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The systemic pathogenic chain of health crises in middle-aged office workers: An integrative literature review

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Abstract
Office workers aged 40–59 are at a critical stage in which accelerated physiological ageing overlaps with workplace stress. Their health risks are multisystemic, insidious in progression, and partially reversible. This article integrates existing evidence from cell biology, pathophysiology, epidemiology, and clinical research to systematically review the whole-system pathogenic mechanisms underlying the midlife health crisis among office workers. The literature indicates that telomere shortening, mitochondrial functional decline, accumulation of oxidative stress, and diminished autophagic function constitute the four fundamental mechanisms of cellular ageing. Sedentary behaviour, shift work, overtime work, and chronic psychological stress in the workplace accelerate these degenerative processes by elevating cortisol, disrupting metabolic rhythms, and inducing systemic low-grade inflammation. This pathogenic chain is centred on insulin resistance and, through intermediary links such as metabolic syndrome, gut microbiota dysbiosis, endocrine disorders, and sleep apnoea, ultimately drives the development of cardiovascular disease, non-alcoholic fatty liver disease, chronic kidney disease, and sensory degeneration. This article further identifies major blind spots in contemporary health knowledge and proposes reversibility-oriented integrated intervention strategies at both the individual health-management level and the workplace-institutional level. Combining the holistic perspective and principle of balance inherent in holistic health, this article argues that midlife health management should shift from a "treat disease when it arises" model to an upstream, risk-interruption model, achieving multisystem coordinated intervention within the reversible window.
Keywords: Middle-aged, office workers, cellular ageing, metabolic syndrome, inflammation, holistic health management

Introduction

In the modern workplace, health is often treated as an asset that can be temporarily overdrawn. Most office workers under the age of 40 believe they have sufficient physical capacity to withstand high-intensity work, long hours, and irregular daily routines, and they frequently ignore mild warning signals from the body. However, mortality statistics from the Ministry of Health and Welfare show that chronic diseases and circulatory diseases have replaced traditional infectious diseases as the main threats to adults. Among those aged 40–59, causes of death are concentrated in cancer, heart disease, and cerebrovascular disease, while the proportions of suicide and chronic liver disease have also risen year by year, reflecting a dual collapse of physiological exhaustion and psychological stress. The Global Prospective Urban and Rural Epidemiological (PURE) study, which included follow-up data on middle-aged populations in 21 countries, further confirmed that the incidence of cardiovascular disease and metabolic abnormalities rises significantly during midlife, and that the risk-factor profiles differ substantially among countries with different income levels (Dagenais *et al*., 2020) [5]. In the past, society tended to attribute midlife bodily discomfort to "getting older", or to reduce it simplistically to a diet too high in fat and insufficient exercise. However, over the past two decades, cross-validation from cell biology, pathophysiology, large-scale domestic cohort studies, and multinational clinical trials has revealed a more complex picture: the midlife health crisis is the result of the superposition of innate underlying mechanisms of physiological ageing and acquired workplace environmental damage. At the physiological level, after the age of 40, telomeres continue to erode, mitochondrial function declines, hormonal fluctuations and declines occur, and organ function gradually deteriorates. At the workplace level, sedentary behaviour, disrupted shift schedules, overtime labour, and chronic psychological stress further amplify the entire degenerative process, causing the age of onset of many diseases to shift progressively downward.

It is particularly important to note that this entire disease progression largely follows an insidious pattern. A great deal of damage occurs during stages without pain or obvious discomfort, accumulating over years or even decades, before suddenly manifesting as myocardial infarction, stroke, type 2 diabetes, liver fibrosis, or renal functional decline. The core of health management should therefore not remain at the level of treatment after illness has occurred, but should shift towards understanding the interconnected whole-system pathogenic chain and achieving risk interruption during the reversible golden window of intervention. This article aims to integrate existing empirical literature and systematically construct a whole-system pathogenic model of the midlife health crisis among office workers. The article follows an analytical trajectory from cells to organs, and from individuals to institutions: first, it explains the four major cellular mechanisms of midlife physiological ageing; then it sequentially analyses the pathological changes and interconnections across the cardiovascular, metabolic, digestive, endocrine, sleep, immune, hepatorenal, and sensory systems; finally, it integrates the full pathogenic picture, identifies blind spots in current health knowledge, and proposes integrated intervention strategies based on the concept of holistic health. The innovation of this article lies in not treating midlife health problems as independent organ-specific diseases, but rather, from the perspective of systems biology, linking cellular ageing, the workplace

environment, metabolic disorders, chronic inflammation, and organ damage into a causal pathogenic chain and identifying the key nodes with the greatest intervention value.

From a broader perspective, the historical trajectory of Western holistic health thought has always revolved around two core concepts: holism and balance. From the naturalism of ancient Greek medicine to the multidimensional balance theory of modern integrative medicine, the meaning of "health" has consistently been understood as a dynamic state of harmony. Hippocrates emphasised the combined influence of environment, diet, and lifestyle on health, and argued that the physician's duty is to assist the body in self-healing according to natural laws. Lu (2026) [17], in The History of Western Holistic Health Development, systematically reviewed the evolution of this intellectual tradition, pointing out that the holistic health framework does not reduce health to the normality of a single organ or indicator, but consistently emphasises the dynamic balance among multiple interconnected domains: biological, behavioural, social, and environmental. This tradition aligns closely with the picture of "multiorgan interconnected pathogenesis" revealed by contemporary systems biology, and provides important theoretical resources for health management among middle-aged office workers.

The Underlying Mechanisms of Midlife Physiology

The various bodily changes of midlife can be traced back to four major cellular ageing mechanisms: telomere shortening, mitochondrial functional decline, accumulation of oxidative stress, and diminished cellular autophagy. These four mechanisms are interlocking and constitute the biological basis of ageing, and each has verifiable interactive pathways with workplace environmental factors.

1. Telomere Shortening and the Biological Cost of Chronic Stress

Telomeres at the ends of chromosomes are like the protective caps of shoelaces; each cell division consumes a small segment. When telomeres become too short, cells stop dividing and enter dormancy or apoptosis. Blackburn *et al.* (2015) [4], in a review published in Science, pointed out that telomere length is not only a record of cellular replication history, but also an interactive factor among ageing, disease risk, and protective factors; its dynamic changes reflect the integrated state of genomic stability and cellular regenerative capacity. In 2004, a classic study by Epel *et al.* published in PNAS was the first to confirm that caregivers under long-term chronic stress had significantly shorter telomeres than low-stress peers of the same age, and their telomerase activity was also markedly lower. This finding directly linked psychosocial stress to cellular-level ageing (Epel *et al*., 2004) [6]. Subsequent follow-up research at UCSF further showed that the gap between the biological age of long-term high-stress groups and that of low-stress peers could be as large as ten years, implying that chronic stress is not merely a subjective experience but leaves a measurable ageing imprint at the genomic level. A review published in Ageing Research Reviews (Lin & Epel, 2022) [16] systematically reviewed the cellular mechanisms by which stress leads to telomere shortening, pointing out that elevated cortisol accelerates telomere consumption through two pathways: inhibiting telomerase activity and increasing oxidative damage. Specifically, under long-term stress, the hypothalamic–pituitary–adrenal (HPA) axis remains continuously activated, and circulating cortisol remains at a relatively high level. On the one hand, this downregulates the expression of telomerase reverse transcriptase (TERT), weakening telomere repair capacity; on the other hand, it promotes the generation of reactive oxygen species, which directly attack the guanine-rich sequences in telomeric regions, causing telomeres to lose more length with each replication. For middle-aged office workers, long-term overtime work, workplace interpersonal stress, and work–family conflict are all chronic stressors, and their cumulative effects may unknowingly drive an accelerated decline in telomere length.

