Advances in Predictive, Preventive and Personalised Medicine
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Wei Wang *Editor*

All Around Suboptimal Health

Advanced Approaches by Predictive, Preventive and Personalised Medicine for Healthy Populations

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What this book series is about… Current healthcare: What is behind the issue? For many acute and chronic disorders, the current healthcare outcomes are considered as being inadequate: global figures cry for preventive measures and personalised treatments. In fact, severe chronic pathologies such as cardiovascular disorders, diabetes and cancer are treated after onset of the disease, frequently at near end-stages. Pessimistic prognosis considers pandemic scenario for type 2 diabetes mellitus, neurodegenerative disorders and some types of cancer over the next 10-20 years followed by the economic disaster of healthcare systems in a global scale. Advanced healthcare tailored to the person: What is beyond the issue? Advanced healthcare promotes the paradigm change from delayed interventional to predictive medicine tailored to the person, from reactive to preventive medicine and from disease to wellness. The innovative Predictive, Preventive and Personalised Medicine (PPPM) is emerging as the focal point of efforts in healthcare aimed at curbing the prevalence of both communicable and non-communicable diseases such as diabetes, cardiovascular diseases, chronic respiratory diseases, cancer and dental pathologies. The cost-effective management of diseases and the critical role of PPPM in modernisation of healthcare have been acknowledged as priorities by global and regional organizations and health-related institutions such as the Organisation of United Nations, the European Union and The National Institutes of Health. Why integrative medical approach by PPPM as the medicine of the future? PPPM is the new integrative concept in healthcare sector that enables to predict individual predisposition before onset of the disease, to provide targeted preventive measures and create personalised treatment algorithms tailored to the person. The expected outcomes are conducive to more effective population screening, prevention early in childhood, identification of persons at-risk, stratification of patients for the optimal therapy planning, prediction and reduction of adverse drug-drug or drug-disease interactions relying on emerging technologies, such as pharmacogenetics, pathology-specific molecular patters, sub/cellular imaging, disease modelling, individual patient profiles, etc. Integrative approach by PPPM is considered as the medicine of the future. Being at the forefront of the global efforts, The European Association for Predictive, Preventive and Personalised Medicine (EPMA, http://www.epmanet.eu/) promotes the integrative concept of PPPM among healthcare stakeholders, governmental institutions, educators, funding bodies, patient organisations and in the public domain. Current Book Series, published by Springer in collaboration with EPMA, overview multidisciplinary aspects of advanced bio/medical approaches and innovative technologies. Integration of individual professional groups into the overall concept of PPPM is a particular advantage of this book series. Expert recommendations focus on the cost-effective management tailored to the person in health and disease. Innovative strategies are considered for standardisation of healthcare services. New guidelines are proposed for medical ethics, treatment of rare diseases, innovative approaches to early and predictive diagnostics, patient stratification and targeted prevention in healthy individuals, persons at-risk, individual patient groups, sub/populations, institutions, healthcare economy and marketing.

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Editors

About the Book Series Editor

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He has had an interest in forensic medicine and global health for almost 30 years. In addition to his role as Professor in the School of Medical and Health Sciences at ECU, Professor Wang is also the Chief Scientist, Institute of Glycome Studies, SUMC, China, Adjunct Professor, School of Public Health, Shandong First Medical University (SFMU), China, and Director of the Beijing Municipal Key Laboratory-Centre of Excellence on Clinical Epidemiology, Capital Medical University (CMU), China.

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Professor Wang was the Foundation Chief Editor of the *Journal of Family Medicine and Community Health* (BMJ). Currently, he is Associate Editor of *EPMA Journal* (Springer), and regional editor of *Journal of Global Health* (University of Edinburgh Press), *OMICS: A Journal of Integrative Biology* (Mary Ann Liebert), *Journal of Human Hypertension* (Nature Publishing Group), *Clinical and Translational Medicine* (Wiley), *Engineering* (*CAE-Elsevier*), and *PloS ONE* (PLoS).

Professor Wang holds the degrees of Doctor of Medicine from China Medical University and Doctor of Philosophy from Oita Medical University, Japan.

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Suboptimal Health Management in the Framework of PPP Medicine

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Abbreviations

CTD	Connective tissues dysfunction
EPMA	European Association for Predictive, Preventive and Personalised Medicine
ET-1	Endothelin-1
FS	Flammer syndrome
GAH	Gestational arterial hypertension
GD	Gestational diabetes
PE	Preeclampsia
PPPM/3PM	Predictive, preventive and personalised medicine
SH	Suboptimal health

1 Suboptimal Health (SH) Definition

Suboptimal health (SH) can be easily defined as the reversible phase of the health-to-disease transition. Consequently, the time-frame between the SH condition onset and related clinically manifested disorder is the operational window to protect the affected person against the disease which he/she is predisposed to [1].

2 Cost-Effective Prevention of Persons in SH Conditions from the Health-to-Disease Transition Is One of the Highest Priorities of PPP Medicine Concepts in Primary and Secondary Care

Prevention of people from the health-to-disease transition is a highly comprehensive approach based on predictive diagnostics and intervention tailored to the individualised health. Cost-effectiveness inversely correlates with the suboptimal severity grade and level of care. Consequently, PPPM management of subtle health alterations in primary care is the most cost-effective approach compared to irreversible health-to-disease transition and disease progression (secondary care). Contextually, major efforts have to be dedicated to the population screening focused on early stages of SH conditions, precisive diagnosis followed by the targeted individualised prevention. Corresponding paradigm shift from delayed-reactive medical services to advanced PPPM approach in biomedical sciences and daily practice is propagated by the EPMA (European Association for Predictive, Preventive and Personalised Medicine) (https://www.epmanet.eu) who is considered the world leader in PPPM [2].

PPPM research and implementation rely on a robust conceptual and technological innovation including multi-professional expertise (researchers, caregivers, educators, technologists, policy-makers, diagnostic and pharmaceutical industry), application of artificial intelligence in medicine, education provided to professionals and general population, active involvement of patient organisation and affected individuals into the doctor–patient collaborative process (participatory medicine), amongst others. This can be exemplified by the newly proposed mitochondrial health quality check-up.

3 A Holistic Approach by the Mitochondrial Health Quality Check-Up (MHQC)

An evident reciprocity between mitochondrial and organismal health status is clearly reflected in the health-to-disease transition and systemic damage. Therefore, a routine non-invasive mitochondrial health quality control test is strongly recommended as the holistic predictive diagnostics to benefit both primary and secondary care. With the highest priority, MHQC is proposed to implement for the pre-pregnancy check-up, health-to-disease transition check-up, accompanying diagnostics in sport medicine and coached body exercise, physiotherapeutic and well-being services, and therapy efficacy monitoring for personalised treatments, e.g. in chrono- and sleep-medicine, chronic fatigue and burnout syndrome, mood disorders and systemic impairments, amongst others [3, 4].

4 Microbiome-Related Health-Maintaining Technologies in PPPM

Microbiome-related health-maintaining technologies is a promising PPPM approach in SH as reviewed by the recently released book “Microbiome in 3P Medicine Strategies – The First Exploitation Guide” [5]. Microbiome demonstrates holistic effects on human health, i.e.: a multi-functional interplay between the individual health status and microbiome profile composed of microflora on skin, in nasal/oral cavities, in airways, and also in gastro-intestinal and urogenital tracts. The microbiota colonisation starts at birth in humans, demonstrating two levels, i.e., local and global ones, of the immune response. Microbiota composition is a modifiable risk factor that can be modulated being therefore an attractive target for overall SH management.

5 Needs of Young Populations Are in Focus of SH Concepts in PPPM

In order to be effective for healthcare systems, PPPM approach has to be implemented early in life of each individual. Per accumulated scientific evidence, health condition of the mother and offspring to great extent is created during the pregnancy because of highly increased haemodynamic stress which mother is exposed to. In case of maternal sub-optimal health that is usually overlooked in pre pregnancy period, progressive abnormalities will get progressed and visible during pregnancy and post-partum. Following the principles of PPPM, advanced screening programmes applied to young populations as well as timely companion diagnoses during pregnancy have been promoted by the EPMA expert working group in the area of PPPM in youth [6] to early diagnose and cost-effectively prevent post-partum health risks of the mother and child. Great clinical utility of the proposed PPPM concept has been recently demonstrated as summarised in Fig. 1.

