induce adverse reactions such as localized swelling. From the perspective of the "spleen (stomach)-lung-nose axis" theory, current treatments predominantly focus on local inflammation control ("manifestation"), failing to comprehensively and systematically address the dysfunction of lung and spleen functions ("root cause"), leading to prolonged and recurrent disease courses.

The "Spleen-Stomach-Lung-Nose" axis is a functional system driven by viscera, with qi, blood, and essential substances as mediators. The Spleen (Stomach), located in the middle burner, serves as the source of qi and blood production and governs ascending the clear to transport essences to the Lung. The Lung, situated in the upper burner, governs diffusion and descending to distribute essences to the nasal orifice. The nose, as the orifice of the Lung, relies on nourishment from qi and blood to maintain ventilation and defensive function. These three components form a longitudinal linkage of "generation-transportation-nourishment": a robust Spleen and Stomach ensure a sufficient source of qi and blood; unobstructed Lung qi diffusion guarantees orderly

distribution; and well-nourished nasal passages maintain a solid barrier. Conversely, Spleen deficiency impairs transportation, depleting the source of qi and blood and weakening the axis's starting point; this leads to Lung deficiency with impaired diffusion, blocking transmission; ultimately, the nasal passages lose nourishment, rendering the mucosa vulnerable to invasion by external pathogens and resulting in disease.The core pathogenesis of Allergic Rhinitis (AR) is understood as an imbalance in the transmission of qi and blood along this axis due to Spleen and Lung deficiency. This imbalance arises from a combination of congenital factors, such as an inherent weakness in the Spleen, Lung, and nasal orifice, and acquired factors, including external pathogens (wind-cold) and improper diet. The clinical goal of Traditional Chinese Medicine (TCM) is to restore homeostasis by regulating the internal environment and immune function, ultimately correcting the imbalance of the “Spleen (Stomach)-Lung-Nose” axis to alleviate or eliminate AR symptoms. With the resurgence of TCM, its application as an alternative or complementary therapy for AR is becoming increasingly widespread, often becoming the first choice for many patients. A significant body of animal experiments and clinical trials (Xu et al., 2024; Fan et al., 2024; Yin et al., 2023) has confirmed that TCM formulas targeting Lung-Spleen Qi deficiency pattern AR, can regulate inflammatory factors like IgE, IL-4, and IL-33. By controlling immune imbalance, they improve clinical symptoms, enhance quality of life, regulate immune status during non-acute phases, and even mitigate inflammatory responses upon allergen exposure, achieving the goal of “preventing disease before it arises.” TCM emphasizes “treating the manifestation in acute conditions and the root cause in chronic conditions.” Therefore, clinical treatment should be tailored to the patient's specific needs, leveraging the complementary advantages of both Chinese and Western medicine. Given their synergistic mechanisms, a phased, integrated strategy is recommended:

Acute Phase: The primary goal is the safe and rapid relief of symptoms like nasal congestion and rhinorrhea. While decongestants were once used, their significant side effects have limited their clinical application. As an optimized alternative, Western Medicine (nasal glucocorticoids) can be combined with Local Acupuncture Therapy targeting the “Nose.” Intranasal acupuncture at points like Neiyingxiang (ST26) and Biqiu (M-HN-14) can significantly reduce turbinate swelling, decrease mucus secretion, and improve nasal ventilation. This can be further supported by Chinese Herbal Medicine with exterior-releasing formulas to expel pathogens.

Remission Phase: The focus shifts to preventing recurrence by adjusting the patient's constitution. This phase fully utilizes TCM's strengths by targeting the “Spleen and Lung.” Chinese Herbal Medicine (Spleen-Lung axis), such as Yu Ping Feng San or modified Bu Zhong Yi Qi Tang, is the primary treatment, selected based on pattern and constitution. This can be complemented by appropriate technologies like herbal sachets. For patients with a clearly identified single allergen, a gradual integration of Allergen-Specific Immunotherapy (AIT) can be initiated to induce immune tolerance.

Recalcitrant Cases: For patients with poor response to conventional Western medicine, TCM becomes the mainstay even during acute phases, focusing on exterior-releasing methods with supplementary support for the Lung and Spleen. For recurrent and stubborn cases, the strategy builds upon the first two pillars by incorporating Constitutional Regulation and Microecological

Adjustment. This deeper level of intervention aims to address the patient's fundamental predisposition and restore internal balance, preventing recurrence at its roots.

This phased approach embodies a “three-dimensional integration pathway” which strategically combines treatment according to the disease phase, targets the “Spleen-Lung-Nose” axis, and progressively deepens the intervention from symptomatic relief to constitutional and microecological regulation, fully reflecting the design philosophy of “axis linkage, phased focus, and holistic synergy.”

5. Summary

In conclusion, the analysis of the pathogenesis of AR based on the “spleen (stomach)-lung-nose axis” theory reveals that “inherent deficiency” “impaired Wei-defensive qi” “insufficient production and transportation of qi and blood” and “abnormal transformation and transportation of body fluids leading to water retention” are linked to modern medical factors including genetic susceptibility, damage to the nasal mucosal epithelial immune barrier, endoplasmic reticulum stress-autophagy pathway effects, hypersecretion of nasal mucus, and increased vascular permeability. These associations may constitute causal relationships. Based on these, we proposes an integrated TCM-Western medicine therapeutic strategy. This approach aims to combine the strengths of both medical systems to provide a more comprehensive and effective treatment plan for allergic rhinitis, with the goal of alleviating patient symptoms, improving their quality of life, and ultimately reducing social and economic burdens.

With the continuous advancement of medical technology, the prospects for integrated traditional Chinese and Western medicine in treating AR of the lung-spleen qi deficiency type appear particularly promising. Future research should delve deeper into the mechanisms of integrated traditional Chinese and Western medicine in treating AR of the lung-spleen qi deficiency type, with the expectation that more high-quality evidence-based medical data will be available to promote the application and popularization of this integrated approach in AR management.

Author Contributions:

All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

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A New AI-Enabled Model for Tiered Management of Care Resources for Elderly People with Disabilities in Communities

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Abstract

As China's population ages at an accelerating pace and the number of elderly people with disabilities continues to rise, the traditional family-based care model faces severe challenges, making community-based home care an increasingly important option. However, current community care services suffer from issues such as uneven resource allocation, insufficient service precision and a shortage of professional staff, with a particular lack of intelligent assessment and tiered management mechanisms tailored to elderly people with disabilities .This study, using three communities in Wenzhou, Zhejiang Province as pilot sites, explores the construction of a new integrated community care model—'assessment-classification-intervention-feedback'—linked by AI-enabled technology. The research comprehensively employs questionnaire surveys, field research, VR virtual simulation training, artificial intelligence predictive models and principal component analysis to establish a four-level coding system based on the Barthel Index, thereby achieving intelligent identification of functional impairment levels among the elderly and differentiated health management.The VR system was utilised for the standardised training of medical student volunteers, thereby enhancing the quality of data collection and service delivery capabilities; the AI predictive models can effectively identify key risk factors for disability; when combined with a digital health management platform, they enable dynamic resource allocation and a closed-loop service system.

Keywords: Elderly People with Disabilities; AI-Enabled; VR Training; Tiered Management; Smart Care for the Elderly

1.Introduction

Currently, the ageing of China's population is accelerating, and this demographic shift has become a major challenge facing the country's social development. According to data from the '2024 National Report on the Development of Ageing Affairs' published by the Ministry of Civil Affairs and the National Committee on Ageing, by the end of 2024, the national population aged 60 and over had reached 310.31 million, accounting for 22.0% of the total population;the population aged 65 and over stood at 220.23 million, accounting for 15.6% of the total population. According to relevant statistics, by the end of 2022, the number of elderly people in China suffering from chronic diseases exceeded 190 million, with approximately 35 million elderly people with disabilities; this figure is projected to reach 46 million by 2035. Projections indicate that during the 14th Five-Year Plan period, the total population aged 60 and over will exceed 300 million, accounting for more than 20% of the total population, marking the entry into a moderately aged society; by around 2035, the population aged 60 and over is expected to exceed 400 million, accounting for over 30% of the total population, marking the entry into a severely aged society.

Faced with this severe demographic ageing situation, the traditional family-based care model is no longer sufficient to meet the growing demand for elderly care. With the trend towards smaller and more nuclear family structures, the proportion of elderly people living alone is rising steadily, the capacity for family-based care has declined significantly, and the proportion of elderly people opting for community-based home care continues to increase (Zhou et al., 2024). Against this backdrop, community-based home care services have gradually become an integral part of the elderly care service system. However, current community-based home care services still face numerous challenges in practice: issues such as a scarcity of community medical resources and low utilisation rates, uneven distribution of elderly care resources, and a shortage of professional personnel are becoming increasingly prominent (Li et al., 2024; Liu et al., 2025).

Furthermore, the care needs of older people in the community are diverse, particularly for those who are incapacitated or partially incapacitated, who urgently require professional healthcare services and greater support and care. However, most care facilities are only able to provide assistance with daily living activities, with medical rehabilitation, nursing care and emotional support severely lacking (Song et al., 2019). Community service providers struggle to accurately gauge the needs of the elderly, and service delivery models tend to be perfunctory and rigid in content, resulting in a waste of elderly care resources (Du & Ma, 2024).

Against this backdrop, this study aims to explore a new approach to the regulation of care resources for elderly people with disabilities, centred on AI-enabled solutions, and to establish an integrated 'assessment-classification-intervention-feedback' smart care for the elderly service system. Specific objectives include: (1) developing an AI predictive model to enable intelligent forecasting and precise coding of frailty levels among the elderly (classified into four tiers: green, orange, yellow and red) based on multi-dimensional health data, thereby providing a scientific basis for tiered health management; (2) To establish a standardised assessment system for the functional abilities of elderly people with disabilities, and to train medical student volunteers using a VR simulation system to ensure the quality of data collection; (3) To build a digital health

management platform that utilises AI algorithms to optimise the allocation of community care resources, thereby achieving a service closed-loop characterised by “precise identification, tiered services and dynamic management”.

The theoretical significance of this study lies in enriching research on the digitalisation of community-based home care services and providing a new theoretical perspective for the field of smart care for the elderly. Its practical significance lies in alleviating the pressure of insufficient primary healthcare resources through in-depth collaboration between medical institutions and communities, improving the quality of life and health of the elderly, and providing a replicable practical model for the national strategy to address population ageing.