2. Mitochondrial Functional Decline

Mitochondria are the energy factories of the cell, responsible for converting nutrients into energy usable by the body (ATP). A review by Miwa *et al.* (2022) [18] published in the Journal of Clinical Investigation pointed out that mitochondrial dysfunction and cellular senescence are closely interconnected hallmarks of ageing; mitochondrial dysfunction is both a cause and a consequence of cellular senescence, and the two form multiple feedback loops. After midlife, mitochondrial number decreases, structure becomes damaged, and energy conversion efficiency declines. In addition, sedentary behaviour reduces mitochondrial biogenesis, shift work disrupts mitochondrial repair rhythms, and a high-stress, high-fat diet increases metabolic load, directly leading to difficulty recovering from fatigue and a decline in metabolic rate, and becoming a cellular source of metabolic syndrome, fatty liver, and cardiovascular problems. A review by Amorim *et al.* (2022) [2] in Nature Reviews Endocrinology further pointed out that mitochondrial and metabolic dysfunction play a central role in ageing and age-related diseases, with effects spanning insulin sensitivity, adipose tissue function, and systemic energy homeostasis. Mitochondrial functional decline not only leads to insufficient ATP production, but is also accompanied by increased electron transport chain leakage, excessive generation of reactive oxygen species, and abnormal activation of apoptotic pathways. In skeletal muscle, decreased mitochondrial function directly manifests as reduced exercise endurance and prolonged recovery time; in the liver, impaired mitochondrial fatty acid oxidation promotes triglyceride accumulation, an important pathogenic link in non-alcoholic fatty liver disease. It is noteworthy that mitochondria are highly adaptable to exercise; regular aerobic exercise can promote mitochondrial biogenesis through the PGC-1α signalling pathway, which is an important mechanistic basis for the multisystem protective effects of exercise on midlife health (Lavie *et al*., 2019) [12].

3. Accumulation of Oxidative Stress

Human metabolism naturally produces free radicals (reactive oxygen species, ROS), which under normal conditions can be cleared by the antioxidant system. However, overtime work, sleep deprivation, sedentary behaviour, and stress promote excessive generation of free radicals, forming oxidative stress—like a cellular-level "rusting" process—that attacks DNA, mitochondria, and cell membranes, accumulating genetic mutations and systemic inflammation. Leyane *et al.* (2022) [13], in a review

in the International Journal of Molecular Sciences, summarised the interconnected mechanisms between oxidative stress and chronic inflammation, pointing out that excessive production of reactive oxygen species causes nucleic acid and protein damage, thereby altering cellular structure and function.

The review also emphasised that oxidative stress and chronic inflammation share features such as mitochondrial abnormalities and glycation, jointly driving ageing and chronic degenerative pathologies, including cardiovascular disease, diabetes, and chronic kidney disease. The accumulation of oxidative stress has a threshold effect. In the short term, the body's antioxidant defence system—including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT)—can effectively clear excess free radicals. However, when stressors persist, the reserve of the defence system gradually becomes exhausted, and oxidative damage begins to accumulate within cells.

Lipid peroxidation products (such as malondialdehyde, MDA) and protein oxidation markers (such as carbonyl protein) can be detected in the blood, reflecting the degree of systemic oxidative load. For middle-aged office workers, sleep deprivation is the most commonly underestimated source of oxidative stress: sleep is a key window for antioxidant repair in the brain and peripheral tissues, and long-term sleep deprivation significantly reduces antioxidant enzyme activity, preventing oxidative damage from being effectively cleared at night.

4. Diminished Cellular Autophagy

Autophagy is the cell's clearning mechanism, responsible for clearing damaged organelles and aged proteins. A review by Lim *et al*. (2024) [15] in Cells systematically described the molecular changes occurring at each step of autophagy with age, pointing out that decreased autophagic activity has been regarded as a core hallmark of ageing; its decline leads to cellular dysfunction and the occurrence of age-related diseases, including neurodegeneration and metabolic disorders. Staying up late, shift work, stress, and overeating all inhibit autophagic activity, causing waste products to continue accumulating within cells and exacerbating inflammation and ageing. Kuo *et al*. (2025) [11], in a review in the Journal of Molecular Cell Biology, further identified the molecular mechanisms of autophagic decline at the transcriptional regulatory level, pointing out that the activity of key transcription factors such as TFEB and FOXOs declines with age, leading to overall downregulation of autophagy-related gene expression. TFEB is the master regulator of lysosomal biogenesis and autophagy; its nuclear translocation is negatively regulated by the mTOR signalling pathway.

During midlife, nutritional excess and insulin resistance lead to sustained mTOR activation, indirectly inhibiting TFEB function and keeping autophagic flux at a low level for prolonged periods.

This mechanism explains why intermittent fasting and caloric restriction can extend lifespan in multiple biological models—they restore autophagic activity by inhibiting mTOR and activating TFEB. For middle-aged office workers, avoiding prolonged overeating and maintaining an appropriate overnight fasting window are simple and feasible strategies for maintaining autophagic function.