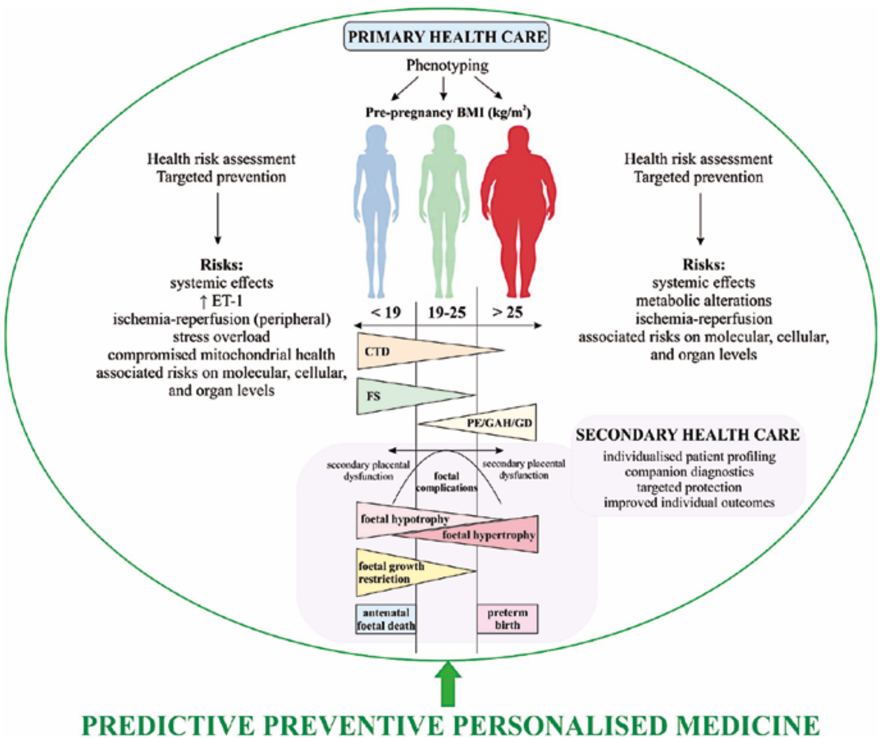

Fig. 1 PPPM approach proposed by the EPMA expert group revealed the susceptible pregnancy-related health risks to mother and child; proposed screening programme based on phenotyping of the mother prior to pregnancy, precisive health risk assessment and individual tailored protective and mitigating measures for primary and secondary care. *Abbreviations*: *CTD* connective tissues dysfunction, *ET-1* enddothelin-1, *FS* Flammer syndrome, *GAH* gestational arterial hypertension, *GD* gestational diabetes, *PE* preeclampsia. Image is adapted from Youth [6]

6 Who Are the Beneficiaries of SH-Innovation in the Framework of PPPM?

The joint position paper released by the EPMA J. in 2021 on behalf of the Suboptimal Health Study Consortium and European Association for Predictive, Preventive and Personalised Medicine [1] stated that below listed medical fields might strongly benefit from the scientific promotion and practical implementation of the SH-related innovation in the framework of PPPM:

- Mental health and physical vitality at any age.
- Reproductive health.
- Planned pregnancies.
- Chrono- and sleep-medicine.
- Sport medicine and coached body exercises.
- Periodontal health.
- Longevity and anti-ageing medicine.
- Disease pre-stages.
- Anti-stress programmes.
- Protection of populations against communicable and non-communicable disorders.

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Definition of Suboptimal Health

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Abbreviations

ASCVD	Atherosclerotic cardiovascular diseases
CFIDS	Chronic fatigue immune dysfunction syndrome
CFS	Chronic fatigue syndrome
CVH	Cardiovascular health

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HELLP	Haemolysis elevated liver enzymes and low platelet count
ME	Myalgic encephalomyelitis
NCDs	Non-communicable chronic diseases
NO	Nitric oxide
PE	Preeclampsia
PVFS	Post-viral fatigue syndrome
RA	Rheumatoid arthritis
SHS	Suboptimal health status
SHSQ-25	Suboptimal Health Status Questionnaire-25
SLE	Systemic lupus erythematosus
TL	Telomere length
UMS	Unexplained medical syndrome
VD	Vaginal dryness

1 Definition of Suboptimal Health

SHS is intermediate condition between optimal health and diseases. SHS is commonly characterised by reversible loss of vitality, decline of physiological function and less capacity for self-adaptation. Individual with SHS suffers from self-perceived general weakness, low energy or health complaints but does not match any criteria of diseases, which increase the predispositions to physical or psychological disorders. It is demonstrated that a variety of non-communicable chronic diseases (NCDs) have a reversible period of SHS prior to specific pathological disorders [1].

Different from either early stage or preclinical period of diseases, SHS is defined as a period preceding the occurrence of diagnosable manifestations of diseases. Individuals in this pre-disease stage are healthy who cannot be diagnosed as any of the specific virtual diseases. In contrast, individuals in preclinical period of specific disease usually have the specific signs or indications of the disease and need to be treated with targeted therapies that contribute to prevent or delay the process of the disease. By reference to the guideline of PPPM, persons with SHS are considered to require nonspecific health promotion management, including physical activities, prudent dietary practices, quitting smoking and psychological counselling, which lead to reversion of health status, and reduction of likelihood of disease. However, compared with commonly-recognized pre-disease, the features of SHS make it feasible to identify the persons who suffer from SHS. In addition, the well recognition of SHS may motivate the specific preventive approaches to prevent SHS-related diseases.

Even though SHS is common, only 23% of SHS are reported to seek immediate medical services [2], and approximately 80% of them showed no improvements in health condition within 6 months [3]. Therefore, it is urgently needed to call for concerted efforts and positive contributions to the timely detection of persons with SHS, which are advocated by the professionals of PPP medicine [4].

2 Examples of SHS-Associated Disease and Dysfunctions

Since early diagnosis, accompanied with targeted intervention is crucial for the prevention and control of NCDs, it is demanded for clinic practitioners to shift their perspective from clinical intervention for diagnosable disease to the priority of identifying persons at SHS stage [5]. However, it is difficult, at present, to discriminate those with SHS from generally apparent healthy individuals, due to the variety of health-related perceptions, and heterogeneous somatic complaints. Commonly, five domains are of interest for screening SHS-associated problems: fatigue, cardiovascular system, digestive tract, immune system and mental state (Fig. 1).

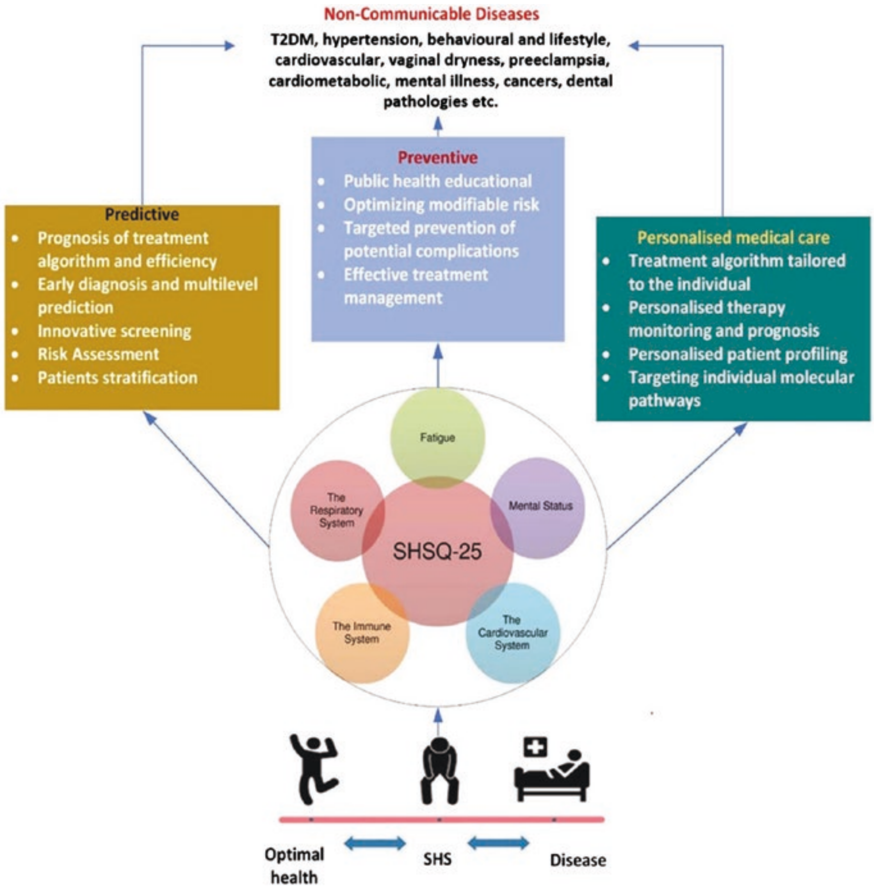

Fig. 1 Suboptimal health status is instrumental for health care of non-communicable diseases. The figure is adapted from Ref. [6]

The key role of SHS in the pathogenesis and progression of health damages or dysfunctions has been investigated. The findings on SHS-associated diseases and dysfunctions offer a window opportunity to reserve the progression of damages to the health.

2.1 Cardiovascular System

SHS is associated with poor cardiovascular health (CVH) metrics that consist of high blood pressure, dyslipidaemia and hyperglycaemia, smoking, overweight, lack of physical activity and irregular diet [7]. Multi-ethnicities studies also confirmed that SHS is closely correlated to hypertension, hyperglycaemia and dyslipidaemia [4, 8]. A Russian study revealed that endothelial function is associated not only with overall SHS, but also with individual sub-domains of SHS, including fatigue, mental and cardiovascular system [9]. With regard to behavioural factors, SHS is attributable to cigarette smoking, irregular breakfast, lack of physical activity and alcohol consumption [4, 10]. Therefore, SHS can be used as one of the behavioural candidates for indicating a healthy lifestyle. Meal composition and timing can influence metabolic patterns that may lead to the occurrence of SHS. Skipping breakfast reduces insulin sensitivity, resulting from pre-loading and distortion of energy metabolism [11]. The improved belief and practice of healthy breakfast behaviours will consequently lead to the improvement of health conditions.