2. Domestic and International Research

2.1. Current State of Domestic Research

2.1.1. Research on Community-Based Home Care Services

Following the reform and opening-up, China entered a phase of rapid modernisation, rendering traditional elderly care models incapable of meeting contemporary needs. Research indicates that Chinese households are becoming smaller and more nuclear in structure, with an increasing proportion of elderly people living alone and a decline in the capacity of families to provide care. Consequently, the proportion of older adults opting for community-based home care continues to rise. The preferred care arrangements of older adults are influenced by multiple factors, and community-based home care has become the mainstream choice.

With regard to the home environment in the community, studies have shown that older adults who fear falling tend to have poorer physical function; therefore, making the community age-friendly is a key measure for improving the quality of home-based care for older adults (Sebastiao et al., 2024). Community renovations centred on optimising lighting systems, levelling road surfaces, and installing barrier-free facilities can effectively reduce the risk of falls among the elderly, as well as lower the risk of depression and disability (Ni et al., 2024). A systematic analysis of the current status and challenges of community-embedded elderly care in China has revealed issues such as a lack of baseline data, delays in information updates, and insufficient data accuracy.

2.1.2. Research on Community-Based Integrated Healthcare and Elderly Care

The ‘Guidelines for Home-based and Community-based Integrated Medical and Care Services (Trial Version)’, issued by the General Office of the National Health Commission, clearly defines the scope of community-based integrated medical and care services to include medical outreach services, home-based hospital bed services, home-based medical services, and traditional Chinese medicine services. Family doctors enhance older adults’ awareness of self-care and their ability to prevent and treat illnesses, demonstrating distinct advantages in managing the health of older adults with multiple chronic conditions (Zhang et al., 2015). Implementing continuous community health management for older adults with multiple chronic conditions can effectively improve their health status and increase life expectancy (Zhuang et al., 2021; Di & Wang, 2025).

In terms of mental health, a study using network analysis examined the relationship between loneliness, depression and anxiety among elderly people with disabilities in the community. It was found that frailty restricts the elderly's range of activities, leading to severe feelings of loneliness. Meanwhile, the decline in the ability of elderly people with disabilities to care for themselves, coupled with the significant disparity arising from the transition from self-reliance to dependence on others, is likely to induce psychological issues such as depression and anxiety (Cao et al., 2024). There are numerous adverse factors contributing to psychological depression and anxiety among elderly people in the community (Buzgová et al., 2024), including marital status, chronic illnesses, living alone, and self-efficacy; timely psychological intervention is therefore warranted (Hu et al., 2024).

2.1.3. Research on Digital Empowerment and Smart Care for the Elderly

Overall, research on community-based home care in China has followed the pace of national policy, gradually exhibiting development trends towards digital empowerment, the integration of medical care and elderly care, and a multi-faceted, integrated approach.Smart aging care has a significant positive impact on the health of older adults (Zhou et al., 2024). In 2023, Zhongshan City attempted to integrate existing resources and actively promoted the establishment of a 'Five-Community Collaboration' support system for elderly care services, comprising communities, social workers, community-based social organisations, medical student volunteers, and community charitable resources. It explored elderly care service models such as 'Party Building + Elderly Care', 'Culture + Elderly Care', and 'Mutual Aid + Elderly Care'. At the same time, it continued to deepen the 'Internet + Elderly Care'service model, utilising information technology and leveraging internet platforms to provide smart care for the elderly services that combine online and offline approaches.

2.2. Current State of Research Abroad

2.2.1. Research on Elderly Care Models in Developed Countries

As nations that entered an ageing society relatively early, the UK, the US and Japan have accumulated extensive experience through their long-term ageing processes. Research in the US has evolved from focusing on the quality of care in care homes and the training of care personnel, to emphasising the mental health of older people and innovating care models, and finally concentrating on the provision of personalised care services and the development of older people's potential. This in-depth and wide-ranging research has resulted in a relatively mature elderly care service system (Li et al., 2019).

Japan has proposed a regional integrated care service system, embedding elderly care facilities within the planning and design of community spaces to form a comprehensive and coordinated care network. Elderly care services in Japan's ageing cities are characterised by small-scale, decentralised and community-embedded models, providing personalised services that meet the diverse needs of older people and effectively alleviating the imbalance between supply and demand for care services (Luo et al., 2024).

In their practice of integrating medical and elderly care within the community, both the UK and Japan have continuously explored and moved towards 'integration', achieving a unified approach

to medical, elderly, and rehabilitation care. This integration is rich and comprehensive, encompassing all aspects of daily life, including clothing, food, housing and transport (Tang et al., 2024). In the UK, different types of care services are provided by various care providers, such as social care teams and shelters; in Japan, care is divided into home care and facility-based care, covering all aspects of medical, elderly care, and rehabilitation services.

2.2.2. Research on Smart Care for the Elderly and Chronic Disease Management

With regard to healthy ageing and the management of chronic diseases, scholars abroad have been actively exploring and proposing a range of measures. Some studies categorise these primarily into five main areas: multidisciplinary collaborative care, evidence-based nursing, patient self-management, clinical information systems, and lifestyle interventions (Ye et al., 2023).

The UK Life Trust was the first to propose the concept of 'smart care for the elderly', which involves leveraging technologies such as the internet, big data and the Internet of Things to organically integrate all stakeholders within the elderly care service system, thereby breaking down the constraints of time and space inherent in traditional care models and providing older people with higher-quality care services (Xi et al., 2014). Within the "smart care for the elderly" framework, Japan has adopted the e-Japan strategy to develop a model that prioritises both institutional design and technological advancement (Hussain et al., 2015); the UK considers community-based home care to be the model best suited to its national context, with the core of its smart care for the elderly model centred on community development. This involves establishing smart care for the elderly service centres at the community level to create convenient and diverse service conditions for elderly residents to age in place.

A comparative study of smart care for the elderly at home both domestically and internationally reveals that foreign countries began developing this sector earlier, with relatively mature technologies and more comprehensive service systems, providing important insights for the development of smart care for the elderly in China (Yan et al., 2023; Xu & Wang, 2019).

2.3. Research Review

A synthesis of domestic and international research reveals the following: (1) Community-based and home-based elderly care has become a key model for addressing population ageing; however, the assessment of disability levels among the elderly lacks intelligent methods, and the precision of services and the efficiency of resource allocation remain to be improved; (2) Medical student volunteers possess professional advantages when participating in community care services, yet there is a lack of a standardised training system to support high-quality data collection; (3) The use of digital technology to empower care services is a common global trend, but domestically, the application of AI predictive models in the classification and management of disability levels remains in its exploratory phase; (4) Existing research largely focuses on the application of single technologies or service models, lacking systematic studies centred on AI-based classification and coding that integrate volunteer training with community care resources.

Building upon existing research, this study aims to innovatively construct a new model centred on AI-enabled classification of elderly people with disabilities. Through the integration of 'AI predictive models + VR training + digital platforms', it seeks to achieve the precise identification,

tiered management and intelligent regulation of community care resources, thereby addressing the aforementioned research gaps.

3.Research Subjects and Methods

3.1. Study Sites

This study selected Luosi Community, Meiquan Community and Gaojiao Boyuan Community in Wenzhou City, Zhejiang Province as pilot communities.Inclusion criteria: (1) aged 60 years or older; (2) having resided in the pilot communities for at least six months; (3) being of sound mind and able to cooperate with the assessment; (4) the participant or a family member signing an informed consent form. Exclusion criteria: (1) those suffering from severe mental illness or cognitive impairment that prevents cooperation with the assessment; (2) those in the acute phase of an illness; (3) those who refuse to participate in this study.

3.2. Research Methods

3.2.1. Questionnaire Survey Method

A self-developed ‘Survey Questionnaire on the Health Needs of Community-Dwelling Older Adults’ and the ‘Older Adults’ Age-Friendly Renovation Needs Scale’ were employed to collect data on older adults’ basic information, health status, functional abilities, and service needs. The questionnaires underwent reliability and validity testing, yielding a Cronbach’s α coefficient of 0.87 and a test-retest reliability of 0.85.

In 2023, the research team conducted field research in Wenzhou communities using a questionnaire survey. A total of 610 questionnaires on the health management needs and self-management behaviours of elderly patients with chronic diseases were distributed across eight communities, with 588 valid questionnaires returned.

3.2.2. Field Research Method

Medical student volunteers were organised to visit pilot communities such as Luosi, Meiquan and Gaojiao Boyuan. Through home visits, community activities and health lectures, they established contact with older adults and their families, conducting face-to-face interviews and observations to gather first-hand data.

Leveraging the strengths of medical institutions, the team actively engaged in social practice and research, conducting fieldwork in communities through daily interactions and questionnaire distribution; they actively integrated into the daily lives of the elderly through health management services such as activities of daily living assessments, chronic disease management, psychological counselling, and dietary and exercise guidance.

Medical student volunteers, having obtained informed consent from the community, the elderly residents’ families and the elderly residents themselves, communicated with the elderly and their families regarding the project before conducting home visits to record information and collect relevant data, whilst ensuring data security and the legitimacy of data usage.

3.2.3. Virtual Reality (VR) Technology

The project uses a self-developed VR system for assessing the living abilities of disabled elderly individuals to comprehensively train medical student volunteers both theoretically and practically. The system comprises three main modules: theoretical learning, scenario simulation, and assessment evaluation. Volunteers use VR equipment to enter a virtual community home environment to complete the Barthel Index assessment tasks. The training effect was evaluated using a pre- and post-training design: both theoretical tests (full score 100 points) and practical assessments (evaluation accuracy) were conducted before and after training. A total of 120 volunteers were trained; post-training, theoretical scores increased from (68.5±7.2) points to (86.3±5.1) points ($t=18.6$, $P<0.001$), evaluation accuracy increased from (72.4±8.3)% to (91.7±4.2)% ($t=15.2$, $P<0.001$), service confidence index (1-5 points) increased from (2.8±0.6) points to (3.9±0.5) points ($t=13.8$, $P<0.001$), and the training period decreased from (4.5±1.2) weeks to (2.7±0.8) weeks ($t=9.4$, $P<0.001$).