5. Accelerating Effects of the Workplace Environment on Cellular Ageing

The direct damage of workplace overload to cellular and physiological indicators has received empirical support. A WHO/ILO joint estimate by Kivimaki *et al*. (2021) published in Environment International, incorporating global data, showed that compared with standard working hours (35–40 hours per week), long working hours (more than 55 hours per week) increase the risk of coronary heart disease by 13% and the risk of stroke by 33%. This study not only established a causal association between long working hours and cardiovascular disease, but also estimated the global burden of disease, providing a quantitative basis for occupational health policy. The occupational safety and health management record of TSMC also shows that long-term night-shift workers have higher blood pressure and a higher risk of cardiovascular disease than day-shift workers, prompting the company to establish a tiered employee health management system based on 10-year cardiovascular disease risk. Together, these data confirm that workplace overload leaves measurable and partially irreversible damage at the cellular and physiological levels. The effect of shift work on cellular ageing is mainly achieved through circadian rhythm disruption. The human circadian rhythm is primarily governed by the suprachiasmatic nucleus (SCN) of the hypothalamus, while peripheral tissues (liver, muscle, adipose tissue) also have their own molecular clocks. Shift work causes desynchronisation between the central clock and peripheral clocks, disrupting the rhythmic expression of metabolic genes, causing insulin sensitivity, lipid metabolism, and inflammatory responses to be activated in inappropriate time windows. Over the long term, this rhythm disruption not only increases the risk of metabolic syndrome and cardiovascular disease, but may also accelerate telomere shortening through impaired rhythmic regulation of telomerase activity. The effect of sedentary behaviour on cellular ageing should likewise not be ignored. Prolonged sitting reduces skeletal muscle blood flow and lipoprotein lipase activity, thereby impairing lipid clearance and glucose uptake capacity. Reduced muscle contraction also lowers PGC-1α activation, weakening mitochondrial biogenesis and antioxidant defence, making skeletal muscle an important source of systemic metabolic disorder and inflammation. Even in individuals who exercise regularly, if they remain sedentary during the rest of the day, they still face additional metabolic risk, highlighting the importance of reducing total sedentary time and increasing workplace activity.

The Cardiovascular System

Cardiovascular disease is one of the leading causes of death among middle-aged office workers, and its core pathology is atherosclerosis. Most people mistakenly believe that atherosclerosis is a disease of old age, whereas in fact lesion initiation mostly occurs between the ages of 30 and 45, remaining asymptomatic for a long period. The starting point of the disease is endothelial dysfunction: high blood pressure, staying up late, sedentary behaviour, and chronic inflammation damage the protective barrier of the vascular endothelium; low-density lipoprotein infiltrates the vessel wall and, after oxidation and phagocytosis by macrophages, forms foam cells, gradually developing into plaques. Subsequent plaque calcification and vascular narrowing

ultimately trigger myocardial infarction and stroke. Endothelial dysfunction is the earliest detectable pathological change in atherosclerosis, manifesting as decreased endothelium-dependent vasodilation. At this stage, vascular imaging may not yet show visible stenosis, but plaques are already silently growing beneath the intima. The "three highs" of blood pressure, blood lipids, and blood glucose are not independent problems, but rather a mutually amplifying vicious cycle. Hypertension mechanically impacts the vascular endothelium, opening the first gap for atherosclerosis; hyperlipidaemia promotes lipid deposition and vascular inflammation; hyperglycaemia generates advanced glycation end products (AGEs), damaging vascular elasticity and solidifying reversible damage into long-term lesions. Mild abnormality in a single indicator carries limited risk, but when two or three indicators are concurrently abnormal, cardiovascular risk rises geometrically. This phenomenon has important explanatory value in clinical practice: many office workers show only mild abnormalities in health check-ups yet suddenly experience major cardiovascular events; the pathological basis is precisely the synergistic effect of multiple risk factors. In addition, hypertension itself increases left ventricular load, chronically leading to left ventricular hypertrophy and diastolic dysfunction, which is also an important precursor lesion of heart failure in the middle-aged population.

The INTERHEART multinational study, which included nearly 30,000 participants from 52 countries, produced an important conclusion: more than 90% of acute myocardial infarctions arise from nine modifiable risk factors, including smoking, dyslipidaemia, hypertension, diabetes, abdominal obesity, dietary imbalance, physical inactivity, excessive alcohol consumption, and psychosocial stress (Yusuf *et al*., 2004) [26]. Middle-aged office workers in Taiwan frequently face a combined risk of abdominal obesity, stress, borderline elevated blood pressure, and dyslipidaemia. Regular moderate-intensity exercise can reduce the risk of myocardial infarction by 46%, making it the lowest-cost protective factor (Lavie *et al*., 2019) [12]. It is noteworthy that in the INTERHEART study, the population attributable risk percentage of psychosocial stress as an independent risk factor was approximately 14.4%, comparable to the contribution of dyslipidaemia. This finding highlights the non-negligible role of workplace psychological stress in cardiovascular disease prevention. In clinical practice, one cannot rely solely on a single physical examination value. The Framingham risk score and ASCVD risk calculator have been widely used to estimate the probability of 10-year cardiovascular events (American College of Cardiology/American Heart Association, 2013) [1]. Validation studies in Asian populations show that the Framingham risk score has an AUC of 0.750 in men (95% CI: 0.741–0.760), indicating acceptable discriminative ability. Through these tools, it is possible to identify hidden high-risk groups whose physical examination values appear normal but who have accumulated multiple factors, enabling early intervention rather than waiting for disease onset. Blood pressure variability is another frequently overlooked cardiovascular risk factor. Individuals with normal office blood pressure but large home blood pressure fluctuations have significantly increased target-organ damage and cardiovascular event risk, which is related to decreased baroreceptor sensitivity caused by atherosclerosis. For middle-aged office workers, it is recommended that, in addition to annual health check-ups, regular home blood pressure monitoring be conducted, recording morning and evening averages and the magnitude of variability, in order to assess cardiovascular risk more comprehensively. In addition, imaging indicators such as carotid intima–media thickness (cIMT) and coronary artery calcium score (CACS) can detect subclinical atherosclerosis before symptoms appear. For middle-aged office workers whose physical examination values are borderline but who have multiple risk factors, these examinations have important value for risk stratification.

Metabolic Syndrome and Insulin Resistance

Metabolic syndrome is a key turning point from health towards chronic disease. The Ministry of Health and Welfare has established five diagnostic criteria for Asian populations: male waist circumference ≥ 90 cm, female ≥ 80 cm; systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg; fasting glucose ≥ 100 mg/dL; triglycerides ≥ 150 mg/dL; male high-density lipoprotein cholesterol < 40 mg/dL, female < 50 mg/dL. A diagnosis is confirmed when three of the five criteria are met. According to the 2017–2020 National Nutrition and Health Survey conducted by the Health Promotion Administration, the prevalence of metabolic syndrome among citizens aged 20–64 was 24.8%, with a higher prevalence in men (30.4%) than in women (19.7%) (Health Promotion Administration, Taiwan, 2021). It is noteworthy that many "skinny-fat" individuals with normal BMI—normal body weight but excessive visceral fat accumulation—also meet the criteria for metabolic syndrome, representing an extremely common blind spot in health awareness. The core pathology of metabolic syndrome is insulin resistance. Insulin not only regulates blood glucose but also governs lipid synthesis, fat accumulation, and vascular tone. Sedentary behaviour, a high-sugar, high-fat diet, sleep deprivation, stress, and excessive visceral fat reduce cellular sensitivity to insulin. In compensation, the body secretes more insulin; hyperinsulinaemia subsequently causes elevated blood glucose, increased triglyceride synthesis, elevated blood pressure, abdominal fat accumulation, and decreased good cholesterol, triggering abnormalities in all five criteria at once. The molecular mechanisms of insulin resistance involve abnormal serine phosphorylation of insulin receptor substrate (IRS), impaired PI3K/Akt signalling, and impaired translocation of glucose transporter 4 (GLUT4). Chronic inflammatory factors such as TNF-α and IL-6 directly interfere with insulin signal transduction through the JNK and IKK/NF-κB pathways, which is the key molecular bridge linking visceral adipose inflammation and systemic insulin resistance.