2.2 Immune System and Reproductive Health

Pregnant women in SHS are exposed to abnormal elevation of oxidative stress and unbalance of pro- and anti-angiogenic growth stimulators [12]. After a 20-week follow-up of normotensive pregnant women in Ghana, persons in the condition of SHS suffered a significantly higher incidence of preeclampsia (PE) and other related adverse pregnancy complications, including intrauterine growth restriction, stillbirth, haemolysis elevated liver enzymes and low platelet count (HELLP) syndrome, acute kidney injury and dyslipidaemia [5]. HELLP syndrome is featured by microangiopathic anaemia, thrombocytopenia and periportal hepatic necrosis, which is one of the causes of eclampsia-associated health disorders during pregnancy [13]. Hepatic involvement in preeclampsia is attributed to the precipitation of fibrin within liver periportal areas and vasospasm, which result in liver cell necrosis and lobular ischemia [14]. The association between SHS and preeclampsia-coexisting HELLP syndrome might also result from mental health indicators. In addition, SHS has a causal relationship with vascular endothelium dysfunction [9], which may also contribute to understanding the relationship between SHS and PE. Endothelial dysfunction is closely related to placental hypoxia, nitric oxide (NO) deficiency and oxidative stress that are induced by poor extravillous trophoblast cell invasion and lack of maternal artery remodelling [15]. Another facet needs to be explained is maternal psychosocial stress since psychosocial stress and fatigue are the SHS-specific syndromes [16]. Vaginal dryness (VD), resulting from hormonal regulation changes in women during the climacteric period, is also considered as a syndrome of SHS [17].

Besides, individuals in different levels of SHS have diversity of IgG N-glycosylation traits, an important post-translation modification of IgG [18]. Glycosylation affects more than 90% of mammalian proteins and enables them normal structure and a variety of biological functions. N-linked glycans modulate the function of IgG between anti-inflammatory and pro-inflammatory and influence the development of not only inflammatory diseases but also chronic and autoimmune diseases, including cardiovascular diseases, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), dyslipidaemia, diabetes, Alzheimer and Parkinson's disease [19]. This enables IgG N-glycans to precisely predict and early diagnose these diseases.

2.3 Fatigue and Labour Efficiency

Employees exposed to psychosocial work hazards (e.g., insecurity, workplace justice) or psychosocial stress (e.g., high demands at work, interpersonal relations and leadership) were in poor health status and predisposed to SHS [20, 21]. The frequencies of sickness absence are associated with the prevalence of chronic conditions during occupation, and the future adverse health outcomes after retirement. A prospective study conducted in a large sample size population demonstrated a long-term association between sickness absence and subsequent SHS, in which workers exposed to more sickness absences were observed of increased risk for SHS over a 14-year follow-up [22, 23]. In addition, individuals with SHS experienced much more non-permanent employment [24].

Objective health measures have been investigated on SHS. For example, telomere, consisting of repetitive sequences at the ends of chromosomes, plays a crucial role in maintaining genomic integrity. Telomere length (TL) is shorter in patients with age-related chronic diseases, including diabetes, cardiovascular diseases, impaired immune function and certain types of cancer [25]. Compared to individuals with ideal health, shorter TL was observed in persons with SHS [25]. Consistently, longer TL has been found in those with better self-reported health conditions [26]. Healthy centenarians have been found to have relatively higher TL compared with those with poorer healthy conditions in a North American study [27]. This partly results from the positive association between TL and CVH parameters. In addition, shorter TL is associated with unhealthy lifestyle, which is also an important contributor to SHS [28].

2.4 Digestive Tract and Metabolites

In spite of the lack of an explicit mechanism, the intestinal microbiota is reported to be associated with SHS, and individuals with SHS have alterations of intestinal microbiota composition compared to those in ideal health conditions [29]. In addition, plasma metabolites in SHS are predominantly different from those with ideal health, including sphingomyelin, sphinganine, sphingosine, pregnenolone, progesterone and bilirubin [30]. As reported, overexpression of sphingomyelin synthase-2 increases plasma sphingomyelin and then aggravates atherosclerosis in animal experiments [31]. Furthermore, a decrease in atherosclerotic lesions and inflammatory disorder has been observed in the mice model of sphingomyelin synthase-2 deficiency [32]. As such, sphingomyelin synthase-2 is a potential therapeutic target for atherosclerotic cardiovascular diseases (ASCVD). The finding on sphingomyelin also evidences that sphingomyelin is associated with the phenotypes of the cardiovascular system in SHS individuals, which provided a new target for the personalised prevention of cardiovascular diseases.

Loss of amino acid, identified by amino acid excretion has been found in persons under one subtype of SHS, i.e., long-term fatigue [33]. A negative nitrogen balance induces the development of sub-optimal haemoglobin production that results in fatigue. Consequently, the particular group of people more susceptible to histidine loss need to supplement appropriate proteins. Early studies carried out in breast cancer radiotherapy patients showed that women who suffered from more fatigue had higher levels of urinary histidine excretion [34].

2.5 Mental Status and Neurological Dysfunctions

Complaint of psychological or mental health is one of the important domains of SHS. As such, studies have investigated the association of psychological and mental symptoms with SHS [35]. It is notable that adolescents with SHS have an increased incidence of self-reported suicidal ideation during a one-year follow-up [36], suggesting more studies on SHS amongst adolescents than expected.

The association between SHS and cognitive impairment was analysed in middle-aged and older Chinese populations, among whom SHS is observed to be linked to the decrease of cognitive function [37]. SHS and other multifactorial risk factors (e.g., genetic predisposition, toxic chemical, endogenous and exogenous stress, systemic ischemia-reperfusion and mitochondrial vulnerability) are involved in neurodegenerative processes, which result in multiple neurological symptoms and irreversible impairment of nervous systems [38–40].

3 Summary/Outlook

SHS, by reference to its apparent features and implications, is understood as closely associated with a range of health outcomes, i.e., unexplained medical syndrome (UMS), chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME), post-viral fatigue syndrome (PVFS) and chronic fatigue immune dysfunction syndrome (CFIDS) [41]. More studies are advocated to elucidate the key role of SHS in the development of NCDs, by which targeted healthcare services can be developed to improve optimal well-being.

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Mitochondrion: The Subordinated Partner Who Agreed to Come Short But Insists in Healthy Life

Olga Golubnitschaja

Abbreviations

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BHI	Bio-energetic health index
CO_2	Carbon dioxide
CoA	Coenzyme A
CoQ	Coenzyme Q
Cyt c	Cytochrome c
ETC	Electron transport chain
$FADH_2$	Flavin adenine dinukleotide
GTP	Guanosine triphosphate
MHI	Mitochondrial health index
mtDNA	Mitochondrial DNA
NADH	Nicotinamide adenine dinucleotide
OXPHOS	Oxidative phosphorylation
TCA	Tricarboxylic acid

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1 Preamble

About two billion years ago in the Earth history, that time, the archaea in a sequence first instead of to combat, started to tolerate some types of invaded bacteria and stepwise learned to adapt them and at the end subordinated them taking advantage of their properties and abilities such as an effective production of heating and energy resources and well-developed sensors towards good versus bad quality of life. By this long way of coming together into business, the unique form of cooperation between eukaryotes and their intimate partner, the mitochondria, had been created.

Although became subordinated by eukaryotes, mitochondria maintain a certain level of their independence, e.g., by possessing own genetic information (mtDNA) for replication and highly dynamic homeostasis (fission, fusion, mitophagy) that enables healthy mitochondria to effectively react towards changing environmental conditions and to remain within their comfort zone despite appearing health risks. Certainly, both partners, mitochondria and human cells, have their interests in common to protect the quality of life. Contextually, they learned to cooperate together on minimising health risks by utilising a spectrum of properties both complementary possess. However, under critical conditions such as toxic environments, from both partners, the subordinated mitochondrion is exactly the partner who always comes short. It is an intention that both partners apparently agreed on with correspondingly well-elaborated synergies. To this end, in contrast to chrDNA that is well protected against stressors, mtDNA remains fully unprotected being therefore the primary target of the damage. Under stress conditions, mitochondria operate via their highly dynamic homeostasis and react promptly towards injury by increased mitophagy (mitochondrial autophagy resulting in mtDNA fragmentation and cell-free nucleic acids), which has a dual function in both—mitochondrial health itself and health of the human body as the cooperation partner, namely:

1. To remove damaged mitochondria which will get substituted by a renewed mitochondrial population later on (the rejuvenation process) and
2. To send warning signals to all systems of the human body for a prompt induction of adaptive mechanisms aimed at increasing the level of systemic protection such as activated anti-oxidant defence and repair machinery.

Only very sick cells are not able to follow the warning signals distributed systemically by mitophagy being, therefore, resistant against cooperation with mitochondria. In particularly severe cases, this results in so-called "vicious circle" characterised by increasingly uncontrolled production of ROS and diminished energy supply—both highly relevant to strongly compromised mitochondrial health, dysfunctional repair machinery and cell populations at organismal level as summarised by Fig. 1.