3.2.4. Artificial Intelligence (AI) Technology

(1) Data Preprocessing

Based on the collected health data of elderly individuals, data cleaning was first conducted: logically erroneous data (such as Barthel index >100 or <0) and outliers such as age <60 were removed; for continuous variables with a missing rate of <5%, multiple imputation was applied, while variables with a missing rate ≥5% (such as cognitive function scores) were handled using a combination of deletion and imputation strategies. Ultimately, 426 valid samples were included in the analysis. The variables included the dependent variable (functional ability level, categorized into four levels based on the Barthel index) and independent variables (age, gender, types and number of chronic diseases, medication adherence, fall history, nutritional status, cognitive function, psychological status, social support, and 12 other characteristics).

(2) Algorithm Selection and Model Training

This study compared the performance of three machine learning algorithms in predicting disability levels: Random Forest, Support Vector Machine (SVM), and Back Propagation Neural Network (BPNN). The dataset was divided into training (298 cases) and testing (128 cases) sets in a 7:3 ratio, and model stability was evaluated using 5-fold cross-validation. The results showed that Random Forest outperformed SVM (82.3%, 80.5%, 79.8%, 80.1%) and BPNN (84.1%, 83.0%, 82.4%, 82.7%) in terms of accuracy (88.5%), precision (87.2%), recall (86.1%), and F1 score (86.6%), with the highest AUC value (0.91 vs. 0.86 vs. 0.88). Feature importance analysis indicated that age, number of chronic diseases, history of falls, and cognitive function scores were key factors influencing disability levels.

(3) Model Robustness Test

A ten-fold cross-validation was used to test the robustness of the random forest model. The accuracy fluctuated between 86.2% and 89.1%, with a standard deviation of 0.9%, indicating good model stability. In addition, external validation was conducted using 60 independently collected samples from March to April 2025. The model's predictive accuracy was 86.7%, which

is basically consistent with the results of the training set, confirming that the model has good generalization capability.

(4) Basis for Setting the Graded Coding Standard

The grading thresholds of the Barthel Index are set with reference to the "Standards for Assessing the Abilities of the Elderly" (MZ/T 039-2013) and relevant clinical studies: a score of 100 indicates full functional ability; 61-99 indicates mild disability; 41-60 indicates moderate disability; ≤40 indicates severe disability. This grading standard is widely applied in clinical practice and demonstrates good validity and reliability.

Based on the results of functional ability assessments or AI model predictions, the functional impairment levels of older adults are assigned codes: Green Code (fully capable), Orange Code (mild impairment), Yellow Code (moderate impairment) and Red Code (severe impairment), providing a foundation for tiered health management. The specific classification criteria are as follows Table 1.

Table 1. Classification and Coding Standards for Disability Levels and Health Management Strategies

Code Level	Level of Disability	Barthel Index	Health Management Strategy
Green Code	Fully capable	100 points	Health education, regular health check-ups, preventive healthcare, exercise guidance
Orange Code	Mild disability	61–99 points	Chronic disease monitoring, medication guidance, rehabilitation training, assessment of age-friendly home modifications
Yellow Code	Moderate disability	41–60 points	Home care, home hospitalisation, regular home visits, psychological support, respite care
Red Code	Red Code	≤40 points	Medical care, rehabilitation therapy, palliative care, training for family carers

3.2.5. Principal Component Analysis

Data standardisation is performed using the zscore function in MATLAB; the correlation matrix is calculated using the corrcoef function; eigenvalues are determined using SPSS software; principal components meeting statistical criteria are identified; a comprehensive evaluation score formula is established to assess service satisfaction and the effectiveness of the feedback mechanism.

The team established a three-party scoring mechanism involving medical student volunteers, carers and third parties, quantifying and assigning scores to the demands of each party and

integrating the analysis of feedback information. Taking the assessment of elderly satisfaction as an example, data was processed using principal component analysis to establish a comprehensive evaluation score formula, and feedback scores from each cycle were aggregated for comparison. Based on objective data results, supplemented by personalised recommendations, a third-party relationship was formed that balances supply and demand.The team established the "Luosi Community Elderly Volunteer Think Tank" data centre to centrally archive multi-party feedback data: medical student volunteer data is used to refine staffing arrangements and incentive mechanisms; caregiver data is used to optimise community staffing and care priorities; and third-party data is used to establish a two-way communication platform between the community and volunteers.

4. Construction of the New Model

4.1. Construction of the Theoretical Framework for the New Model

4.1.1. Theoretical Foundations of the Model

Based on the theories of active ageing, social support and resource dependence, this study constructs a novel model for community-based home care.The theory of active ageing emphasises enhancing the quality of life for older adults through health, participation and security; social support theory focuses on the material and emotional support individuals derive from social networks; whilst resource dependence theory emphasises the complementarity and integration of resources across organisations. These three theories collectively underpin the core logic of the new model: by integrating multiple resources—including medical student volunteers, communities and healthcare institutions—through digital technology, the model achieves the precise provision and efficient regulation of elderly care services.

4.1.2. Core Elements of the Model

The new model comprises four core elements: technological empowerment, driven by AI and VR as twin engines, with AI used to build disability level prediction models for the early identification and tiered management of health risks, and VR employed for immersive training of medical student volunteers to enhance their professional service capabilities; talent support, centred on medical student volunteers, drawing on the specialist strengths of Wenzhou Medical University to form interdisciplinary teams spanning medicine, management and engineering, and cultivating a service team that is both 'competent and compassionate' through systematic training;Service Provision: Centred on tiered health management, the model provides differentiated services based on a four-level coding system—Green Code (fully capable), Orange Code (mild disability), Yellow Code (moderate disability) and Red Code (severe disability)—including health education, chronic disease management, rehabilitation guidance, home care and assessments for age-friendly home modifications;Feedback and optimisation are underpinned by a three-party feedback mechanism, establishing evaluation channels for medical student volunteers, elderly individuals and their families, and community workers. Principal component analysis is employed to quantify satisfaction levels, thereby achieving continuous improvement and optimisation of service quality.

4.1.3. The "Assessment-Classification-Intervention-Feedback" Operational Model

The new model operates according to a closed-loop "Assessment-Classification-Intervention-Feedback" process, with AI-enabled technology serving as the central hub throughout: during the assessment phase, medical student volunteers trained in VR conduct home visits to assess Activities of Daily Living (ADL), or AI models are utilised to make preliminary predictions based on health data;In the classification stage, older adults are categorised into four levels—green, orange, yellow and red—based on the assessment results, and personalised health records are established; in the intervention stage, tailored health management services are provided for each level, including lifestyle guidance, chronic disease monitoring, rehabilitation training and recommendations for age-friendly home adaptations; in the feedback stage, regular follow-ups are conducted to collect feedback from medical student volunteers, older adults and their families, and community workers, enabling dynamic adjustments to service plans, optimisation of resource allocation and the formation of a closed-loop service system.

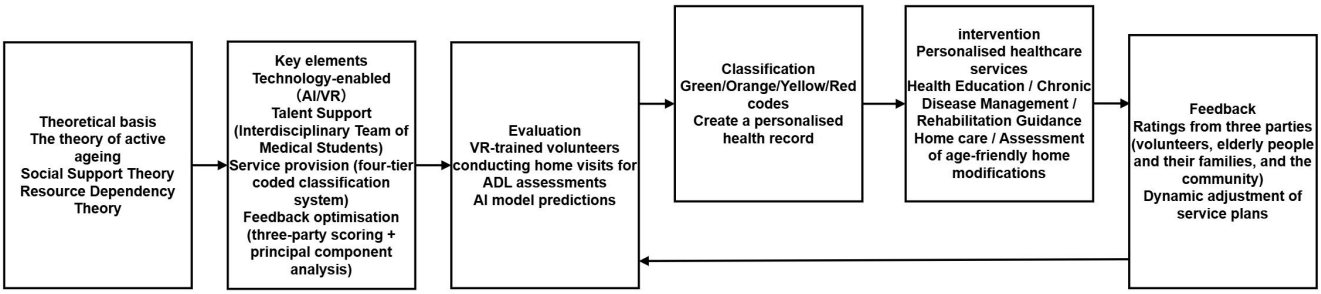


Figure 1. Overall Theoretical Framework

4.2. Application of the VR Simulation System in the Training of Medical Student Volunteers

This project recruits medical, management and engineering student volunteers, providing standardised training using a proprietary VR system for assessing the functional abilities of elderly people with disabilities. Through three core modules—theoretical learning, scenario simulation and assessment—the system enables volunteers to master the Barthel Index assessment criteria and home visit assessment skills. Following VR training, the volunteers achieved an assessment accuracy rate of 92%, their confidence in providing care increased by 35%, and the training cycle was shortened by 40%, thereby providing professional talent support for the collection of high-quality data for AI models.

4.3. Construction of AI Prediction Models and Coding of Disability Levels

4.3.1. Establishment of the Database

Medical student volunteers collected data on community-dwelling elderly residents through social surveys and home-visit functional assessments. The dependent variable was functional ability level (classified into four grades based on Barthel Index scores ranging from 0 to 100),

whilst independent variables included age, gender, types and number of chronic conditions (such as hypertension, diabetes, coronary heart disease, stroke and arthritis),medication adherence, history of falls, nutritional status, cognitive function, psychological state and social support. As of February 2025, the team had completed preliminary surveys of 38 households and formal surveys of 127 households in Luosi Community, and conducted further surveys of 261 households in Meiquan Community and Gaojiao Boyuan Community between January and February 2025, establishing a cumulative total of 426 valid samples.

4.3.2. Training of the AI Prediction Model

A Random Forest algorithm was employed to construct a disability level prediction model. The dataset was split into a training set and a test set in a 7:3 ratio. Feature importance analysis indicated that age, number of chronic conditions, history of falls, and cognitive function scores were key factors influencing disability levels. Following cross-validation, the model achieved an accuracy of 88.5% and an AUC of 0.91, demonstrating excellent predictive performance. The model application process is as follows: key health factors of the elderly are inputted; the AI model predicts the level of disability and generates a preliminary assessment report; medical student volunteers then conduct home visits to verify the findings; and finally, the level is confirmed and a code is assigned.