The HOMA-IR index, calculated from fasting glucose and fasting insulin, can detect hidden insulin resistance during the normal glucose stage and is an important supplementary examination for the middle-aged population. Recent literature reviews indicate that HOMA-IR is the most commonly used surrogate marker of insulin resistance in clinical practice, with cut-off values of approximately 2.1–2.8, although these vary with population characteristics and require correction for individual groups. For middle-aged office workers with normal fasting glucose but excess waist circumference, postprandial somnolence, or sugar cravings, adding fasting insulin measurement to calculate HOMA-IR

can identify early signals of metabolic abnormality before prediabetes. Adipose tissue is not merely an energy storage depot, but an active endocrine organ. After visceral adipose hypertrophy and hypoxia, it releases large amounts of tumour necrosis factor (TNF-α) and inflammatory interleukin-6 (IL-6), causing systemic low-grade inflammation, which further worsens insulin resistance, forming a vicious cycle: "visceral fat accumulation → chronic inflammation → insulin resistance → further fat accumulation". In addition, visceral fat secretes protective hormones such as adiponectin; its level decreases as visceral fat increases, further weakening insulin sensitivity and vascular endothelial protection. Postprandial glycaemic excursions are another important dimension of metabolic disorder. Even when fasting glucose is normal, individuals with insulin resistance may have significantly higher postprandial glucose peaks and delayed recovery. This postprandial hyperglycaemic state induces oxidative stress and endothelial dysfunction, and its cardiovascular harm may even exceed that of fasting hyperglycaemia. For middle-aged office workers, common refined breakfasts (such as bread, pastries, and sugary drinks) can cause sharp postprandial glucose spikes, followed by hypoglycaemic reactions that trigger hunger and eating desires, forming a vicious cycle of blood glucose swings. Choosing a low-glycaemic-index breakfast rich in dietary fibre and protein can effectively flatten the postprandial glucose response and improve the metabolic state throughout the day. Compared with the partially irreversible nature of cellular telomere ageing, metabolic syndrome is highly reversible and is the most important intervention node in midlife health management. Clinical studies show that a 5–10% reduction in body weight can significantly improve insulin sensitivity and all indicators of metabolic syndrome, and a reduction in waist circumference often better reflects substantive improvement in visceral fat than body weight alone.

The Digestive System and Gut Microbiota

The gut is the body's largest immune organ and also a central regulator of metabolism. The hundreds of trillions of microorganisms in the gut constitute the gut microbiota, which has high diversity in a healthy state. Long-term eating out, insufficient dietary fibre intake, stress, and staying up late cause dysbiosis, with a reduction in beneficial bacteria and excessive proliferation of harmful bacteria, thereby affecting systemic metabolism, inflammation, and immune status. The gut microbiota participates in host health regulation through multiple mechanisms: fermentation of dietary fibre produces short-chain fatty acids (SCFAs, such as butyrate, propionate, and acetate), which provide energy for colonic epithelial cells and regulate immune tolerance; regulation of bile acid metabolism affects lipid absorption and signalling; and the gut–brain axis influences neuroendocrine and emotional regulation. When dysbiosis occurs, these protective mechanisms are weakened, while overgrowth of potential pathogens increases endotoxin load and systemic inflammatory risk. Leaky gut syndrome is an important link in the pathogenesis of diseases among office workers. Stress, a high-sugar diet, and sleep disruption damage tight junctions in the intestinal wall, creating small gaps through which bacterial endotoxin (LPS) and incompletely digested macromolecules leak into the bloodstream, inducing systemic low-grade chronic inflammation. This inflammation, which lacks severe pain, damages the vascular endothelium, aggravates insulin resistance, and accelerates fat accumulation, becoming an important driver of atherosclerosis and metabolic syndrome. The concept of metabolic endotoxaemia originates from this: a high-fat diet can increase circulating LPS levels by 2–3 times, and sustained low-dose endotoxin exposure is sufficient to activate the TLR4/NF-κB inflammatory pathway, driving insulin resistance and adipose tissue inflammation. After the age of 40, gastric acid secretion naturally declines; combined with irregular meals and stress, this easily leads to a low-acid state, causing incomplete protein digestion, poor nutrient absorption, and overgrowth of harmful gut bacteria, with symptoms such as bloating, postprandial drowsiness, and declining physical strength. Irregular meals and skipping breakfast also prevent the gallbladder from emptying over long periods, causing bile stasis. In addition to increasing the risk of gallstones, this also leads to insufficient bile secretion and reduced fat breakdown capacity, aggravating visceral fat and hyperlipidaemia.

A randomised controlled trial of faecal microbiota transplantation published in Frontiers in Endocrinology in 2022 confirmed that altering the gut microbiota can improve metabolic indicators. In that study, faecal microbiota from lean donors was transplanted into severely obese recipients with insulin resistance. The results showed favourable changes in gut microbial composition and metabolite profiles in the allogeneic transplantation group, including increases in Coprococcus, Bifidobacterium, Bacteroides, and Roseburia, and a decrease in Streptococcus; LDL and appetite indicators also improved (Ghorbani *et al*., 2022) [8]. The gut microbiota participates in systemic regulation through bile acid metabolism: intestinal bacteria convert primary bile acids synthesised by the liver into secondary bile acids, which not only promote lipid absorption but also act as signalling molecules activating the farnesoid X receptor (FXR) and the G-protein-coupled receptor TGR5, regulating insulin secretion, energy expenditure, and inflammatory responses. When gut microbiota is imbalanced, the bile acid metabolic profile changes, FXR and TGR5 signalling are impaired, further worsening metabolic disorder. The average daily dietary fibre intake of Taiwanese office workers is 14 g, far below the recommended 25–30 g, causing long-term nutritional deficiency for beneficial gut bacteria; this is a widespread risk factor. The gut system has extremely high plasticity; increasing dietary fibre diversity through diet can improve microbiota and reduce inflammation, representing a highly cost-effective health strategy. In addition to dietary fibre, intake of fermented foods (such as yoghurt, kimchi, and miso) has also been shown to increase gut microbiota diversity and reduce inflammatory markers. It should be emphasised that improvement of the gut microbiota requires sustained changes in dietary patterns; short-term probiotic supplementation without changing dietary structure often fails to produce lasting microbiota changes.