The phenomenon of "vicious circle" is well-described for compromised mitochondrial health, reduced population of functional mitochondrial and mitochondrial

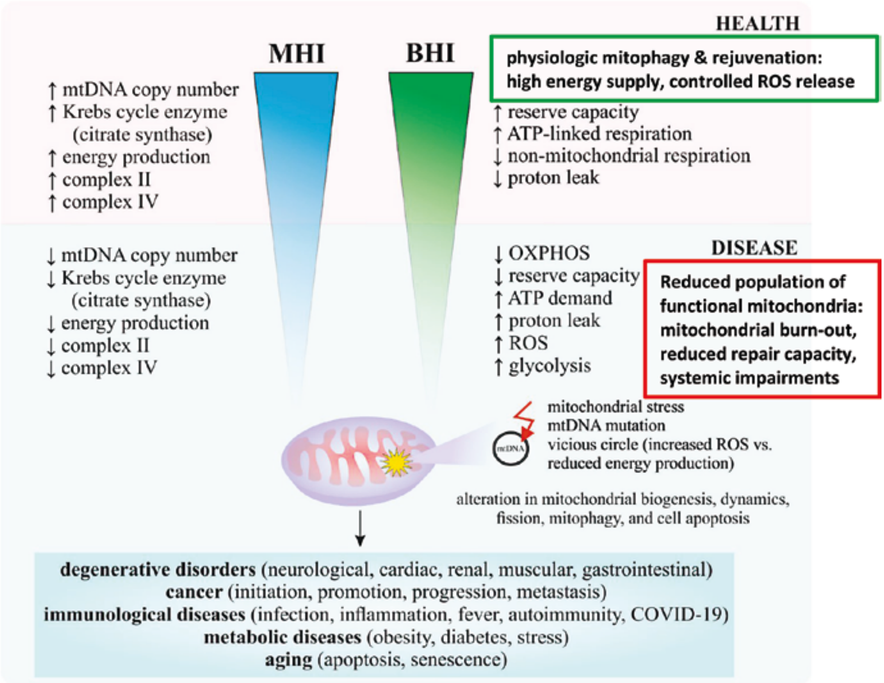

Fig. 1 The complexity of MitochondiralHealth Index (MHI) and Bioenergetic Health Index (BHI) is illustrated for both—physiologic processes and transition from health-to-disease to be predicted and cost-effectively prevented in primary care; these concepts are promoted by EPMA, Brussels; the image is adapted from Ref. [1]

burn-out leading to reduced repair capacity and systemic impairments per evidence involved in the manifestation of severe pathologies such as progressive Alzheimer's disease and metastatic breast cancer [1, 2]. Acting as effectors and targets of injury, mitochondria are considered a novel hub for resuscitation from cardiac arrest and effective cardio-protection against myocardial infarction, sudden heart attack and arrhythmias [3–7].

Above summarised abilities and functions of mitochondria and synergies in their cooperation with human cells create a spectrum of instruments to be used for predictive diagnostics, targeted prevention and personalisation of treatment algorithms for the paradigm shift from reactive medicine to PPPM promoted by the European Association for Predictive Preventive and Personalised Medicine (EPMA, Brussels) [8]. The prominent examples are presented below to demonstrate the clinical relevance of the mitochondrial medicine and to highlight its essential involvement into protection against health-to-disease transition in suboptimal health conditions relevant for both primary and secondary care.

2 To Maintain and Enhance the Population of Functional Mitochondria Is the Highest Priority

How to reach this highly ambitious goal? The issue is not as simple as just an antioxidant intake to mitigate mitochondrial "corrosion" caused by the ROS release as the high costs we have to pay for the way human cells and mitochondria agreed to go together for the energy supply. The measures are complex and focused on beneficial systemic effects considering individually optimised lifestyle, appropriate behavioural and dietary habits, rejuvenation of mitochondrial populations and multi-modal anti-stress programme including respiratory and physical exercises, high quality of sleep, vitamin and nutrient supplements, physio-therapy and meditation, amongst others.

2.1 Mitochondrial Transplantation in Clinically Manifested Disorders May Significantly Improve Individual Outcomes in Secondary Care

There are innovative approaches under consideration such as intranasal mitochondrial transplantation focused on a non-invasive delivery of intact mitochondria to human cells affected by quantitative and qualitative mitochondrial deficits [9]. This research area is motivated by growing evidence on enriching populations of functional mitochondria as the central target in the treatment of devastating neurological and neurodegenerative pathologies such as Parkinson's disease. Indeed, the feasibility of the mitochondrial internalisation has been demonstrated in pre-clinical study sets bypassing the blood–brain barrier and improving overall disease manifestation parameters measured. Promising results by mitochondrial transplantation have been demonstrated also for antitumour approach, including improved mitochondrial dynamics and mitigated chemo-resistance in breast cancer cells [10]. This area clearly demonstrates that maintaining and enhancing populations of functional mitochondria is the highest priority in treatment of severe pathologies being therefore highly relevant for improving individual outcomes in the secondary care, when mitochondrial health is compromised and associated pathologies are clinically manifested. However, for the paradigm shift from reactive to predictive, preventive and personalised medicine, a cost-effective protection on individuals against the health-to-disease transition utilising the protection of mitochondrial health and maintaining their functional populations, is highly attractive and realistic as demonstrated below.

2.2 *Targeted Application of the Phyto-Medical Approach Is Highly Attractive for Maintaining Functional Mitochondrial Populations in Primary Care: Clinically Relevant Examples*

There is well-justified multi-professional interest in nutraceutical substances as dietary supplements to protect individuals against clinically manifested disorders with a great cost-efficacy of corresponding treatments. In the context of mitochondrial health, below we exemplify clinically relevant nutraceutical substances.

2.2.1 *Acetyl-L-carnitine (ALC)*

Acetyl-L-carnitine (ALC) is a well-tolerated nutraceutical substance. In general, carnitine profiling is a useful diagnostic and prognostic tool under neuropathological and altered metabolic conditions such as diabetes mellitus with neurodegenerative complications [11] ,neurotoxicity and mental disorders [12]. ALC demonstrates beneficial effects on the ageing brain and in overall protection against stress-related disorders, and strengthens antidepressant mechanisms including aspects of serotonergic, noradrenergic and GABA neurotransmission. L-carnitine (biologically active stereoisomer) transports long-chain fatty acids from cytoplasm to mitochondria for the energy production (the beta-oxidation pathway via acetyl-CoA formation) and removes short- and medium-chain fatty acids preventing their accumulation in mitochondria. ALC acts as the "mitochondrial nutrient" by reversing stress- and age-related mitochondrial dysfunction and mitigating inadequate reactions of aged and impaired mitochondrial populations.

2.2.2 Quercetin

Anti-ageing and rejuvenating effects of quercetin have been demonstrated in many pre-clinical studies [13]. Quercetin and its derivatives act as a proteasome activator with anti-oxidant properties strongly influencing cellular lifespan, survival and viability of human fibroblasts: Significant rejuvenating effects and improved homeostasis have been observed on senescent fibroblasts. The mechanism underlying rejuvenation effects by quercetin is linked to restoring physiologic levels of mitophagy and mitochondrial health quality control (the Sirt1-agonist function), resulting in renewing functional populations of mitochondria [2]. Positive effects of quercetin supplementation were demonstrated for the reproductive medicine, namely the sperm motility, plasma membrane integrity, viability, and overall parameters of the mitochondrial health were significantly improved [14].

2.2.3 Resveratrol

Both *resveratrol and metformin* act as the AMPK-activators and have been proposed for supporting compensatory mechanisms of targeted treatments that prompt mitochondria to enhance ATP production by overexpressed anti-oxidants and respiratory complex subunits [2]. Resveratrol (3,4′,5-trihydroxystilbene; $C_{14}H_{12}O_3$) is a common bioactive constituent found in grapes, berries, peanuts and wines and demonstrated to improve mitochondrial function under both in vitro and in vivo conditions. The positive effects of this natural polyphenolic phytoalexin are evident for mitochondrial populations with its strong anti-inflammatory, anti-apoptotic and anticancer capacity [15, 16]. Resveratrol is of great pharmacological value being a systemic multi-functional gene-expression modulator that stimulates mitochondria biogenesis via gene-regulating effects including protein deacetylase sirtuin 1 and the nuclear factor-E2-related factor-2 pathways and reduces mitochondrial superoxide generation within the pathway of endothelial nitric oxide-synthase.

2.2.4 Melatonin

The reciprocity has been demonstrated between mitochondrial functionality and melatonin metabolism. The melatonin–mitochondria axis effectively attenuates adverse systemic effects such as pro-inflammatory and carcinogenic processes [17]. Remarkable cardio-protective properties of melatonin are linked to maintaining mitochondrion bio-energetic homeostasis [18]. Consequently, the chronotherapeutic approach restoring nocturnal melatonin production and/or dietary melatonin supplementation is strongly recommended for shift work as the circadian misalignment to prevent systemic mitochondrial dysfunction-associated damage [19]. In preclinical studies, melatonin treatment has been demonstrated as highly beneficial for the amelioration of ageing-related impairments in mitochondrial function [20].

2.2.5 Allicin

Allicin (S-allyl prop-2-ene-1-sulfinothiolate) is the main bioactive compound of garlic (Allium sativum) demonstrating clinically relevant properties including immune-modulatory, anti-stress and anti-inflammatory, anti-biotic/parasitic, anticancer as well as cardio- and neuro-protective activities. The cornerstone of corresponding protection mechanisms is the promotion of mitochondrial homeostasis (fusion) and function via NRF2 and HSP70 pathways as reviewed by Mocayar Marón et al. [21].

3 Cardio-Respiratory Fitness (CRF) Linked to the Mitochondrial Health Is a Crucial Biomarker for the Health Risk Assessment in Primary Care

CRF indexes an individual capacity of two synergic systems, namely the circulatory and respiratory ones to supply O_2 to mitochondrial populations in human skeletal muscles for the concomitant energy production during physical exercises. This biomarker is crucial for the health risk assessment as stated by several professional organisations in the area [22]. It is believed that only 40% of US American youth demonstrate physiological values of CRF influenced by non-modifiable and modifiable factors. The latter consider inadequate dietary habits as a strong risk factor of CRF being directly linked to mitochondrial health and functionality. To this end, the nutritional contribution to the CRF quality is rooted in the efficiency of mitochondrial energetics, and optimal dietary patterns rich in polyphenols and omega-3-fatty acids promote both—an appropriate mitochondrial bioenergetics and physiologic CRF values.