4.3.3. Grading, Coding and Health Management Strategies

Based on the results of AI predictions and manual assessments, a scientific four-level coding system has been established to enable precision health management. The core value of this grading system lies in the early identification and dynamic monitoring of disability risks through the AI model, thereby breaking away from the traditional ‘one-size-fits-all’ service model. This allows limited community care resources to be allocated differentially according to the actual degree of disability among the elderly: those with a ‘green code’ focus on preventive healthcare, whilst those with a ‘red code’ receive priority medical care, truly realising ‘precision measures and tiered management’ (Figure 2).

4.4. Establishment of the Digital Health Management Platform

The digital health management platform adopts a B/S architecture and comprises four major functional modules: the data collection module supports data entry via mobile apps, integration with wearable devices, and data import from hospital information systems (HIS); The AI analysis module integrates disability prediction models, health risk warning algorithms and a resource matching recommendation system; the service dispatch module automatically assigns tasks to the relevant volunteer teams based on the tiering results and tracks the service process; the feedback evaluation module collects feedback data from three parties—medical student volunteers, elderly individuals and their families, and community workers—to generate service quality reports and support principal component analysis.

The platform’s core functions encompass four key areas: dynamic health record management, which updates elderly residents’ health data in real time and supports multi-dimensional queries and statistical analysis; an intelligent early warning system, which automatically alerts volunteers and community doctors to abnormal fluctuations in physiological indicators such as blood

pressure and blood glucose; optimised resource allocation, which uses AI algorithms to analyse the supply and demand of community healthcare resources and propose allocation recommendations—for example, prioritising community health lectures for ‘green code’ elderly residents and ensuring home-based bed services for ‘red code’ elderly residents; AI-powered aged community simulation: Constructs a virtual aged community based on real-world data, featuring AI-generated elderly characters with varying levels of functional impairment, to simulate their behavioural patterns in community hospitals, rehabilitation centres and activity venues, thereby assessing the rationality of health management plans and resource allocation.

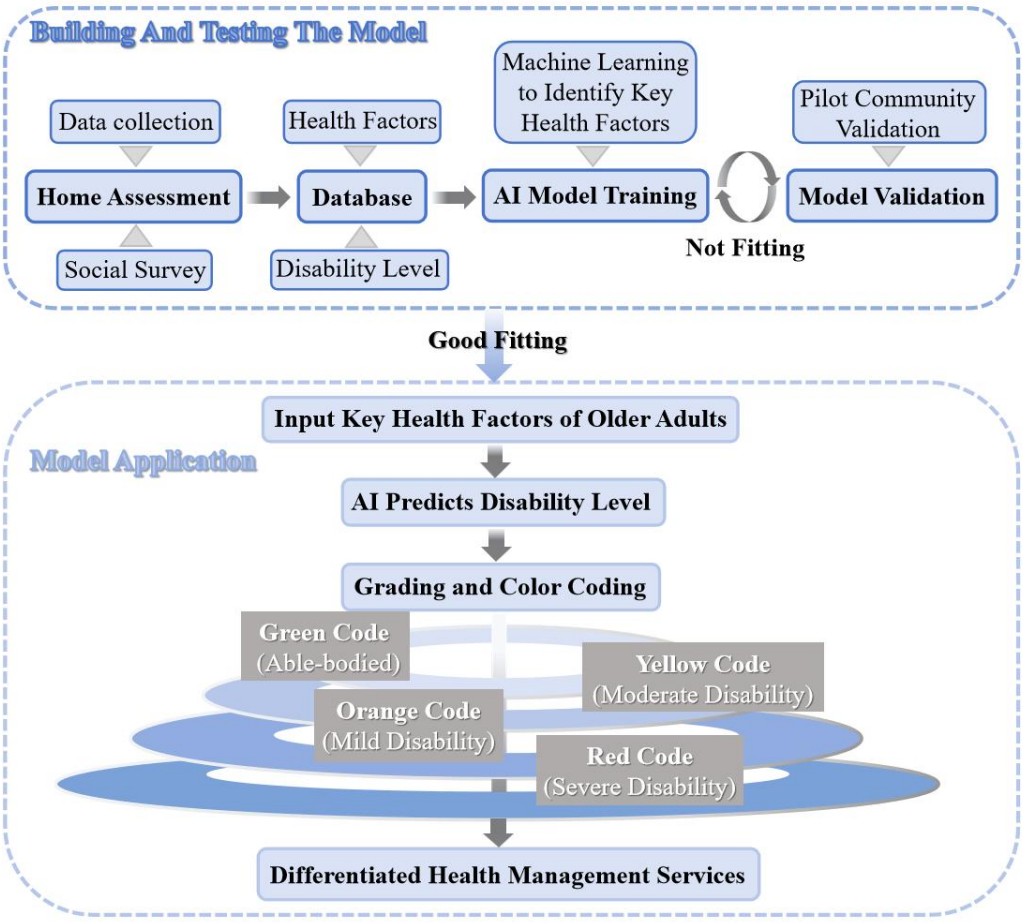


Figure 2. Flowchart of AI Prediction and Tiered Coding Process

5. Comparison of Innovations and Marginal Contributions

To clarify the marginal innovation of this study, three representative domestic studies (Zhongshan City's 'Five-Community Collaboration' model, Hangzhou City's 'Smart Elderly Care' pilot, and Shanghai City's 'Medical and Nursing Integration' platform) were selected for comparative analysis from four dimensions (Table 2).

Comparative analysis shows that the unique innovations of this study are: (1) Technological integration innovation — VR training and AI prediction are simultaneously applied to community elderly care, achieving full digitalization of the 'training-assessment-management' process; (2)

Management loop innovation — constructing a complete 'assessment-classification-intervention-feedback' loop, rather than optimizing a single link; (3) Resource integration innovation — establishing a 'school-community co-construction' model that connects university talent resources with community service needs; (4) Feedback mechanism innovation — combining quantitative feedback from three main entities with principal component analysis to achieve measurable and evaluable service quality.

Table 2. **Comparison and Analysis Table of Each Mode**

Dimension	This study	Zhongshan 'Five-Community Coordination'	Hangzhou 'Smart Elderly Care'	Shanghai 'Integration of Medical Care and Elderly Care'
Technica Application	AI and VR dual technology integration	Single information platform	Intelligent terminal devices	Medical information system
Management process	"Assessment - Grading - Intervention - Feedback" full closed loop	Service dispatch as the main focus	Health monitoring as the main focus	Medical service coordination
Resource integration	"University-Community-Hospital" Tripartite Collaboration	Internal Community Resources	Government-Enterprise Cooperation	Integration of Medical Institutions
Feedback mechanism	Three-Subject Quantitative Feedback (Principal Component Analysis)	Qualitative Follow-up	Satisfaction Questionnaire	Medical Quality Assessment
Hierarchical Management	Four-level coding (green/orange/yellow/red) precise stratification	No clear grading	Graded by age	Graded by disease type

6. Discussion and Outlook

As of February 2025, the new model has organised 12 large-scale volunteer service initiatives in the community, deploying 600 volunteer shifts, with a 60% rate of elderly disability information entered into the database. The pilot has achieved preliminary results in four areas: regarding the optimisation of medical resources, outpatient visits at community hospitals have increased by 25%, and the rate of elderly people seeking primary care has risen by 18%;in terms of improved health literacy, awareness of chronic diseases among elderly participants in health lectures rose from 45% to 72%; regarding satisfaction, elderly satisfaction with community elderly care services increased from 68% to 85%; and concerning volunteer development, over

90% of volunteers acquired knowledge of primary healthcare management and service provision, whilst over 80% mastered social survey skills.

The innovative value of this model is reflected in four aspects: technological integration innovation, which for the first time simultaneously applies VR training and AI prediction to the community elderly care sector, achieving full-process digitalisation of 'training assessment management'; resource integration innovation, which establishes a tripartite 'university community hospital' collaborative model to address the shortage of grassroots medical personnel; mechanism innovation, which establishes a quantitative feedback mechanism involving three key stakeholders to achieve closed-loop management of service quality; Conceptual innovation: it proposes the concept of an AI-enabled ageing community, offering forward-looking exploration for future smart care for the elderly. This model possesses strong replicability and can be adapted to suit the economic levels, degree of ageing, and medical resource conditions of different regions. It is planned to be rolled out to at least six communities in Wenzhou by 2026, and gradually expanded across the province and the country, providing a practical model for the national strategy to address population ageing.

Of course, the exploration and research of this new model also present certain challenges: the scope of the communities currently involved in the pilot scheme is not yet sufficiently broad, and it has not yet met the criteria for comprehensive testing and roll-out; simultaneously, our data collection is largely confined to the Wenzhou region, and the collection and analysis of relevant data samples for regions where full replication and roll-out are envisaged remain inadequate. Moving forward, we will continue to focus on enhancing the model's scalability and replicability, collecting relevant data more comprehensively and extensively for classification, organisation and analysis, thereby making our own contribution to the wider promotion and implementation of this new model!

Author Contributions:

Conceptualization, Yueyang Jiang; methodology, Wanting Lin.; software, Luyao Pan; validation,Wanting Lin.; formal analysis, Luyao Pan.; investigation, Yueyang Jiang.; resources, Yueyang Jiang.; data curation, Wanting Lin.; writing—original draft preparation, Luyao Pan; writing—review and editing, Han Chen.; visualization, Han Chen.; supervision, Yueyang Jiang.; project administration, Xiangyu Chen; funding acquisition, Yueyang Jiang. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest:

The authors declare no conflict of interest.

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Research Progress on Comorbid Depression in Epilepsy

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Abstract

Comorbid depression in epilepsy is a prevalent and severe clinical condition that significantly increases the psychosocial burden of patients. In recent years, with advances in research on its pathological mechanisms, the core biological processes underlying comorbid depression in epilepsy have become increasingly clarified. Its pathogenesis involves multiple pathways, including neurotransmitter imbalance, inflammation, genetic variations, and neuroendocrine abnormalities. This review summarizes the core pathological mechanisms of comorbid depression in epilepsy from four perspectives: neurotransmission, neuroendocrinology, hippocampal structure, and neuroinflammation, aiming to provide theoretical support for clinical diagnosis and treatment.