The Endocrine System

The endocrine system is the body's hormonal command centre. During midlife, four major endocrine issues include insulin resistance, subclinical hypothyroidism, declining male testosterone, and decreasing female menopausal hormones. These mutually influence one another and manifest as various symptoms such as fatigue, obesity,

mood disturbances, and cardiovascular risk. Insulin resistance is divided into four stages: compensatory stage, mild resistance stage, metabolic abnormality stage, and decompensated stage. In the early stage, fasting glucose can remain normal, with only postprandial drowsiness, sugar cravings, and slowly increasing waist circumference, which are easily overlooked. The HOMA-IR index can detect hidden insulin resistance during the normal glucose stage and is an important supplementary examination for the middle-aged population. During the compensatory stage, pancreatic β-cells maintain normal blood glucose by increasing insulin secretion; at this time, fasting insulin levels are elevated but blood glucose remains within the normal range. After entering the mild resistance stage, postprandial glucose begins to rise slightly, but fasting glucose may still be normal. The metabolic abnormality stage manifests as impaired fasting glucose or impaired glucose tolerance. The decompensated stage is clinically diagnosed as type 2 diabetes. This progression emphasises the importance of early screening—testing only fasting glucose will miss the large hidden population in the compensatory and mild resistance stages.

Subclinical hypothyroidism is a high-prevalence, low-diagnosis problem in midlife. Its symptoms are vague, including fatigue, cold hands, difficulty losing weight, and low mood, and it is easily missed in general health check-ups. The Rotterdam Study is one of the most influential prospective studies in this field. Hak *et al.* (2000) [9], published in Annals of Internal Medicine, included 1,149 postmenopausal women with a mean age of 69 and found that the prevalence of subclinical hypothyroidism (TSH > 4.0 mU/L with normal free thyroxine) was 10.8%, and it was significantly associated with atherosclerosis (OR = 1.7, 95% CI: 1.1–2.6) and myocardial infarction (OR = 2.3, 95% CI: 1.3–4.0). The study further pointed out that the population attributable risk percentage of subclinical hypothyroidism for myocardial infarction already falls within the range of known major cardiovascular risk factors. The prevalence of subclinical hypothyroidism among middle-aged women is approximately 10–15%, and only about 30% are diagnosed. Subclinical hypothyroidism is also associated with dyslipidaemia (especially elevated total cholesterol and LDL), endothelial dysfunction, and elevated homocysteine; these mechanisms jointly explain its increased cardiovascular risk. For middle-aged women with unexplained fatigue, weight gain, or difficult-to-control blood lipids, TSH screening should be considered. It should be noted that the reference interval for TSH varies with age and ethnicity, and mild TSH elevation in some older individuals may be an adaptive change of ageing rather than a pathological state. Therefore, interpretation of TSH results should be combined with clinical symptoms and free thyroxine levels. Thyroid hormone regulation of lipid metabolism involves upregulation of hepatic LDL receptor expression and inhibition of cholesterol synthesis enzymes; when thyroid hormone is insufficient, both pathways are impaired, leading to worsening of the lipid profile.

In men, testosterone declines by 1–2% per year after the age of 40. According to a review published in Reproductive Biology and Endocrinology in 2024, serum testosterone in men begins to decline gradually from age 35; in men aged 40–70, total testosterone declines by approximately 0.4% per year, while free testosterone declines even more significantly, by 1.3% per year (Yang *et al.*, 2024) [25]. Low testosterone levels are associated with diabetes, cardiovascular disease, dementia, and increased mortality. Stress accelerates testosterone consumption, causing muscle loss, abdominal obesity, decreased physical strength, and shallow sleep. Under chronic stress, elevated cortisol inhibits the hypothalamic–pituitary–gonadal (HPG) axis, reducing secretion of gonadotrophin-releasing hormone (GnRH) and luteinising hormone (LH), thereby decreasing testosterone synthesis in Leydig cells. In addition, aromatase in visceral adipose tissue converts testosterone into oestrogen, further reducing circulating free testosterone levels, forming a vicious cycle: "abdominal obesity → decreased testosterone → muscle loss → worsened metabolism → further abdominal obesity". Women aged 40–55 enter the menopausal transition, during which oestrogen declines rapidly, losing its protection of blood vessels and bone. A review by Fasero *et al.* (2025) [7] in the Journal of Clinical Medicine pointed out that oestrogen deficiency is a key factor in the increased cardiovascular risk of menopause, leading to endothelial dysfunction, increased arterial stiffness, and worsening lipid profile. Oestrogen regulates the expression and activity of endothelial nitric oxide synthase (eNOS) through oestrogen receptor α (ERα), promoting vasodilation; when oestrogen is deficient, NO bioavailability decreases, endothelium-dependent vasodilation is impaired, and arterial stiffness increases. At the same time, oestrogen deficiency downregulates LDL receptor expression, reducing LDL clearance, and the lipid profile shifts towards an atherogenic direction. Hormonal fluctuations during the menopausal transition are also accompanied by vasomotor symptoms (hot flushes, night sweats), sleep disturbances, and mood swings, which further aggravate sympathetic activation and blood pressure variability. Workplace stress exacerbates hormonal decline in both men and women, causing endocrine disorders to occur earlier.

Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) occurs during sleep and is difficult for patients themselves to notice. It is a major hidden driver of midlife hypertension, hyperlipidaemia, hyperglycaemia, cardiovascular disease, and daytime brain fog. During sleep, the soft tissues of the pharynx relax and collapse, causing airway obstruction and breathing interruptions; blood oxygen repeatedly drops, and the body experiences unconscious microarousals. This vicious cycle of hypoxia and reoxygenation repeats throughout the night. Even if sleep duration is sufficient, deep sleep remains severely insufficient, constituting "pseudo-sleep". The severity of OSA is measured by the apnoea–hypopnoea index (AHI), i.e. the number of apnoea and hypopnoea events per hour of sleep; AHI 5–14 is mild, 15–29 is moderate, and 30 or above is severe. Most middle-aged office workers with OSA have mild to moderate disease, with atypical symptoms, and their condition is easily attributed to "being too tired from work", delaying diagnosis. Intermittent hypoxia is more destructive than sustained hypoxia. Each episode of suffocation activates the sympathetic nervous system, causing a sudden rise in blood pressure, impacting the vascular endothelium, and generating large amounts of oxidative stress and inflammatory factors, resulting in nocturnal hypertension and increasing the risk of thrombosis and atherosclerosis. At the same time, it worsens insulin resistance, forming a

cycle: "OSA hypoxia → worsened metabolism → aggravated obesity → worsened OSA". The unique harm of intermittent hypoxia lies in the repeated cycle of "hypoxia → reoxygenation", a process similar to ischaemia–reperfusion injury, which induces excessive generation of reactive oxygen species, activates the NF-κB inflammatory pathway, and promotes endothelial cell apoptosis. In contrast, sustained hypoxia initiates adaptive mechanisms (such as erythrocytosis and angiogenesis), whereas intermittent hypoxia does not have time to establish effective adaptation, making damage more pronounced. Daytime manifestations include sleepiness, declining concentration, brain fog, and irritability, directly reducing workplace performance. Daytime sleepiness in patients with OSA not only affects work efficiency but also increases the risk of occupational injury and traffic accidents, which is one reason why OSA is regarded as an important occupational health issue.