4 Multi-Modal Life-Style Intervention for Well-Functional Mitochondria

From the above-listed facts, it is getting clear that for maintaining well-functional mitochondrial populations, a multi-modal lifestyle intervention is essential in both health and disease. This statement is well-justified by CRF in primary care to prevent health-to-disease transition as well as in secondary care to stabilise the health of affected individuals. To this end, specifically, the multi-modal lifestyle approach focused on mitochondrial health and functionality restoration has been proven as particularly promising for treating severe systemic disabilities such as progressive multiple sclerosis that remains uncurable and demands an innovative concepts' development [23]. Below a spectrum of methods is considered to promote the concept of innovative multi-modal lifestyle intervention taking advantage of unique properties of mitochondria.

4.1 Coached Respiratory and Physical Exercise

Exercise intervention is the cornerstone in maintaining, enriching and rejuvenation of mitochondrial populations, disease prevention and treatment including respiratory, cardio-cerebral-vascular, nervous, immune, motor and digestive metabolic systems [24]. Specifically, mitochondrial respiratory capacity is the metabolic biomarker, indicating health stability in a holistic way [25]. Preclinical studies demonstrated distinguishable mitochondrial phenotypes specific for sedentary *versus* exercise-trained animals [26]. Whereas in the exercise-train animals, exercise protects cardiac mitochondria against ischaemia-reperfusion injury, in untrained animals, the long-lasting exercise causes ROS overproduction, mitochondrial stress and increased level of damaged mitochondrial subpopulation that altogether mimics ischaemia-reperfusion injury [27]**.** The exercise-induced fatigue linked to transient mitochondrial damage in acute high-intensity exercise is described for athletes followed by initiating exercise-induced mitochondrial adaptation [28]. Furthermore, several research groups involved in the field emphasise that the type of exercise is decisive for the successful treatment of pathologies. Therefore, the critical role of individually couched physical activities and sport exercises is concluded for both—healthy lifestyles and disease treatments. Finally, an individualised post-exercise approach is essential to be kept in mind. To this end, specifically, the *massage therapy* in physical rehabilitation is strongly recommended: per evidence, massage mitigates cellular and mitochondrial stress resulting from myofiber injury by promoting mitochondrial biogenesis and reducing inflammation [29]**.** Moreover, *manual acupuncture and electro-acupuncture* can protect cells from injury related to acute and intensive sport activities maintaining mitochondrial populations at high level and thereby mitigating exercise-induced fatigue and prolonging the working time of muscles, preventing skeletal muscle cells from the acute damage [30].

4.2 Acupuncture

Beneficial health effects of manual acupuncture and electro-acupuncture, per evidence, function via increasing the mitochondrial population mass in both healthy and diseased individuals [31]. High level of clinical utility of the approach has been demonstrated in rehabilitation and sport medicine [30]**,** improved neurological outcomes in the ischaemic stroke and intracranial haemorrage, myocardial and cerebral ischaemia-reperfusion, dementia of Alzheimer’s and non-Alzheimer’s type [32–37].

4.3 Electromagnetic Stimulation: Promotor or Antagonist?

Accumulated scientific evidence demonstrates mitochondrial oscillation that is distinguishable between healthy conditions and disorders [38]. To this end, specifically under metabolic stress perturbing ROS generation against scavenging capacity, the mitochondrial network changes the frequency/amplitude oscillation mode resulting in the energy dissipation. This leads to depolarization and suppression of the electrical excitability/Ca^{2+} handling—the main attributes of cardiac cells the functionality of which is hampered in this way as reflected, for example, by fatal arrhythmias. Due to the high physiologic utility of the fine oscillation, mitochondrial health and functionality are highly sensitive to electro-magnetic environmental noises. For example, the impacts of different music types on the mitochondrial function are significant ranging from evidently beneficial effects (increased ATP production, anti-oxidant and -stress protection) to significantly harmful ones including the ROS overproduction and mitochondrial stress, causing the reduced cell viability [39]. Contextually, extremely low-frequency pulses of faint magnetic field (which is weaker than the geomagnetic field) have been proposed to treat ageing mitochondrial population for neuro- and cardio-protection of affected individuals. The underlying mechanism is the induced mitophagy by inhibiting the electron flux in the ECT complex II, translocating PARKIN and PINK1 to the mitochondria and recruiting LC3-II [40]. The induced mitophagy restarts the PGC-1-alpha-medicated mitochondrial biogenesis rejuvenating mitochondrial population.

5 Concluding Remarks

Keeping in mind the reciprocity of mitochondrial and human cells partnering and consequent interdependencies, interests of both sides should be thoroughly considered when choosing for most suitable

- Life-style options
- Dietary and behavioural habits
- Vitamins and supplements intake
- Health-supportive therapies
- Medications and
- Treatment algorithms tailored to the individualised patient profile.

Figure 2 illustrates the mitochondrial health index and mitophagy as the predictive and prognostic biomarker-panel and powerful diagnostic tools. Specifically, mitophagy is considered highly instrumental for health risk assessment and therapy monitoring as well as effective target for treatment of sub-optimal health conditions [2].

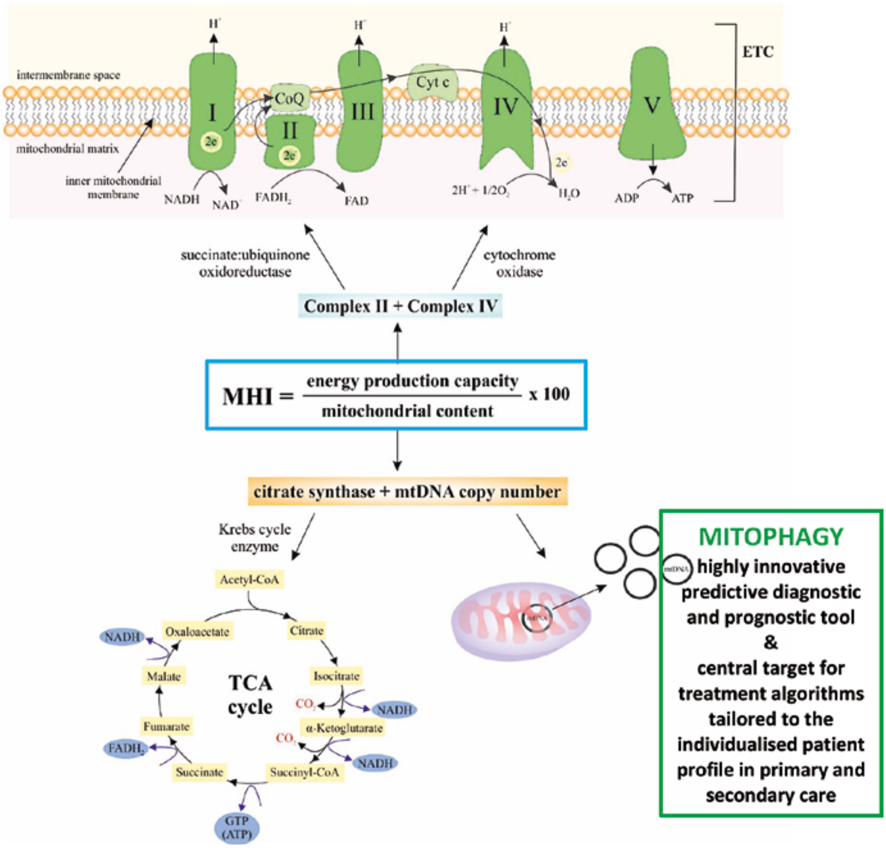

Fig. 2 Mitochondrial Health Index (MHI) and mitophagy as the predictive and prognostics biomarker-panel and powerful diagnostic tools; specifically, mitophagy is considered highly innovative and effective target for treatment of sub-optimal health conditions; ETC and TCA enzymes are specified in the figure; the image is adapted from Ref. [1]

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Suboptimal Health and the Economic Impact to Healthcare from the Perspective of PPP Medicine

Monique Garcia and Wei Wang

Abbreviations

CVD	Cardiovascular disease
HPA	Hypothalamic-pituitary-adrenal axis
PPPM/3PM	Predictive, preventive, and personalised medicine
SAM	Sympatho-adrenomedullary axis
SH	Suboptimal health
SHSQ-25	Suboptimal health status questionnaire-25
T2DM	Type 2 diabetes mellitus
WHO	World Health Organisation

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1 Suboptimal Health (SH) Definition

The definition of "health" according to the World Health Organisation (WHO) is "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [1]. Suboptimal Health (SH) is considered to be an intermediate state between health and disease, identified through the self-reporting of general malaise and ambiguous health complaints in the absence of a diagnosable condition [2]. It is when a person moves away from ideal health, and towards chronic disease. SH is a "reversible, subclinical stage of pre-chronic disease" [2].