Keywords: Epilepsy; Depression; Comorbidity; Pathogenesis

1. Introduction

The prevalence of depression is rising year by year, and comorbid depression in patients with somatic diseases has attracted increasing attention in both clinical practice and scientific research. Among common neurological comorbidities, depression comorbid with epilepsy has become a major research focus owing to its high prevalence and severe clinical impacts. Comorbid depression not only worsens the frequency and severity of epileptic seizures but also significantly increases the risk of sudden unexpected death in epilepsy (SUDEP). The pathogenesis of depression comorbid with epilepsy is complex and heterogeneous, and exploring its key regulatory nodes and core pathways is of great research significance. Therefore, a systematic review of its pathophysiological mechanisms is clinically critical for the early identification, precise intervention, and optimized management of this comorbidity.

2. Monoamine Neurotransmitter Mechanisms

Monoamine neurotransmitter dysfunction erves as a key mechanism underlying epilepsy comorbid depression, which is accompanied by overlapping structural and functional alterations in the central nervous system. The primary neurotransmitters involved incude 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA).

2.1. Serotonin System

5-HT is widely distributed in the raphe nuclei, prefrontal cortex, and hippocampus, where it modulates emotion, behavior, and epileptogenesis. In depression, downregulation of the 5-hydroxytryptamine 2A receptor (5-HT_2A receptor) in the medial prefrontal cortex induces excessive glutamate (Glu) release, impaired synaptic plasticity, neuronal dysfunction, and depression-like behaviors (González-Arias et al., 2023). Such excessive Glu disrupts the excitation/inhibition balance and increases seizure susceptibility. Notably, reduced 5-HT levels and metabolism are observed in both depression and epilepsy. Using the 5-HT_2A agonist Cimbi 36, Erritzoe et al. (2023) directly measured brain 5-HT release in 17 depressed patients and 20 healthy controls, demonstrating reduced 5-HT levels and confirming 5-HT dysfunction as a core feature of depression. Consistently, impaired central 5-HT signaling is closely associated with epileptic activity, identifying the central 5-HT system as a key hub in epilepsy–depression comorbidity.

In temporal lobe epilepsy (TLE) models, reduced extracellular 5-HT is a hallmark of comorbid depression. 5-HT depletion reduces 5-hydroxytryptamine 1A receptor (5-HT_1A receptor) binding potential, whereas increasing 5-HT signaling exerts seizure-inhibitory effects (Bølling-Ladegaard et al., 2023). Recurrent seizures induce neuronal damage, impair 5-HT metabolism, and thereby promote depressive symptoms (Schönhoff et al., 2021). 5-HT deficiency appears critical in this comorbidity, as the severity of comorbid depression correlates negatively with serum 5-HT concentrations (Sun et al., 2024). Furthermore, lacosamide exerts both antiepileptic and antidepressant effects by elevating 5-HT levels and reducing Interleukin-6 (IL-6) expression (Li et al., 2025), supporting the 5-HT system as a critical mechanistic link between epilepsy and depression.

2.2. Norepinephrine System

Dysfunction of the NE system is closely associated with the occurrence and progression of epilepsy and depression. NE not only directly modulates epileptic seizures but is also closely linked to SUDEP. NE and 5-HT neurons participate in the regulation of SUDEP through synergistic effects, with the dorsal raphe nucleus (DR)–locus coeruleus –parabrachial nucleus (PBN) circuit serving as the key neural pathway. This pathway can inhibit seizure-induced respiratory arrest associated with epileptic seizures by activating 5-HT_2A receptors and NE-α_1 receptors in the PBN, thereby reducing the risk of SUDEP (Xu et al., 2025). Under stress, the lateral habenula–locus coeruleus circuit forms a positive feedback loop that drives persistent neural hyperactivity and depression-like behaviors (Xin et al., 2024). In focal epilepsy models, the emergence of depressive-like behaviors is associated with reduced NE levels (Kumar et al., 2016). Region-specific NE regulation follows a ‘compensation-injury’ pattern: increased NE in

the locus coeruleus–cortex pathway acts as an acute adaptive antiepileptic response, whereas decreased hippocampal NE promotes neuroinflammation and epileptogenesis (Gu et al., 2025). NE also exerts antiepileptic effects by modulating free fatty acid release, linking peripheral metabolic status to central neuronal excitability (Li et al., 2025).

2.3. Dopamine System

Dopaminergic circuits regulate emotional processing, reward function, and neuronal excitability. Dopamine receptors are divided into two major families. D1-like receptors (D1LR) generally promote seizures, whereas D2-like receptors (D2LR) exert antiepileptic effects (Bozzi & Borrelli, 2013). In genetic generalized epilepsy, upregulated D1LR and downregulated D2LR in the prefrontal cortex enhance seizure susceptibility (Birioukova et al., 2024). Optogenetic manipulation of dorsal striatal neurons bidirectionally modulates epileptic seizures. Specifically, D2LR activation inhibits thalamocortical synchronous discharges, suppressing seizure motor manifestations and duration without altering the onset of epileptiform discharges (Hyder et al., 2025).

Dopaminergic imbalance contributes to epileptogenesis and mediates depressive symptoms in individuals with epilepsy. Chronic unpredictable stress suppresses DR neuronal activity and disrupts synaptic input to DA neurons; DR-DA projections to dorsal striatal $CaMKII^{++}$ neurons modulate depression-related behaviors (Wang et al., 2024). Similarly, chronic stress impairs dopaminergic transmission, whereas nucleus accumbens stimulation alleviates depressive behaviors by enhancing DA release (Song et al., 2024). In epileptic rats, DA system abnormalities are concentrated in the medial prefrontal cortex (Birioukova et al., 2024), a major target of ventral tegmental area (VTA) DA neurons (Gunaydin et al., 2014), suggesting a shared neural circuit basis for epilepsy and depression. The DA system may therefore serve as a key molecular bridge between the two disorders, informing mechanistic studies of their comorbidity.

The nigrostriatal DA pathway regulates the duration of absence seizures; its degeneration reduces DA levels and triggers compensatory increases in 5-HT, thereby prolonging spike-wave discharges (Tugba et al., 2022). This links DA dynamics to seizure activity and electroencephalography (EEG) alterations, offering potential biomarkers for comorbid disease. The serotonergic raphe nucleus–prefrontal cortex pathway and dopaminergic VTA–nucleus accumbens pathway display functional vulnerability prior to seizure onset. Chronic epilepsy progressively impairs these pathways, reducing neurotransmitter release and contributing to the development of comorbid depression (Medel-Matus et al., 2017).

D2LR agonists exert antiepileptic effects by activating parvalbumin-positive interneurons (Brodovskaya & Kapur, 2021). Although DA signaling is clearly involved in the pathogenesis of epilepsy-comorbid depression, related pharmacotherapeutic and mechanistic studies remain limited, warranting further preclinical and clinical investigations for targeted therapeutic development.

3. Hypothalamic-Pituitary-Adrenal Axis

The Hypothalamic-Pituitary-Adrena (HPA) axis connects neuroinflammation and the endocrine system, integrating neural, endocrine, and immune signals. Both epilepsy and depression disrupt HPA axis function via cytokines, and HPA hyperactivation further promotes inflammatory mediator release, forming a vicious cycle.

Overactivation of the HPA axis impairs temporal lobe structure and function, and epileptic seizures further exacerbate this injury, thereby weakening the HPA axis's normal negative feedback regulation (Basu et al., 2022; Gulyaeva, 2021) . As unpredictable stressors, epileptic seizures activate microglia to secrete inflammatory mediators including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6),which modulate HPA axis activity (Pereira et al., 2022) and contribute to the development of depressive symptoms.

Glucocorticoids (GC), the core effector molecules of HPA axis stress responses, alter hippocampal network function and related mood, learning, and memory processes when present in excess (Joëls, 2001). Recurrent seizures induce hippocampal neural network abnormalities, neuronal loss, glial proliferation, and synaptic remodeling (Choy et al., 2022), which increases neuronal spontaneous electrical activity—suggesting GC may participate in epilepsy-depression comorbidity by disrupting hippocampal structure and function. GC exert effects via the glucocorticoid receptors (GR) and mineralocorticoid receptors (MR); a central imbalance in the GR/MR ratio is key to HPA axis dysfunction and susceptibility to mental diseases (Harris et al., 2013). FK506 binding protein 5 regulates the GR pathway, with reduced expression enhancing HPA axis negative feedback (Lin et al., 2021). Meanwhile, the GR antagonist mifepristone shows promise for treating major depressive disorder (MDD) in patients with childhood trauma (Linsen et al., 2023).Hippocampal MR maintains HPA axis inhibition under basal low cortisol levels, and collaborates with GR in negative feedback regulation under stress-induced high cortisol conditions (De Kloet, 2022) . Using an in vivo dual-color reporter system, Han (Han et al., 2021)et al. first demonstrated that hippocampal GR inhibition of nuclear factor-κB (NF-κ, a key inflammatory transcription factor) occurs in three temporal phases, with late GR inactivation serving as a key switch for the transition from inflammation to depression—highlighting GR and MR as core mechanisms underlying comorbidity.

Clinical studies show that MDD patients with elevated adrenocorticotropic hormone (ACTH) levels have increased Glu and glutamine and decreased glutathione (GSH, a key antioxidant) and γ-aminobutyric acid (GABA, the major inhibitory neurotransmitter) in the dorsal anterior cingulate cortex; Notably, GSH and GABA independently predict depression severity, indicating HPA axis hyperactivity contributes to depression and cognitive impairment via an excitation-antioxidant imbalance (Tian et al., 2024). Additionally, ACTH treatment transiently reduces levels of inflammatory factors (IL-6, interferon-gamma, monocyte chemoattractant protein-1) in infants with drug-resistant epilepsy (Kaczorowska et al., 2023), indicating that ACTH may regulate seizures through immune-inflammatory modulation-neuroinflammation, epilepsy, and depression.

4. Hippocampus

As a component of the limbic system located in the medial temporal lobe, the hippocampus—comprising the hippocampus proper, dentate gyrus, subiculum, entorhinal cortex, and hippocampal remnant—regulates memory, spatial orientation, emotion, and visceral activities. Hippocampal sclerosis (HS), the most common pathological feature in TLE, is associated with a 34.5% prevalence of comorbid depression in TLE-HS patients(Visoná De Figueiredo et al., 2021).Elevated serum IL-6 and morning cortisol levels are independent risk factors for comorbid depression in TLE-HS patients (Aljafen et al., 2024). A meta-analysis reported that HS increases depression risk by 58% , with an overall prevalence 42% (Cai et al., 2023), confirming hippocampal structural abnormalities elevate epilepsy-depression comorbidity risk.