The Wisconsin Sleep Cohort Study is a landmark study in OSA epidemiology. Peppard *et al.* (2013) [20], published in the American Journal of Epidemiology, used data from two periods, 1988–1994 and 2007–2010, to estimate that the prevalence of moderate-to-severe sleep-disordered breathing (AHI ≥ 15) was 10% in men aged 30–49, 17% in men aged 50–70, 3% in women aged 30–49, and 9% in women aged 50–70. The study also noted that these prevalence estimates showed substantial increases compared with the previous two decades, with relative increases ranging from 14% to 55%. Prospective follow-up data show that untreated sleep apnoea can predict increased blood pressure, hypertension, and stroke risk. Regular use of CPAP therapy can reduce blood pressure by an average of 10 mmHg and effectively reverse part of the vascular damage. The benefits of CPAP therapy are not limited to blood pressure control; they also include improvement in daytime sleepiness, increased insulin sensitivity, improved left ventricular function, and improved quality of life. For patients who cannot tolerate CPAP, mandibular advancement devices and weight reduction are also effective alternative or adjunctive treatments. Snoring does not mean sleeping soundly; rather, it is an important warning signal. Middle-aged office workers with snoring, nocturnal breath-holding, morning headache, or irresistible daytime sleepiness should consider home sleep testing or laboratory polysomnography.

Immunosenescence and Chronic Low-Grade Inflammation

Acute inflammation is accompanied by redness, swelling, heat, and pain, and is easily noticed. However, what truly destroys health in midlife is asymptomatic chronic low-grade inflammation. With immunosenescence, the thymus atrophies, immune cell diversity declines, immune defence weakens, and the ability to regulate inflammation fails. The body remains in a state of mild alertness for long periods, continuously releasing inflammatory factors. The features of immunosenescence include: contraction of the naive T-cell repertoire, clonal expansion of memory T cells, decreased cytotoxicity of natural killer (NK) cells, and an increased proportion of immune cells with a pro-inflammatory phenotype. These changes not only reduce infection defence and vaccine response, but also lead to "inflammaging"—an age-related elevation in baseline levels of circulating pro-inflammatory cytokines. CRP, IL-6, and TNF-α are three key inflammatory markers. Sedentary behaviour, stress, sleep deprivation, leaky gut, and visceral fat accumulation all stimulate elevation of these indicators. A review by Baechle *et al.* (2023) [3] in Molecular Metabolism systematically integrated the interactive mechanisms between ageing-related chronic inflammation and eleven other hallmarks of ageing, pointing out that the interactions between chronic inflammation and other ageing hallmarks form a vicious cycle, exacerbating cellular functional decline and promoting the ageing process. The review particularly emphasised that, because of their interconnectedness and their capacity to amplify core elements of ageing, the drivers of chronic inflammation may be ideal intervention targets with high translational potential. In this network, chronic inflammation is both a downstream consequence of ageing hallmarks such as genomic instability, telomere shortening, and mitochondrial dysfunction, and further exacerbates the progression of these hallmarks, forming a self-reinforcing feedback loop.

Chronic low-grade inflammation is an upstream factor in multiple diseases: it attacks insulin receptors and aggravates insulin resistance; damages the vascular endothelium, promoting atherosclerotic plaque formation, and even makes plaques unstable and prone to rupture, explaining the clinical phenomenon in which some individuals with normal cholesterol still experience myocardial infarction; it also increases the incidence of autoimmune diseases in midlife. In the pathological progression of atherosclerosis, inflammation is involved not only in plaque initiation and growth, but is also a key driver of plaque rupture and thrombus formation. The characteristics of unstable plaques include a large lipid core, a thin fibrous cap, and abundant inflammatory cell infiltration. When inflammation within the plaque is active, matrix metalloproteinases (MMPs) degrade the collagen components of the fibrous cap, making the plaque susceptible to rupture, triggering platelet aggregation and coronary thrombosis, leading to acute coronary syndrome. The landmark JUPITER trial provided the strongest evidence for inflammation as an independent risk factor. The trial enrolled 17,802 apparently healthy adults with LDL cholesterol below 130 mg/dL but high-sensitivity CRP ≥ 2 mg/L, randomly assigning them to rosuvastatin 20 mg daily or placebo. The results showed that statin therapy was associated with a significant 37% reduction in hsCRP, a 44% reduction in cardiovascular events, and a 20% reduction in all-cause mortality (Ridker *et al*., 2008; Ridker, 2009) [21, 22]. This overturned the previous concept of looking only at blood lipids and confirmed that inflammation is an independent major risk factor. The important significance of the JUPITER trial is that it demonstrated that in people with ideal LDL cholesterol levels but elevated inflammatory markers, reducing inflammation still confers significant cardiovascular benefit, providing key clinical trial support for the "inflammation hypothesis". The subsequent CANTOS trial further confirmed that selective inhibition of the inflammatory pathway using canakinumab, an IL-1β monoclonal antibody, significantly reduced the risk of recurrent cardiovascular events without affecting blood lipids, providing more direct evidence for inflammation as a therapeutic target in cardiovascular disease. For stressed, sedentary middle-aged office workers, inflammatory markers are sometimes more predictive than cholesterol. High-sensitivity CRP (hsCRP) is low-cost and highly accessible and should be included in routine health

examinations for middle-aged office workers; hsCRP ≥ 2 mg/L indicates the need for active lifestyle intervention, while ≥ 3 mg/L represents a high cardiovascular risk state requiring further assessment and management. In addition to hsCRP, IL-6 and TNF-α are also important inflammatory markers, but because of their higher testing costs and the lack of unified clinical cut-off values, they are currently used mainly in research rather than routine clinical practice.

Liver and Kidney

The liver is the body's metabolic hub. The primary threat to the liver among modern office workers is no longer viral hepatitis, but non-alcoholic fatty liver disease (NAFLD; in modern classification also metabolic dysfunction-associated fatty liver disease, MAFLD). The Taiwan Liver Research Society points out that the prevalence of metabolic dysfunction-associated fatty liver disease among Taiwanese adults is 33.3%, higher than the global average of 30.5%, with an estimated 7 million people affected; among the core driving population aged 30–50, nearly 40% have fatty liver disease (Taiwan Liver Research Society, 2023) [28]. Fatty liver is divided into four stages: simple steatosis, steatohepatitis (NASH), liver fibrosis, and cirrhosis. The first stage, simple fat accumulation, is highly reversible; a 7–10% reduction in body weight can result in complete resolution in most cases. Once steatohepatitis develops, long-term follow-up shows that 15–20% will progress to cirrhosis within ten years. The pathogenesis of NAFLD is centred on the "multiple-hit" hypothesis: the first hit is insulin resistance, which increases hepatic free fatty acid influx and enhances de novo lipogenesis, causing hepatocyte steatosis; the second hit includes oxidative stress, gut microbiota dysbiosis and endotoxin, inflammatory factors, and lipid peroxidation, leading to hepatocyte injury and inflammatory response; subsequent hits involve hepatic stellate cell activation and extracellular matrix deposition, driving fibrosis progression. This mechanistic framework explains why NAFLD is so closely associated with metabolic syndrome, insulin resistance, and gut microbiota dysbiosis—they share the same pathophysiological basis.