2 A Paradigm Shift

SH shifts the paradigm from reactive to proactive healthcare by providing a unique window of opportunity to prevent chronic disease [3]. Chronic diseases are an international issue and a serious threat to human health, defined as diseases of long duration, slow progression, and are the major cause of adult morbidity and mortality in the world (WHO). Each year, chronic diseases account for 71% of total global deaths and kill more than 41 million people. Cardiovascular disease (CVD), cancer, respiratory disease and type 2 diabetes mellitus (T2DM) are responsible for over 80% of all chronic disease-related deaths [4]. Globally, CVD remains the leading cause of death, causing 30% of all deaths and about 50% of all chronic diseases [4].

3 Reactive Healthcare

The current biomedical model of health has been reactive in its response to managing chronic diseases, typically initiating treatments only after the clinical manifestation of disease [3]. The impact of chronic diseases on both healthcare and economies is enormous. A recent economic study forecasted an increase of 22% in total global cost for CVD from 2010 (US$863 billion) to 2030 (US$1044 billion) [4]. Similar predictions were made for other chronic diseases including cancer, mental disorders, T2DM and chronic obstructive pulmonary disease (COPD). Another economic report measured the "value of lost output" from cancer, CVD, respiratory disease, T2DM and mental disorders, and estimated the total cost from 2011 to 2030 to be US$ 47 trillion [4]. For context, the entire economic output for Europe in 2016 amounted to $17.8 trillion [4].

4 Proactive Healthcare

Disease prevention strategies are highly effective tools for the reduction of chronic diseases and the promotion of better health [5]. Whilst the literature clearly articulates the obvious benefits of primary prevention, including millions of lives saved, and indeed billions of dollars saved, investment in such strategies remains dismally low, with most nations spending approximately 2–4% of total health sector budgets on disease prevention programs [6, 4]. Effective disease prevention measures, including screening tools for the detection of SHS, that can markedly decrease their economic impact on health systems, should be explored [4]. Considering the WHO's recent recommendations calling for empirical, low-cost disease prevention strategies, SH should be given urgent priority [6].

SH has a proactive approach to healthcare by predicting a person's risk of developing certain chronic diseases, an outcome shared by predictive, preventive and personalised medicine (PPPM) [1, 6, 7]. The conceptual framework of PPPM lies in its ability to predict an individual's predisposition to disease before its onset, followed by the timely delivery of personalised, disease prevention and treatment strategies [6]. In line with PPPM, SH allows a window of opportunity for disease prevention by initiating targeted interventions in at-risk individuals before the onset of clinical symptoms, altering the course of disease trajectories, and potentially preventing the disease from occurring altogether [7]. SH's unique capacity to prevent disease also confers economic benefits, directing funding and resources to exactly where it is needed [7]. At a time when global healthcare is overcome by the perpetual growing burden of chronic diseases, SH, with all its potential, should be adopted as the new gold standard in the fight against chronic diseases from the perspective of PPPM.

5 Theoretical Background of SH—Stress

SH was first identified as a public health challenge in China, with its prevalence expected to escalate worldwide. Stress has been identified as a key contributing factor to SH. With our increasingly chaotic lifestyles, societal changes, social media use and work pressures, the stress-related disease epidemic has become an important public health issue [2].

6 The Human Stress Response

The human stress response is an evolutionarily conserved, dynamic process that aims to overcome a stressor (a real or perceived threat), promote survival and restore homeostasis [3]. The role of the two major components involved in the stress response—the sympatho-adrenomedullary (SAM) axis and hypothalamic-pituitary-adrenal (HPA) axis, respectively, is well documented [3, 8].

6.1 SAM Axis

The SAM axis responds to both physical and psychological stressors by mounting a rapid, short-term, physiological response [9]. This is achieved via the release of catecholamine-filled vesicles (epinephrine and norepinephrine) from chromaffin cells within the adrenal glands [3, 8–10]. Catecholamines travel in the bloodstream and prepare the body for “fight or flight”, activating the sympathetic nervous system by targeting alpha- and beta-adrenergic receptors [3, 8–10]. This induces physiological changes in blood vessels, smooth muscles, organs and glands. The effects of SAM axis activation include an increase in blood pressure, maintained alertness, increased contractility of the cardiac muscle, elevated heart rate, pupil dilation, pilo-erection, heightened blood glucose levels via gluconeogenesis and glycogenolysis, lipolysis, relaxation of smooth muscles in the gastrointestinal and urinary tracts, as well as the bronchioles (resulting in increased oxygen consumption), elevated respiratory rate, thermoregulation, decreased insulin secretion, and the inhibition of mast cells and basophils [3, 8–10].

6.2 HPA Axis

The HPA axis also responds to both physical and psychological stressors, but via a slower, more protracted pathway than the SAM axis [3, 8–10]. The HPA axis produces and releases cortisol, the main glucocorticoid hormone in humans. The function of the HPA axis is to quickly mobilise energy stores and improve the chances of survival (e.g., running away from a lion). Under normal conditions, cortisol is secreted in a pulsatile fashion with higher levels observed upon waking, followed by a gradual decline to basal levels at night [3]. Cortisol follows a circadian pattern and is controlled by the suprachiasmatic nucleus that communicates with the paraventricular nucleus (PVN) in the hypothalamus [3]. Corticotropic releasing hormone (CRH) and vasopressin (VP) are released into the hypophyseal portal system to the pituitary gland, where corticotropes subsequently release adrenocorticotropic releasing hormone (ACTH). ACTH travels to the adrenal cortex via the systemic circulation, activating the production of cortisol [3]. Cortisol is transported back to the systemic circulation where it exerts its effects on target tissues. As a steroid hormone synthesised from cholesterol, cortisol crosses cell membranes and binds to receptors in the cytoplasm, with the cortisol–receptor complex then crossing the nuclear membrane to affect gene transcription [9]. The effect of cortisol includes increased blood glucose to the brain, increased gluconeogenesis and decreased glycogen synthesis in the liver, decreased glucose uptake and increased protein degradation in the muscles, increased lipolysis in adipose tissue, suppression of B cells antibody production and decreased migration of neutrophils in the immune system, and decreased insulin secretion and increased glucagon secretion in the pancreas [10]. Finally, the presence of cortisol augments the function of catecholamines [3, 8–10].

7 Acute Stress Versus Chronic Stress

During acute stress, the SAM axis is activated within seconds, expeditiously releasing catecholamines epinephrine and nor-epinephrine [9]. This is followed by recruitment of the HPA axis, with peak cortisol levels observed 15–20 min after the initial onset of stress [3]. Once the stressor has passed, negative feedback loops restore homeostasis, and hormone levels return to basal levels [3]. During chronic stress, however, these processes become maladaptive, and cortisol levels remain elevated [3]. In chronic stress, hypothalamic activation of the pituitary switches from CRH to vasopressin, decreasing the metabolism of cortisol [3]. Elevated cortisol levels and long-term cortisol exposure result, which are toxic to the human body and lead to chronic disease [3]. Our health is influenced by multiple factors including genetics, access to quality healthcare services and exposure to “upstream” risk factors [4]. Risk factors include health behaviours such as diet/physical activity, environmental factors such as our work environments, as well as socioeconomic, demographic and cultural factors [4]. Chronic diseases arise from a combination of modifiable (such as poor diet) and non-modifiable risk factors (such as genetic make-up) [4]. Modifiable risk factors can lead to chronic diseases through both classical risk factors—including obesity, high blood glucose levels, blood pressure and cholesterol, and through non-classical risk factors such as chronic stress [4]. SHS is associated with both classical (direct) and non-classical (indirect) modifiable risk factors of chronic disease, including CVD and T2DM [11, 15].

8 Development of an Instrument for Measuring SH

In response to the stress-related disease epidemic and SH, researchers sought to develop a screening tool that could effectively measure SHS [2].

8.1 Study 1: Questionnaire Development

Stress was identified as a major aspect leading to poor health by all participants involved in the focus group discussions [2]. The initial questionnaire consisted of 42 items; 37 statements (describing health complaints caused by stress) resulted from focus group discussions; 7 items were derived from a questionnaire study of SHS and 9 items were derived from the Cornell Medical Index [2]. The questionnaire was approved for content validity by 4 clinicians, followed by a pilot study being conducted at three hospitals, with the questionnaire distributed to 30 individuals [2]. These individuals had numerous health complaints yet were otherwise free from disease. The results were reviewed, and the questionnaire was consolidated, consisting of a 25-item questionnaire related to SHS. Known as the SHSQ-25, the 25 items were categorised into 5 subscales measuring health across domains. These included fatigue (9 items), mental status (7 items), immune system (3 items), digestive tract (3 items) and the cardiovascular system (3 items) [2].

8.2 *Study 2: Validity of the SHSQ-25*

A total of 2799 participants completed the SHSQ-25 questionnaire, with all participants also undergoing physical examination. Participants were asked to rate each item on the SHSQ-25, according to how often they have felt that way over the last 3 months [2]. Raw scores of 1–5 on the questionnaire will be recorded as 0–4. An individual's total suboptimal health score is calculated by adding the ratings from all items together [2]. The SHSQ-25 score ranges numerically from 0 to 100, with 0 indicating optimal health, and 100 indicating the poorest health. The cut-off value for SHS was initially determined using the median score of all participants surveyed;, however, more recently, the SHS cut-off value has been determined using a one-tailed 90% upper limit of SHSQ-25 scores, improving accuracy [2]. The SHSQ-25 showed good test–retest reliability and internal consistency. Confirmatory factor analysis showed a reasonable fit of the data to the multidimensional structure of the questionnaire. It was also found the SHSQ-25 had a discriminative ability between individuals with good health and those with suboptimal health [2]. Convergent validity showed the scores for SHS and stress to be statistically significant (Pearson's $r = 0.57$, $p = <0.001$). The SHSQ-25 was established as a valid, subjective health measure for the detection of SHS.