The hippocampus has CA1-CA4 subregions. Among them, CA1-CA3 are closely linke to epilepsy and depression, while CA4-related studies are limited. CA1 chandelier cells inhibit abnormal neuronal discharge via GABAergic synapses during seizures (anti-epileptic effect), and blocking their transmission exacerbates seizures (Li et al., 2026). Post-status epilepticus (SE), CA1 upregulates inflammation- and excitability-related genes, promoting epileptogenesis (Galvis-Montes et al., 2023).Psychological stress increases formaldehyde, damaging CA1 neurons, inducing apoptosis, inactivating 5-HT/DA systems, and triggering depressive-like behaviors (Wu et al., 2026). Chronic stress can downregulate the expression of Dickkopf-related protein 3 in hippocampal CA1 neurons, enhancing microglial phagocytosis of excitatory synapses and inducing depression/anxiety-like behaviors (Chen et al., 2025).CA2 neurons modulate hippocampal network excitability, and their dysfunction is associated with psychiatric disorders. In a pilocarpine-induced TLE model, CA2 pyramidal neurons show hyperexcitability and hypoinhibition; chemogenetic silencing reduces chronic seizures by 42% (Whitebirch et al., 2022), and early silencing shortens SE, improves EEG abnormalities and social behaviors (Lisgaras et al., 2023). Deletion of Efhd2-related factor 3B in the CA2 region leads to social cognitive deficits and reduced neuronal excitability (Chen et al., 2025), indicating it is a key comorbidity regulatory target. In the SE model, the complement component 3–complement component 3a receptor pathway mediates microglia-astrocyte crosstalk in CA3, participating in epilepsy-related neurodegeneration (Wei et al., 2021). Mecamylamine inhibits CA3 epileptiform discharges (Zapukhliak et al., 2021), and CA3-expressed TGR5 regulates depressive-like behaviors (Li et al., 2024). Collectively, these findings indicates that hippocampal subregional abnormalities constitute a key mechanism underlying epilepsy-depression comorbidity.

Hippocampal neuroplasticity, which refers to adaptive structural and functional changes, underpins learning, memory, and cognition. It modulates neuronal proliferation, differentiation, and synaptogenesis mainly through the Wnt/β-catenin and brain-derived neurotrophic factor (BDNF)–tropomyosin receptor kinase B (TrkB) pathways. In mouse models, cystine-rich intestinal protein-like protein 5 deficiency in glutamatergic neurons results in elevated hippocampal BDNF expression and enhanced activation of its receptor TrkB, thereby mediating spontaneous seizures (Zhu et al., 2023). BDNF-TrkB also maintains SE neuronal excitability via GluN2B-containing N-methyl-D-aspartate (I) receptors (De Luca et al., 2025). BDNF participates in epileptic memory consolidation (Lai et al., 2024), and exogenous irisin increases

BDNF, reducing seizures and neuronal damages (Yu et al., 2022). BDNF interacts with 5-HT and the HPA axis: activation of hippocampal 5-HT_1A receptors, which is regulated by GC, elicits an antidepressant effect (Wang et al., 2025). Chronic corticosterone drives dentate gyrus hyperactive autophagy, degrading BDNF and inducing depressive-like behaviors, reversible by neuron-specific autophagy-related gene 5 knockout (Zhang et al., 2023).

BDNF and 5-HT synergistically regulate comorbidity: BDNF upregulation in 5 -HT neurons activates hippocampal TrkB, improves 5-HT signaling, and enhances stress resilience, forming a BDNF–TrkB–5-HT–HPA axis regulatory mechanism that links the hippocampus, monoamines, and endocrine system (Leschik et al., 2022).

5. Cytokines and Neuroinflammation

Neuroinflammation is a key process in both epilepsy and depression. Chronic inflammation contributes to depressive behaviors through glial activation, inflammatory mediator release, and disrupted neurotransmitter metabolism. Microglia play a central role: seizures activate microglia to release proinflammatory cytokines, destabilize neural networks (Prinz et al., 2019), and increase seizure susceptibility. Stress-induced glial activation in the lateral habenula promotes depressive-like behaviors (Xin et al., 2024).

5.1. IL-6

IL-6 is a pivotal proinflammatory factor linking epilepsy and depression, and a risk factor for adult epilepsy recurrence, with its levels negatively correlated with the time to recurrence (Fang et al., 2024). In a chronic TLE rat model, hippocampal upregulation of IL-6 induces indoleamine 2,3-dioxygenase 1 expression, which increases the kynurenine/tryptophan ratio while reduces the 5-HT/tryptophan ratio, thereby triggering epilepsy-related depressive-like behaviors (De Luca et al., 2025). Additionally, a Mendelian randomization study further indicated a causal relationship between IL-6 receptor (IL-6R) antagonist and reduced epilepsy risk, underscoring that IL-6 exerts a dual regulatory effect on epilepsy and its concomitant neuropsychiatric disorders (Yu et al., 2024).

In a mouse depression model induced by chronic social defeat stress (CSDS), microglial activation elevates IL-6, promoting astrocyte apoptosis and atrophy in the hippocampal CA1, ultimately resulting in dendritic spine loss and depressive-like behaviors (Shen et al., 2025). Notably, knockdown of the IL-6R significantly reduces its expression in astrocytes and effectively reverses CSDS-induced astrocyte atrophy, as reflected by a marked increase in cellular branch numbers. Furthermore, Lactobacillus reuteri L6 alleviates depressive-like behaviors by inhibiting IL-6 expression, upregulating BDNF and 5-HT levels, and enhancing GABAergic signaling (Ma et al., 2024), which provides a novel approach for intervening in epilepsy comorbid with depression through intestinal flora regulation.

5.2. TNF-α

Elevated TNF-α levels are closely and significantly associated with depressive symptoms, further supporting the "inflammation-depression" causal pathway (Martino et al., 2025).

Specifically, increased peripheral TNF-α elevates the central self-stimulation threshold in mice, reduces reward sensitivity and induces anhedonia—a core clinical symptom of depression (Van Heesch et al., 2013). Peripheral TNF-α levels are significantly elevated within 24 hours after epileptic seizures, which promotes Glu release, impairs GABAergic inhibitory function, and further disrupts the excitation-inhibition balance of neurons (Han et al., 2018). Excessive TNF-α signaling can further exaggerate Glu release and suppress GABAergic transmission, thereby exacerbating subsequent epileptic seizures and neuronal injury (Han et al., 2018). Accumulating evidence has demonstrated that decreasing TNF-α levels, inhibiting NF-κB pathway activation, and restoring hippocampal 5-HT levels effectively ameliorate depressive- like behaviors (Tarwani et al., 2025). These findings collectively provide a potential novel therapeutic target for the management of epilepsy comorbid with depression.

5.3. IL-1β

Elevated plasma IL-1β levels are specifically associated with epilepsy-related depression (Vieira et al., 2015). As a critical proinflammatory cytokine, IL-1β exerts dual pathogenic effects by disrupting neuronal function and triggering neuroinflammatory responses, which collectively contribute to the progression of both epilepsy and depression.

Specifically, IL-1β promotes Glu release and inhibits GABA function, which disrupts the balance between excitatory and inhibitory neurons, enhances neuronal hyperexcitability, and thereby increases seizure susceptibility. Concurrently, IL-1β induces the activation of the NF-κB pathway in microglia, which in turn upregulates the production of nitric oxide (NO) (Ferreira et al., 2010). Notably, NO exerts a concentration-dependent effect on neuronal function: low concentraions exert neuroprotective effects, whereas high concentrations inhibit the activity of neuronal mitochondrial cytochrome oxidase, leading to neuronal depolarization and further promoting Glu release (Bal-Price & Brown, 2001). Abnormally elevated levels of Glu and NO then overactivate NMDA receptors, ultimately inducing abnormal neuronal discharge and exacerbating both epileptic seizures and neural damage. Beyond its effects on epileptogenesis, excessive IL-1β contributes to depressive phenotypes through multiple pathways. It induces intracellular calcium overload in neurons, which further aggravates neuronal apoptosis and brain injury. Moreover, IL-1β can cross the blood-brain barrier to activate the HPA axis, promoting the overproduction of cortisol; this excessive cortisol release not only exacerbates neuroinflammation (Sălcudean et al., 2025) but also disrupts the balance of neurotransmitters closely associated with depression, including 5-HT and DA (Kim et al., 2016).

Furthermore, accumulating evidence highlights the link between IL-1β and cognitive as well as emotional dysregulation in depression. Serum IL-1β levels are positively correlated with the severity of cognitive impairment in patients with depression (Jin et al., 2020). In addition, IL-1β serves as a critical regulator of pathways that modulate abnormal functional connectivity between the middle frontal gyrus and mid-anterior cingulate cortex/insula, which in turn exacerbate depressive symptoms in patients with bipolar II depression (Xiao et al., 2024).

Collectively, these findings indicate that IL-1β acts as a central mediator in the “inflammation-brain network-emotion” axis, providing a novel IL-1β-targeted therapeutic strategy for the

tripartite intervention of epilepsy, depression, and their comorbidity.

6. Conclusion

The pathophysiological mechanism of comorbid depression in epilepsy involves a synergistic effect of multiple pathways, including NE dysregulation, abnormal signaling between 5-HT neurons and astrocytes, and neuroinflammation. The interactive relationships and final effects of these pathways are shown in the mechanism diagram (Figure 1). Elucidating these mechanisms supports early screening, targeted therapy, and prognostic evaluation. However, most current studies focus on single mechanisms rather than integrated networks, and core drivers remain unclear. Additionally, evidence is largely derived from animal and basic research, with insufficient high-quality clinical cohort and longitudinal studies. Therefore, further translational research is needed to characterize the human pathophysiology of epilepsy-comorbid depression.