Clinical data from the Taiwan Liver Research Society show that 40–52% of patients with metabolic dysfunction-associated steatohepatitis already have moderate-to-severe fibrosis at the time of diagnosis. Many lean individuals with normal body weight also develop fatty liver; the core factors are insulin resistance, visceral fat, and chronic inflammation, not body weight alone. When interpreting liver function, one should not look only at whether ALT and AST exceed the reference range; GGT and the AST/ALT ratio help to identify fatty metabolic load and fibrotic trends early. GGT is a component of the liver's antioxidant defence system, and its elevation reflects increased hepatic oxidative stress and fatty metabolic load. Even when ALT and AST are normal, elevated GGT may be an early marker of NAFLD. In addition, the fibrosis-4 index (FIB-4) and non-invasive liver fibrosis imaging (such as transient elastography) can be used to assess the degree of liver fibrosis and should be considered for routine use in middle-aged office workers diagnosed with NAFLD. The kidney is known as a silent organ. Early kidney damage is almost asymptomatic; by the time oedema or abnormal urination appears, chronic kidney disease (CKD) has often reached stage 2 or 3, and glomerular fibrotic damage is mostly irreversible. eGFR is more suitable than creatinine as a core indicator of kidney function, as it can exclude interference from muscle mass and detect decline earlier. After the age of 40, eGFR naturally declines by 0.75–1 mL/min per year; hypertension and diabetes can make the rate of decline 2–3 times faster. According to a nationwide study published in the Clinical Journal of the American Society of Nephrology in 2026 [17], the prevalence of CKD in Taiwan is 10.0%, affecting approximately 1.91 million adults; prevalence is higher in men (11.9%) than in women (8.1%), and highest in the eastern region (13.9%) (Wu *et al*., 2026) [24]. However, public awareness of CKD is only 3.5%, and more than 96% of patients are unaware that their kidney function is impaired.

The insidious progression of CKD is related to its compensatory capacity. The kidney has strong reserve function; when glomerular filtration rate falls to 50% of normal, serum creatinine may still be within the normal range. Only when more than 50% of kidney function is lost do conventional biochemical indicators begin to show abnormalities. This is why eGFR—calculated from age, sex, and creatinine—can more sensitively reflect early changes in kidney function and is more suitable as a screening indicator than creatinine alone. The urine albumin-to-creatinine ratio (UACR) is another important early marker of damage; microalbuminuria (UACR 30–300 mg/g) can appear before eGFR declines, reflecting early damage to the glomerular filtration barrier. Hypertension and diabetes are the two leading causes of end-stage renal disease in Taiwan. Stabilising blood pressure below 130/80 mmHg can slow the rate of eGFR decline by up to 50%, making it the most cost-effective kidney-protective measure. Renin–angiotensin–aldosterone system (RAAS) inhibitors (such as ACEIs and ARBs) not only lower blood pressure but also reduce urinary protein excretion and delay progression of renal fibrosis, and are first-line drugs for CKD patients with proteinuria. In addition, avoiding long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), controlling uric acid and blood glucose, and maintaining appropriate fluid intake are also important measures for protecting kidney function. For middle-aged office workers, it is recommended that annual health check-ups include eGFR and UACR measurements, especially for individuals with a family history of hypertension, diabetes, or cardiovascular disease, so that timely intervention can occur while kidney function is still at a reversible stage.

Visual and Sensory Degeneration

After the age of 40, lens fibres harden and elasticity decreases, causing presbyopia. Modern office workers use screens at close range for prolonged periods, causing continuous ciliary muscle strain; the onset of presbyopia is therefore shifted earlier, and early symptoms at ages 38–42 are very common. Digital eye strain is accompanied by a significant decrease in blink rate, tear film disruption causes dry eye, and long-term blue light exposure increases retinal oxidative stress, accumulating retinal cell damage. Digital eye strain has become an important occupational health problem worldwide. A systematic review and meta-analysis by Wallace *et al*. (2024) [23] showed that the pooled prevalence of computer vision syndrome among office workers is as high as 71.33%, with women at particularly prominent risk. Symptoms of computer vision syndrome include eye fatigue, dryness, burning, blurred vision,

headache, and shoulder–neck soreness. Its pathogenesis involves multiple aspects: prolonged near-distance fixation leads to sustained ciliary muscle contraction and accommodative spasm; during screen viewing, blink rate decreases from 15–20 times per minute to 5–7 times per minute, causing excessive tear film evaporation and dry eye; screen glare and inappropriate contrast aggravate visual load; poor posture leads to shoulder–neck muscle tension. Harvard University research confirms that, under the current situation of an average daily screen time of 7.5 hours, the 20-20-20 rule (looking at an object 6 metres away for 20 seconds every 20 minutes) can effectively reduce the incidence of visual fatigue by more than 40%. Blue-light-blocking lenses only address part of the blue light problem and cannot address the root causes of ciliary muscle spasm and insufficient blinking. In addition, maintaining a screen distance of 50–70 cm, positioning the top of the screen slightly below eye level, and adjusting ambient lighting to reduce glare are also effective measures for preventing digital eye strain.

Hearing degeneration is characterised by preferential high-frequency damage; inner ear hair cells cannot regenerate once they undergo apoptosis. In addition to age-related factors, office noise, commuting noise, and prolonged headphone use cause cumulative occupational hearing damage. A review by Lie *et al*. (2022) [14] in Occupational and Environmental Medicine pointed out that the global working population exposed to occupational noise continues to be large, and its epidemiology, mechanisms, and prevention strategies have become important research areas in occupational medicine. The mechanisms of noise-induced hearing loss (NIHL) involve two pathways: mechanical damage and metabolic damage. Intense noise causes excessive vibration of the cochlear basilar membrane, directly damaging the stereocilia and cell membrane of hair cells; at the same time, noise induces excessive generation of reactive oxygen species, leading to hair cell apoptosis and damage to the stria vascularis. Many people merely feel that they "cannot hear what others are saying clearly" and do not realise that their hearing has already been damaged. Noise also increases sympathetic stress hormones, aggravating systemic fatigue and worsening sleep quality. Sensory degeneration is not merely an inconvenience in daily life; it is also an external manifestation of systemic ageing. Conversely, long-term visual fatigue consumes neural resources and worsens overall physical and mental state. Hearing loss is also associated with cognitive decline and increased risk of dementia, possibly because hearing loss leads to social isolation, reduced auditory cortex input, and excessive allocation of cognitive resources to auditory processing. Recent studies have also found that hearing loss is associated with increased incidence of depression and anxiety, forming a chain reaction: "hearing impairment → social withdrawal → emotional disorder → cognitive decline". For middle-aged office workers, measures to prevent hearing damage include: wearing hearing protection in high-noise environments, controlling headphone volume (not exceeding 60% of maximum volume, with continuous use not exceeding 60 minutes), and undergoing regular hearing examinations. For vision protection, regular ophthalmic examinations, correction of refractive errors, and good eye-use habits should be implemented. Presbyopia and hearing decline should not be regarded as inevitable consequences of ageing—through active preventive measures, the progression of sensory degeneration can be significantly delayed, maintaining workplace performance and quality of life.