9 SH Is Associated with Objective Biomarkers

The SHSQ-25 has leverage over existing screening tools by virtue of its simplicity—it is quick and easy to use [7]. What makes the SH truly unique, however, is its inclusion of, and association with, objective biomarkers [7]. Since its inception in 2009, the majority of SHSQ-25 studies have sought to investigate the association between the SH and objective biomarkers (Fig. 1). The linkage of subjective and objective markers is not dissimilar to the approach of integrative medicine—where traditional eastern (subjective) meets modern western (objective) medicine [7]. Indeed, closing the gap between traditional and modern medicine is the goal of SH, with the hybridised mind-body approach combining the advantages of both disciplines to improve patient outcomes [7]. The inclusion of subjective and objective biomarkers demonstrates that SH is associated with chronic diseases.

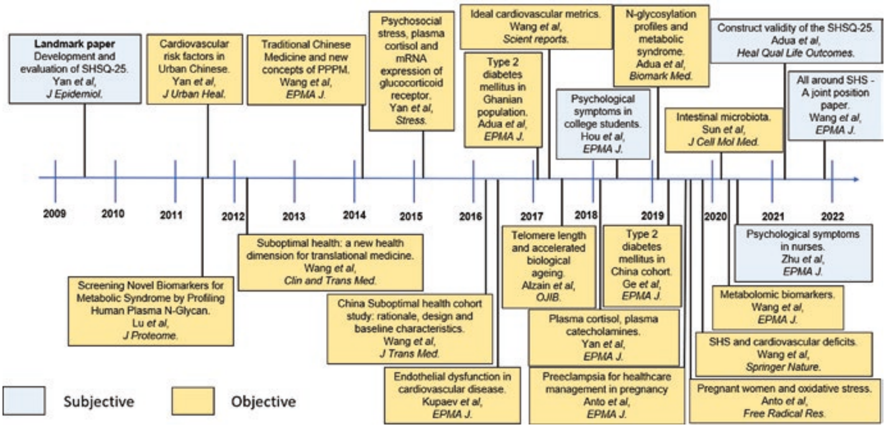

Fig. 1 SH research timeline

10 SH Confers a Significant Economic Benefit to Healthcare Systems

SH confers substantial economic benefits to healthcare by discriminating between individuals at high versus low risk: avoiding under- and over-diagnosis. Previous investigations have demonstrated that SH can distinguish between at-risk individuals for T2DM, and that high systolic and diastolic blood pressure were statistically associated with SH. Another study discovered that the risk of T2DM development increased as the SH performance of the affected person increased. Another study found that SH is associated with chronic stress, with SH individuals having higher levels of both psychosocial stress and cortisol than those with optimal health. Furthermore, SH stratified individuals into high- and low-risk groups for CVD, showing that high SH scores were associated with classical risk factors (including high cholesterol and endothelial dysfunction) and certain health metrics (such as smoking and sedentary behaviour) of CVD, whereas low SH scores were associated with ideal CVD metrics (such as ideal dietary intake and never smoked), acting as an independent protection factor for SHS.

11 The Under- and Over-Diagnosis of Disease

The under- and over-diagnosis of chronic diseases only serve to contribute to the significant economic burdens of healthcare [12]. Underdiagnosis is defined as "the failure to recognize or correctly diagnose a disease or condition especially in a significant proportion of patients" [17]. Overdiagnosis occurs when a person is diagnosed with, and treated for, a disease that wouldn't have ordinarily led to clinical symptoms or complications, with the effects of treatments outweighing any possible benefits [12, 13]. This chapter uses a series of case studies to illustrate how

SH discriminates between individuals at high versus low risk: circumventing the under- and over-diagnosis of disease, with substantial economic benefits to healthcare.

12 Underdiagnosis

Effective screening of chronic diseases is key to PPPMs mission to reduce their prevalence [6]. Early detection of diseases affords timely interventions to be employed and can reduce long-term complications [14]. A reliable, low-cost screening instrument is urgent [2]. Among the new approaches of screening tools, the SHSQ-25 deserves special attention [2].

12.1 Case Study One: Suboptimal Health Is Associated with Psychological Symptoms

A recent study investigated the prevalence of SH and its correlation with psychological symptoms along with SH-related risk factors [20]. A total of 4119 undergraduate students were recruited for the study from two universities. Participants were evaluated for SH using the SHSQ-25, and psychological states using the Symptom Checklist (SCL-90) [20]. The SCL-90 is a 90-item scale measuring somatic and psychological symptoms. The 90 items are categorised into 10 domains, such as somatisation and depression. Participants were asked to rate how they've been feeling over the past week. Participants who score 160 or above are considered to exhibit psychological symptoms. Students completed the two questionnaires that took under 30 min to complete [20]. The results found college students had an SH prevalence of 21% [20]. Furthermore, participants with SH also had higher SCL-90 scores (159.0 (quartile 135.0—190.0)) than healthy participants (108.00 (quartile 98.0–126.0)), showing that SH participants experienced more psychological problems than healthy students [20]. Further analysis showed a high correlation between SH scores and SCL-90 scores, with somatisation, obsessive-compulsive, interpersonal sensitivity, depression and sleep and diet problems being the key factors positively associated with SH [20]. Specifically, female students, sophomore students, medical students and students from rural regions were all identified as vulnerable subpopulations who were at the highest risk of SH and psychological problems [20]. This research highlighted the utility of the SHSQ-25 in conjunction with the SCL-90 to identify students with SH and psychological problems who are at risk of developing disease [20].

12.2 Case Study Two: Integration of Suboptimal Health Evaluation as a Criterion for Prediction of Preeclampsia

This study sought to understand the utility and applicability of the SHS-25 for the screening and prediction of normotensive pregnant women (NTN-PW) at risk of developing preeclampsia (PE) in Ghana [14]. A condition that develops exclusively in pregnancy, PE is diagnosed by the presence of proteinuria and hypertension from 20 weeks gestation in pregnant women who have otherwise been normotensive [21]. The prospective study recruited 593 normotensive, healthy, pregnant females aged between 18 and 45 years. Participants underwent a physical examination and assessment by an obstetric specialist prior to inclusion in the study. Participants then underwent a baseline examination at 10–20 weeks gestation to measure their general health [14]. Data collected included the SHSQ-25 subjective health measure, sociodemographic and obstetric information, and clinical assessment. The clinical assessment included blood pressure (mmHg) measurements, BMI and presence of proteinuria (via urine reagent dipstick). Clinical assessment was measured at three separate points: baseline, 21–31 weeks, and again at 32–42 weeks. A total of 498 pregnant women returned at delivery, with 301 women presenting as normotensive and without proteinuria (NTN-PW) (controls), and 197 presenting with PE (cases). A total of 49.8% (248/498) of pregnant women were found to have SH at baseline, whilst 50.2% (250/498) of pregnant women had optimal health. Of the 248 women who had high SH at baseline, 61.7% (153/248) progressed to PE (95 did not). Of the 250 women who had optimal health at baseline, 17.6% (44/250) progressed to PE (206 did not). It was also found that the incidence of PE increased as the individual SH domain scores increased. Normotensive pregnant women with high SH at baseline were found to be at four-fold increased odds of developing PE, demonstrating a significant, independent association between SH and PE. This study showed the versatility and applicability of employing the SHSQ-25 as an independent risk stratification tool for the detection of pregnancy-related health problems, such as PE. The SHSQ-25 has the potential to circumvent underdiagnosis of adverse pregnancy outcomes in women in developing countries such as Ghana, with a significant economic impact to healthcare.

12.3 Case Study Three: SH and Metabolomic Biomarkers

This case–control investigation sought to identify metabolic biomarkers for the detection of SH [22]. Metabolites are intermediate or end products of metabolism essential for cellular functions [23]. Metabolites mirror genome encoding, environmental modifications and downstream cellular processing, providing valuable insights into the functions of biological systems and aiding in the diagnosis of chronic diseases via metabolic signatures [24]. Therefore, the authors of this study hypothesised that the metabolic signatures in participants with SH might be altered [22]. Participants included Chinese undergraduate students between the ages of 18–20 years who were free from disease from the province of Shandong [22]. Participants completed the SHSQ-25 at baseline, and again after 3 months. Lifestyle data, anthropometric measurements and blood samples for biochemical analysis were collected [22]. Individuals with an SH score of >35 were included as cases, while individuals with an SH score of <35 were included as age- and sex-matched controls. The results showed that 24 metabolites were significantly different between participants with SH and participants with optimal health [22]. Further analysis revealed that three metabolic pathways were specifically involved: taurine metabolism, sphingolipid metabolism and steroid hormone biosynthesis [22]. Four metabolites were able to be used as predictive biomarkers to discriminate between participants with SH and participants with optimal health (sensitivity of 94.0%, specificity of 90.0% and an AUC of 0.977). These results demonstrated that metabolic biomarkers had a high predictive power for detecting SHS [22]. The SHSQ-25 could be used in population-level screening strategies, with the ability to early detect SH-related metabolic changes, thereby avoiding the underdiagnosis with a significant economic impact to healthcare.

These case studies serve as powerful examples of how SH avoids the underdiagnosis of chronic diseases [11, 14, 22]. Detection of SH, via the SHSQ-25, has particular relevance in developing countries. Indeed, screening for SH at a population level would circumvent the inherent economic barriers that result in a lack of laboratory tests and treatments, facilitating PPPM, and thus leading to substantial benefits to healthcare [14].