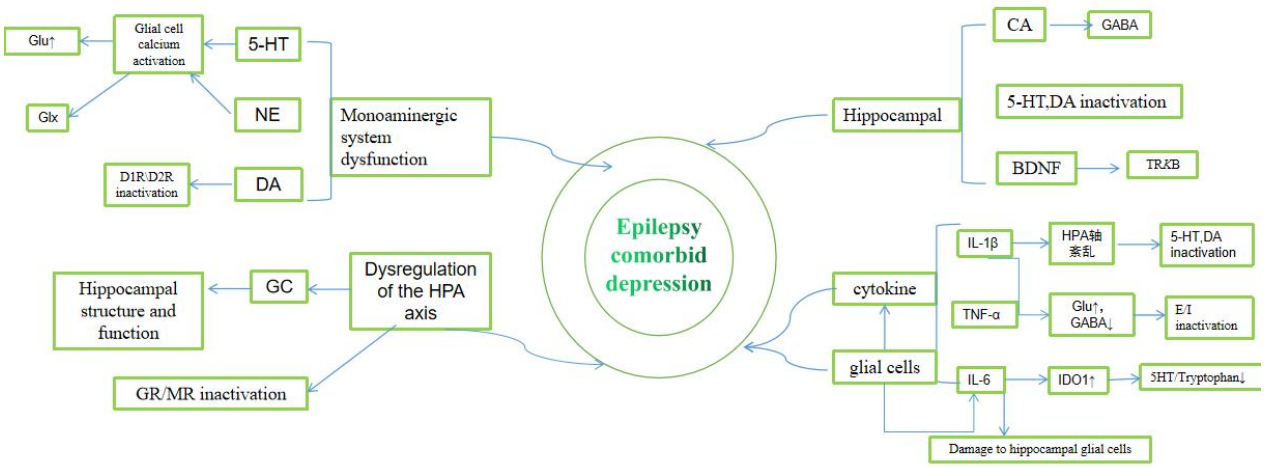


Figure 1. The mechanism diagram

Appendix:

Appendix1. List of abbreviations

English abbreviation	Full name
SUDEP	Sudden unexpected death in epilepsy
5- HT	5- hydroxytryptamine
NE	Norepinephrine
DA	Dopamine
5-HT_2A receptor	The 5-hydroxytryptamine 2A receptor
Glu	Glutamate

TLE	Temporal lobe epilepsy
5-HT$_1$A receptor	5-hydroxytryptamine 1A receptor
DR	Dorsal raphe
PBN	parabrachial nucleus
D1LR	D1- like receptors
D2LR	D2- like receptors
VTA	Ventral tegmental area
EEG	Electroencephalography
HPA	Hypothalamic-pituitary-adrenal
IL-1β	Interleukin-1β
TNF-α	Tumor necrosis factor-α
IL-6	Interleukin-6
GC	Glucocorticoids
GR	Glucocorticoid receptors
MR	Mineralocorticoid receptors
MDD	Major depressive disorder
NF-κB	Nuclear factor-κB
ACTH	Adrenocorticotropic hormone
GABA	γ-aminobutyric acid
HS	Hippocampal sclerosis
SE	Status epilepticus
BDNF	Brain-derived neurotrophic factor
TrkB	Ttropomyosin receptor kinase B
NMDA	N- methyl- D- aspartate
IL-6R	IL-6 receptor
CSDS	Chronic social defeat stress
NO	Nitric oxide

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A Theoretical Study on Consumer Adoption Intentions for Digital Health Products from the Perspective of Information Framing Theory

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Abstract

This paper adopts Information Framing Theory as its core perspective to conduct a theoretical exploration and conceptual framework construction on existing research regarding consumer adoption intentions for digital health products. The study clarifies the core concepts of Information Framing Theory, constructs an integrated theoretical model combining Information Framing Theory, the Theory of Planned Behavior (TPB), and the Technology Acceptance Model (TAM), and identifies key factors influencing user adoption of digital health products. On this basis, the paper compares the differences in the effects of various information frames and behavioral characteristics of adoption across different scenarios. With a particular focus on the unique characteristics of Traditional Chinese Medicine (TCM) health management scenarios, the paper proposes market optimization strategies based on information framing design. Finally, this paper summarizes the core findings and limitations of the research, offers recommendations for future research directions and corporate practices, and aims to provide theoretical references and practical guidance for the market promotion of TCM-oriented digital health products.

Keywords: Information Framing; Digital Health Products; Consumer Adoption Intentions; Traditional Chinese Medicine Health Management; Theory of Planned Behavior; Technology Acceptance Model

1. Introduction

Digital health products have achieved widespread adoption in the global market. According to the Digital Health Industry Data Book released by Grand View Research in January 2023, the global digital health market exceeded $211 billion in 2022, with a projected compound annual growth rate (CAGR) of 15.1% from 2021 to 2028. However, consumer adoption rates show

significant regional disparities: while the penetration rate of mobile healthcare applications exceeds 40% in Europe and the United States, it remains around 10% in some emerging markets. This gap highlights that the delivery mode of health information is a core factor influencing user decision-making and product adoption efficiency. As a core theory explaining individual decision-making behavior, Information Framing Theory can guide consumers' value perception through differentiated information presentation design, thus providing a theoretical solution to the industry pain point of uneven adoption rates. Meanwhile, existing studies have confirmed the key role of information presentation in health technology adoption: Pournik et al. (2025) found in their analysis of the ADLIFE digital personalized care platform based on the UTAUT framework that perceived ease of use and performance expectancy have a significant positive impact on platform adoption behavior, while technology anxiety is a core barrier, which further verifies the moderating effect of information framing design in the user adoption process.

Although existing research has preliminarily confirmed the moderating role of information framing in health technology adoption, there are still significant research gaps in the field of consumer adoption of digital health products. First, most existing studies focus on traditional health behaviors (such as disease screening and vaccination) or general mobile health applications, while there is insufficient systematic research on the information framing design of digital health products that integrate technical attributes and health service functions, and the mechanism between different types of information (benefit, risk, emotion) and product characteristics is still unclear. Second, the contextual boundaries of information framing effects have not been fully clarified: the moderating mechanisms of variables such as individual health literacy, risk perception, technology trust, and cultural identity on framing effects have not been systematically sorted out, and existing research mostly stays at the analysis of single factors, lacking an integrated theoretical perspective. Most importantly, digital health products based on TCM health management face unique cultural perception barriers and trust-building challenges, but existing information framing research has rarely involved this field, let alone culturally embedded framing design. How to organically integrate traditional TCM concepts such as "preventive treatment of disease" and "yin-yang balance" with information framing design remains an unexplored research gap.

Based on the above research gaps, this study focuses on three core research questions: First, how do different types of information frames influence consumers' adoption intentions for digital health products, and what are their underlying mechanisms? Second, are the effects of information frames moderated by product usage scenarios (chronic disease management vs. health prevention) and consumer characteristics (health literacy, TCM cultural identity, technology trust)? Third, for TCM health management scenarios, how to construct a culturally adapted information framing system integrated with traditional TCM theories and verify its effectiveness? This study has clear academic and practical value. Academically, existing research on digital health product adoption mostly focuses on single dimensions such as technical features or individual cognition, and has not yet formed a systematic integration of the mechanism of information framing in health communication; this study can fill the gap of fragmented research on framing effects and construct an integrated theoretical model. Practically, the promotion of

TCM digital health products often faces the dual challenges of cultural perception barriers and insufficient functional trust. This study can provide empirical references for optimizing the information dissemination design and market promotion strategies of such products.

2. Core Theoretical Foundationand Integrated Conceptual Model

2.1. Core Concepts of Information Framing Theory

Information Framing Theory originates from Prospect Theory, and its core logic is to influence individual cognition and decision-making preferences through differentiated information presentation methods. In the field of health communication, the theory is classically divided into two core dimensions: rational frames and emotional frames. Rational frames can be further subdivided into gain frames and loss frames: gain frames emphasize the positive health benefits obtained by using the product, while loss frames focus on the potential health losses caused by not using the product. Rothman and Salovey (1997) confirmed in their seminal study on health behavior that the effects of these two frames have significant contextual boundaries, which has become the core basis for health information design. Emotional frames enhance information influence by evoking positive or negative emotions, forming a chain reaction mechanism of "emotional arousal - attitude change - behavioral adoption". The latest research by Yan (2025) shows that the research on information adoption and persuasion mechanisms in health communication is shifting from simple frame comparison to multi-factor interaction analysis, covering cutting-edge topics such as information perceived value, information delivery strategies, and moral licensing effect.

2.2. Theoretical Basis of Health Behavior and Technology Adoption

The Theory of Planned Behavior (TPB) and the Technology Acceptance Model (TAM) are classic analytical frameworks for explaining individual health technology adoption behavior. The core logic of TPB is that individual behavioral intention is mainly affected by three core variables: attitude, subjective norms, and perceived behavioral control (Shlash Mohammad et al., 2024). TAM further refines the core drivers of technology adoption into two key variables: perceived usefulness and perceived ease of use, which can explain 40% of the variance in individual behavioral intention to use information systems across scenarios (Leung et al., 2025). Existing studies have confirmed that integrating Information Framing Theory with TPB and TAM can construct a complete transmission path of "information framing - cognitive change - adoption intention": information framing can exert a significant moderating effect on the core variables of TPB and TAM by changing individuals' perception of product benefits, risks, and operational difficulty, thereby ultimately affecting adoption intention.

2.3. Integrated Conceptual Model of Digital Health Product Adoption

To address the theoretical disconnection in the original research, this study constructs an integrated conceptual model that clarifies the logical relationship between variables, with a structured definition as follows:

Independent Variable: Type of information frame, including rational frames (gain frame/loss frame) and emotional frames (positive emotion frame/negative emotion frame).

Mediating Variables: Core variables of TPB and TAM, including attitude towards the product, subjective norms, perceived behavioral control, perceived usefulness, and perceived ease of use. The mediating path is: information frame influences the mediating variables, which in turn drive the formation of adoption intention.

Moderating Variables: Individual and contextual variables, including user health literacy, TCM cultural identity, technology trust, product usage scenario (chronic disease management/health prevention), and age group.

Dependent Variable: Consumer's adoption intention for digital health products, including initial use intention and continuous use intention.

This model clarifies the core mechanism of information framing affecting adoption intention: information frames shape users' cognitive evaluation of products through rational and emotional paths, act on the core variables of TPB and TAM, and ultimately drive adoption intention; meanwhile, the above paths are regulated by individual characteristics and scenario factors. The subsequent analysis of this paper will strictly follow the logical framework of this model.