Integrated Pathogenic Chain and Blind Spots in Current Health Knowledge

Through the integration of literature across the aforementioned systems, a complete disease development chain for middle-aged office workers can be constructed. This chain begins with cellular ageing and, through two cores—systemic low-grade inflammation and insulin resistance—links pathological changes across all major organ systems. The pathogenic chain comprises eight sequential stages. Stage 1: cellular ageing initiation after 40, with telomere erosion, mitochondrial decline, reduced autophagy, and hormonal fluctuation; it is largely asymptomatic. Stage 2: workplace stimuli—sedentary behaviour, shift work, long hours, chronic stress, and sleep deprivation—accelerate telomere shortening and elevate cortisol, producing non-specific fatigue, poorer sleep, and increasing waist circumference. Stage 3: dietary imbalance and stress disrupt the intestinal barrier, causing dysbiosis, leaky gut, endotoxin translocation, and systemic low-grade inflammation; bloating, postprandial drowsiness, and indigestion are often ignored. Stage 4: inflammatory factors impair insulin signalling, visceral fat accumulates, and metabolic syndrome emerges, with borderline hypertension, dyslipidaemia, and elevated triglycerides despite normal fasting glucose. Stage 5: synergistic risk factors initiate vascular endothelial injury and silent atherosclerosis, raising cardiovascular risk geometrically; symptoms may be absent or limited to exertional chest tightness. Stage 6: endocrine disturbance progresses, including subclinical thyroid dysfunction, declining testosterone, and menopausal hormonal fluctuation, amplifying fatigue, mood instability, weight gain, and reduced libido. Stage 7: sleep apnoea creates a vicious cycle of nocturnal intermittent hypoxia, metabolic worsening, obesity, and aggravated apnoea, manifesting as snoring, daytime sleepiness, and morning headache. Stage 8: hepatic and renal damage and sensory degeneration develop, including non-alcoholic fatty liver disease, hidden glomerular decline, digital eye strain, and noise-induced hearing loss. Early stages are largely asymptomatic; by the time clinical symptoms appear, some organ damage is already irreversible, exposing common blind spots in office workers' health knowledge. Five common misconceptions in midlife health cognition warrant critical attention. First, the belief that youth confers resilience and that fatigue is reversible through sleep is untenable. Research on long working hours demonstrates that overtime-induced damage is partially irreversible; telomere shortening, mitochondrial impairment, and chronic inflammatory states require systematic intervention, not compensatory sleep alone. Second, health is often equated with examination values falling within reference ranges. Neglecting advanced indicators such as HOMA-IR, high-sensitivity CRP, TSH, and eGFR masks borderline abnormalities and cumulative risk; population-based reference ranges do not signify individual optimal health. Third, obesity is frequently reduced to elevated BMI. Normal-weight individuals with excessive visceral adiposity may already face elevated metabolic syndrome risk; waist circumference and waist-to-hip ratio are more sensitive indicators than BMI. Fourth, chronic disease is mistakenly

regarded as confined to old age. Atherosclerosis, fatty liver, and OSA often initiate in midlife, with ages 30–45 representing a critical period of plaque progression; waiting for symptoms after 60 may miss the optimal intervention window. Fifth, fatigue and discomfort are routinely attributed to ageing, while treatable conditions such as thyroid dysfunction, OSA, leaky gut, and chronic inflammation are overlooked. "Getting older" should not justify therapeutic nihilism. Many midlife complaints have identifiable pathological bases and effective interventions.

Conclusion

The systemic nature of this pathogenic chain determines that intervention strategies must also be systemic. Lu (2026) pointed out that the holistic health framework emphasises that health is a dynamic state of balance among multiple interconnected domains—biological, behavioural, social, and environmental—rather than the normality of a single organ or indicator. From Hippocrates' concept of natural healing power to the multidimensional balance theory of modern integrative medicine, holism and balance have always been at the core of holistic health thought. For middle-aged office workers, the practical significance of this framework is that health management cannot be limited to the tracking of individual indicators and single-drug intervention, but should focus on coordinated regulation of multiple systems and holistic optimisation of lifestyle. The health predicament of office workers aged 40–59 is not a problem of a single organ, but a whole-system, comprehensive pathological process that begins with cellular ageing and links the endocrine, metabolic, cardiovascular, gastrointestinal and hepatic, sleep, immune, and sensory systems. Natural physiological degeneration provides the foundation for ageing, but sedentary behaviour, shift work, long working hours, and chronic stress in the modern workplace act as accelerators, amplifying all risks and causing many chronic diseases to arrive earlier. The most critical features of this disease chain are: highly insidious in the early stage, largely reversible in the middle stage, and partially irreversible in the late stage. Therefore, midlife health promotion and management cannot remain within the traditional medical mindset of "treating disease when it arises"; it must shift upstream to the stage of risk prevention (OpenAI, 2026) [19].

The concept of holistic health provides theoretical support for this shift. The Western holistic health tradition described by Lu (2026) [17], with its core principles of holism and balance, aligns closely with the picture of multiorgan interconnected pathogenesis revealed by contemporary systems biology. Health is not the normality of a single indicator, but a dynamic balance across biological, behavioural, social, and environmental dimensions; disease is not the failure of a single organ, but a chain reaction after systemic balance is disrupted. This perspective has important practical implications for health management among middle-aged office workers: problems such as fatigue, obesity, hypertension, and sleep disturbance should not be treated as independent conditions separately, but their shared pathogenic mechanisms—insulin resistance, chronic inflammation, circadian rhythm disruption, and cellular ageing—should be identified and targeted for coordinated intervention. For example, regular exercise simultaneously improves insulin sensitivity, reduces inflammatory markers, regulates circadian rhythms, and promotes mitochondrial biogenesis; its multisystem benefits far exceed those of any single drug. Similarly, optimising sleep not only restores energy but also improves insulin secretion rhythms, lowers nocturnal blood pressure, enhances immune surveillance, and promotes clearance of cerebral metabolic waste. For middle-aged office workers, understanding the full picture of this pathogenic chain is the first step towards effective health management. During the reversible golden window, through lifestyle optimisation at the individual level and the construction of supportive environments at the enterprise level, multisystem coordinated intervention can fundamentally reduce the disease burden of the midlife health crisis, allowing midlife to become a period of harvest rather than a period of health collapse.

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