3. Research Progress on Digital Health Product Adoption from the Perspective of Information Framing

3.1. Heterogeneity of the Effects of Different Information Frames

The differential impact of gain and loss frames is the core topic of existing research, and the effect of frames is realized by influencing users' attitude, perceived usefulness, and perceived behavioral control in the integrated model. Existing research has formed a basic consensus: loss frames are more effective in high-risk scenarios such as chronic disease management, mainly by enhancing users' perceived behavioral control over health risks and negative attitudes towards inaction; while gain frames have a comparative advantage in health prevention scenarios, mainly by improving users' perceived usefulness of products and positive attitude towards health behaviors.

Meanwhile, framing effects show significant population heterogeneity, which is mainly regulated by users' health literacy and age. The unique value of emotional frames has also been widely verified: Yan (2025) pointed out that moderate emotional arousal can maximize users' attention and cognitive engagement, and emotional frames can amplify the influence of rational frames by enhancing the emotional resonance of information, thus further strengthening the prediction of attitude and intention in TPB.

3.2. Characteristics of Adoption Behavior in Different Scenarios

In line with the integrated conceptual model, the effect of information frames in different scenarios is mainly reflected in the differences in the significance of mediating variable paths.

In chronic disease management scenarios, the combined application of gain and loss frames can significantly improve patients' long-term management adherence. In this scenario, loss frames mainly act on perceived behavioral control by highlighting the risk of disease progression caused by non-intervention, while gain frames mainly improve the perceived usefulness of products by presenting the benefits of standardized management. An empirical study by Leung et al. (2025) on elderly patients with chronic diseases in China showed that performance expectancy (perceived usefulness), effort expectancy (perceived ease of use), social influence (subjective norms), and facilitating conditions (perceived behavioral control) have a significant positive impact on users' continuous use intention of mobile health applications. This group is particularly sensitive to the timeliness and relevance of information quality, which will directly affect their perceived ease of use and perceived usefulness of products.

In health prevention scenarios, the effect of frames also shows significant heterogeneity, and gain frames play a more dominant role by improving users' positive attitude and perceived usefulness of products. A study by Zhang et al. (2025) on the integrated TCM preventive treatment service model showed that a digital service model integrating intelligent constitution identification, personalized intervention, remote follow-up, and real-time monitoring can significantly improve patients' treatment adherence (89.7% vs. 74.2%) and satisfaction (95.4% vs. 78.7%). This result verifies that the synergistic optimization of information framing and functional design can significantly enhance users' perceived usefulness and positive attitude, thereby improving adoption intention.

4. Unique Characteristics and Information Framing Optimization Strategies for TCM Health Management Scenarios

4.1. Core Characteristics of TCM Health Management Scenarios

TCM health management scenarios have unique cultural and cognitive characteristics, which are mainly reflected in two dimensions, and also form the core boundary conditions for the application of the integrated conceptual model.

There are significant cultural and cognitive differences in user decision-making. Consumers' recognition of the TCM concept of "preventive treatment of disease" is the core cultural variable affecting the framing effect. Middle-aged and elderly groups have significantly higher recognition of TCM concepts than young groups, and this generational cognitive difference directly leads to differences in product acceptance. Meanwhile, the decision-making preference based on "personal experience" and "interpersonal trust" in traditional TCM health concepts has an inherent tension with the standardized and online characteristics of digital products, which hinders the establishment of user trust. The functional design of digital TCM health products needs professional adaptation based on TCM theoretical system, whose core challenge is to translate the core concepts of TCM such as syndrome differentiation and treatment and "preventive treatment of disease" into interactive digital modules, and ensure the scientificity based on authoritative TCM theories.

To further support the above analysis, this paper introduces a specific case study: the digital TCM constitution identification and health management platform developed by Shanghai Municipal Hospital of Traditional Chinese Medicine (Zhang et al., 2025). The platform has been applied to 216 sub-health patients, and its information framing design is closely combined with TCM theory: for the gain frame, it presents the specific benefits of constitution regulation in the form of "improvement of sub-health symptoms, reduction of disease risk"; for the loss frame, it explains the potential health risks of long-term imbalance of constitution combined with TCM constitution theory. The empirical results show that the platform's constitution identification accuracy reaches 90.4%, the follow-up completion rate reaches 92.5%, and the user compliance reaches 89.7%, which is significantly better than the traditional offline service model. This case provides empirical evidence for the effectiveness of TCM cultural embedded information framing design.

4.2. Optimization Strategies of Information Framing for TCM Health Management Scenarios

Based on the integrated conceptual model and the unique characteristics of TCM scenarios, this paper proposes the following targeted optimization strategies, each of which corresponds to the specific path of the model:

The content optimization of information frames with TCM culture as the core anchor mainly acts on the attitude and perceived usefulness of users in the model. Digital technology can realize the collection and standardization of multi-source TCM clinical data, and reveal the correlation between TCM syndrome phenotype and intervention effect through algorithms, so as to provide data support for translating traditional TCM theories such as "yin-yang balance" and "preventive treatment of disease" into benefit frames. For example, for users with qi deficiency constitution, the gain frame can be designed as "adhere to the personalized conditioning scheme for 3 months, the qi deficiency constitution score is improved by more than 60%, and the symptoms of fatigue and weakness are significantly relieved"; the loss frame can be designed as "long-term qi deficiency without conditioning will lead to the decline of visceral function and the increase of the risk of chronic respiratory and digestive diseases". At the same time, it can be integrated with the emotional frame of traditional TCM health preservation cases to enhance emotional resonance, realize the organic integration of benefit frame and emotional frame, and cover the whole health cycle from prevention to conditioning and rehabilitation.

Complementing this content optimization, the channel and scenario integration with information framing as the core link mainly acts on the subjective norms and perceived behavioral control of users in the model. Online, we can rely on social media platforms such as WeChat, use loss frames to strengthen health risk warnings, and use gain frames to visually present the effect of TCM conditioning; offline, we can transform frame information into tangible user-perceivable experience through community TCM clinics and health preservation center experience activities, so as to enhance the perceived value of products. For example, the digital TCM platform of Gu Sheng Tang has realized the online and offline linkage: offline clinics complete the TCM constitution identification and syndrome differentiation, and the online platform pushes personalized health information according to the user's constitution type, and

designs the information frame combined with the user's actual conditioning effect. The platform's operational data shows that the user retention rate of this online-offline linkage mode reaches 71.2%, which is 38.5% higher than the pure online mode. Meanwhile, Li et al. (2025) found that knowledge personalization, platform information quality and platform service quality have a significant impact on users' utilitarian and hedonic values, among which platform information quality is the most influential factor. This conclusion provides a core direction for the platform operation optimization of TCM digital health products: the platform should ensure the authority and standardization of information, and match the appropriate information frame type according to the user's constitution type and health status.

On the basis of content construction and channel layout, the personalized frame matching based on user characteristics mainly acts on the moderating variables of the model. For users with high TCM cultural identity, we can focus on the information frame integrated with TCM classical theories to enhance their positive attitude towards products; for young users with low TCM cognitive level, we can combine modern medical indicators to design gain and loss frames, reduce the cognitive threshold, and improve their perceived ease of use and perceived behavioral control. For users with low health literacy, we should reduce the proportion of professional TCM terms, and use more visual and emotional frames to convey information; for users with high health literacy, we can provide more detailed theoretical and data support to enhance the credibility of information.

5. Research Summary and Future Prospects

5.1. Core Research Findings

The type of information framing has a significant moderating effect on users' adoption intention of digital health products. The effect of frames is realized through the mediating variables of TPB and TAM: gain frames are more effective in health prevention scenarios by improving users' perceived usefulness and positive attitude, while loss frames have a stronger effect in chronic disease management scenarios by enhancing users' perceived behavioral control of health risks; emotional frames can effectively amplify the influence of rational frames through emotional arousal. The framing effect has significant heterogeneity across scenarios and populations, and variables such as age, health literacy, TCM cultural identity and technology trust play a significant moderating role in the frame effect path. In TCM health management scenarios, the information framing content integrated with traditional TCM theories is more likely to gain user trust, and the online-offline linkage frame delivery mode can significantly enhance users' subjective norms and perceived behavioral control, thereby improving adoption intention.

5.2. Future Research Directions

Empirical research can be designed and implemented based on TCM scenarios. Questionnaire surveys, in-depth interviews, and randomized controlled experiments can be adopted to collect first-hand data from users of TCM digital health products, test the applicability of the integrated conceptual model, and verify the actual effects of the proposed information framing optimization strategies. Further efforts can be made to deepen research on culturally embedded framing design

in TCM scenarios. An information framing system compatible with the theoretical system of TCM can be constructed to explore the differential effects of different TCM theory integration methods on user adoption intention. It is also feasible to carry out research on dynamic frame optimization driven by artificial intelligence technology. Based on users' real-time behavioral data and health status changes, precise matching of frame content can be achieved, and the dynamic adjustment mechanism of frames throughout the user life cycle can be explored.

In terms of corporate practice, enterprises should optimize the information strategy of products based on Information Framing Theory, dynamically adjust the frame design for different user groups and usage scenarios; cooperate with formal medical institutions to enhance the professional authority of product information, and improve users' perceived usefulness and trust; at the same time, promote the deep integration of products into daily health scenarios through online-offline linkage, and enhance users' subjective norms and perceived behavioral control, thereby ultimately improving product adoption rate and user retention.

6. Research Limitations

This study has the following core limitations, which need to be further improved in subsequent research. First, the research conclusions of this paper are mainly derived from theoretical deduction and the integration of existing empirical research, and have not been verified by empirical research targeting TCM health management scenarios and Chinese user groups. The proposed integrated conceptual model and optimization strategies lack the support of first-hand data such as questionnaire surveys, in-depth interviews or randomized controlled experiments, and the stability and applicability of the model need to be further tested. Second, this study mainly focuses on the information framing design at the front end of communication, and does not conduct in-depth analysis on the long-term dynamic change mechanism of framing effects in the user's continuous use stage, and cannot clarify the dynamic adjustment logic of information frames in the whole user life cycle. Third, this study does not involve cross-cultural comparative research, and the proposed optimization strategies for TCM scenarios are only applicable to the Chinese cultural context, and the generalizability of the conclusions in other cultural contexts is limited.

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