13 Overdiagnosis

Overdiagnosis can have significant consequences for not only individuals, but also for adding to the cost burden of healthcare systems; persons are subjected to potentially unnecessary diagnostic tests, procedures, and treatments, and expensive healthcare resources and time are wasted that would be better spent treating or preventing genuine illness [12]. Overdiagnosis costs billions of dollars from healthcare systems annually with approximately $200 billion wasted on unnecessary procedures and treatments in the United States every year [12]. Overdiagnosis assumes that diagnosis will confer no benefit [25]. SH, however, assumes diagnosis confers a benefit. Detection of SH in the first instance provides patient stratification through the prediction of a person's predisposition to disease, allowing clinicians the unique opportunity to prescribe personalised treatment algorithms [15]. Detection of SH effectively circumvents overdiagnosis. We evidence this in the case series below.

13.1 Case Study Four: SH Is Associated with Intestinal Microbiota

Past investigations have demonstrated intestinal microbiota to be linked with specific chronic diseases and have found disturbances in the microbiota of individuals with certain chronic diseases [16]. This case–control study sought to explore the relationship between SH and intestinal microbiota [15]. Participants completed the SHSQ-25 at baseline, and again after 3 months. Individuals with an SH score of >35 were included as cases, and individuals with an SH score of <35 were included as age- and sex-matched controls. Faecal sample collection was performed using a specimen collection kit, and bacterial DNA was extracted using a TIANGEN kit [15]. The results found diversity of the intestinal microbiota in participants with SH was statistically higher than in participants with optimal health [15]. This evidences that intestinal microbiota disturbances are associated with SH [15]. This could provide additional diagnostic tests in the future, thereby avoiding the overdiagnosis of chronic disease from the perspective of PPPM, having a significant economic impact on healthcare.

13.2 Case Study Five: Suboptimal Health and Endothelial Dysfunction as a New Aspect for Risk Evaluation of Cardiovascular Disease

In the context of cardiovascular disease, chronic stress not only directly affects the vessel wall by increasing heart rate and blood pressure, but also causes endothelial dysfunction, a factor known to trigger the development of atherosclerosis.

A recent cross-sectional study ($n = 459$) explored cardiovascular risk assessment using an integrated approach by combining SH evaluation with indicators of endothelial dysfunction [17]. All participants completed the SHSQ-25 questionnaire, physical examination and laboratory measures (including lipid profile). Arterial stiffness and endothelial dysfunction were determined using standard brachial plethysmography. The results found SH is associated with endothelial dysfunction [17]. The index of endothelial function was found to significantly correlate with the overall performance of suboptimal health ($r = -0.31$, $p < 0.05$), as well as with individual sub-scales of the questionnaire SHSQ-25: fatigue ($r = -0.36$, $p < 0.05$), the cardiovascular system ($r = -0.36$, $p < 0.05$), and mental ($r = -0.29$, $p < 0.05$) [17]. There was a significant correlation between SH scores, risk factors for the cardiovascular system, and indicators of endothelial dysfunction ($p < 0.001$), demonstrating that even at a suboptimal health stage, an association between vascular wall stiffness and several traditional determinants (age, body mass index, blood pressure) of cardiovascular disease (CVD) was present [17]. The group with risk factors for CVD had significantly higher levels of systolic blood pressure, diastolic blood pressure, body mass index, smoking index, total cholesterol, triglycerides and low-density lipoprotein cholesterol, confirming SH is associated with risk factors of CVD. The study concluded that the assessment of SH, taken together with the evaluation of endothelial dysfunction, enables the identification of the risk of developing CVD [17].

13.3 Case Study Six: SH Is Associated with Shortened Relative Telomere Length

A retrospective case–control study ($n = 294$ cases; $n = 294$ controls) investigated the association between SH and telomere length (TL) [18]. Participants, who were otherwise free from disease, completed the SHSQ-25 as part of a community survey. A quantitative polymerase chain reaction (PCR) then measured each participant's relative telomere length (RTL) [19]. Telomeres, made of nucleoproteins, are the capped ends of chromosomes protecting chromosomal degradation [20]. With each cell division, telomeres progressively shorten, eventually resulting in cell senescence [21]. Telomere shortening can be accelerated by external factors, including psychological stress [20]. Shorter telomere lengths are associated with chronic disease, whereas longer telomere lengths are linked to better health [20]. It has been postulated that telomere erosion is both modifiable and independent of chronological age [22]. The results of the study showed that individuals with SH had shorter telomeres compared to individuals with optimal health. SH was found to be significantly associated with shorter RTL ($p = <0.005$) [19]. Furthermore, lack of physical activities in males, oversleeping (>9 h per night) in females and memory loss were all associated with shorter RTL [19]. The SHSQ-25 offers an excellent alternative to measuring RTL in low- to middle-income countries where there is a lack of laboratory-based resources to investigate RTL [19]. These findings also have important implications for disadvantaged populations in society who are known to suffer from higher levels of stress. For example, one study investigated the mean telomere length in healthy premenopausal mothers who had either a healthy child (controls) or a child who was chronically ill (carers) [23]. The results found that chronic, psychological stress was significantly associated with shorter telomere length [23]. Alarmingly, the telomeres in mothers who had the highest levels of stress were shorter by approximately one decade of ageing when compared to the telomeres in mothers who had low stress [23]. These findings were validated in a larger study that found the RTL in caregivers with the highest levels of stress had the shortest telomeres that corresponded to an excess of 10–15 years of additional ageing [24]. The association of SH and psychological symptoms in carers should be explored in future research studies to better understand the influence of the caregiving role on SH. Moreover, the SHSQ-25, and its applicability in assessing biological ageing, could be a cost-effective screening tool for carers at the population level to avoid overdiagnosis.

Here we evidence, through a series of case studies, how SH avoids overdiagnosis of chronic diseases, through the effective stratification of individuals into high- and low-risk groups [15, 17]. Distinguishing between individuals at high and low risk allows for the prescription of personalised treatment algorithms in the primary care setting, allocating valuable resources to where they are most effective.

Primary prevention strategies have been shown to be highly cost-effective in healthcare systems [4]. A recent study found that investment in collaborative care that sought to address psychological stress with depression risk and anxiety conditions (that has been associated with diabetes and CVD) found the investment to be a cost-saving initiative, with a positive return on investment of $1.52 for every $1 dollar invested [7]. The cost-effectiveness of primary prevention is greatly improved when the strategy has the capacity to a) discriminate between high- and low-risk populations, and b) target the treatments towards individuals most at risk [4, 6].

In an ideal setting, detection of SH, via the SHSQ-25 should direct people to have their health (clinical/biomarkers) investigated by their doctor. Indeed, an individual with SH may have an undiagnosed disease that requires intervention. This proactive approach to healthcare has the potential to not only change the trajectory of disease but to also have substantial economic benefits for healthcare. SH has the hallmarks of a first-line screening tool for chronic diseases. SH and its vital role in the prediction and prevention of chronic diseases must be considered.

14 Expert Recommendations

Future studies from diverse populations are needed to identify SH in individuals at risk of developing chronic diseases. Assessment of SH in disadvantaged populations that are at greater risk of developing chronic diseases should explored, for example, informal unpaid carers, who are known to experience significantly higher levels of psychological distress than the general population. Such studies would have great significance for women's health, considering the overwhelming majority of carers are female.

15 Conclusions

SH offers a significant economic impact to healthcare by identifying and stratifying persons at high versus low risk, thus avoiding the under- and over-diagnosis of chronic diseases [4, 3]. The utilisation of SH enables targeted interventions to be aimed specifically at persons at risk of developing chronic diseases, directing valuable resources to where they are actually needed. At a time where healthcare systems worldwide are being overwhelmed by the perpetual growth of chronic diseases, failure to adopt SH will only serve to contribute to economic disaster. This is especially urgent considering the calls from multiple leading healthcare sectors for the adoption of cost-effective, evidence-based disease prevention strategies to alleviate the burden of chronic diseases. This book chapter evidences SH as the new gold standard in the global fight against chronic diseases from the perspective of PPPM.

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Tools of Predictive Diagnostics: Status Quo and Outlook

Bo Li and Bingbing Li

Abbreviations

AUC	The area under the receiver operating characteristic curve
CFS	Chronic fatigue syndrome
CI	Confidence interval
MSQA	The multidimensional sub-health questionnaire for adolescents
PPI	Protein–protein interaction
PPPM	Predictive, preventive, and personalised medicine
QOL	Quality of life
RTL	Relative telomere length
SHMS V1.0	The sub-health measurement scale V1.0
SHS	Suboptimal health status
SHSQ-25	The suboptimal health status questionnaire-25
SSS	The sub-health self assessment scale
T2DM	Type 2 diabetes mellitus
TGF-B1	Transforming growth factor-β1
WHO	The World Health Organisation
WHOQOL-100	The WHO Quality of Life-100

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1 Introduction

Suboptimal health status (SHS) refers to the intermediate state between health and disease [1]. It is regarded as a subclinical, reversible stage of chronic disease [2]. When a person is in SHS, no obvious or specific clinical manifestation can be observed, and neither relevant laboratory indexes are helpful, which makes SHS difficult to be assessed. SHS is mainly manifested as a variety of early stages of chronic health conditions. Therefore, the appropriate diagnostic tools are essential for the correct assessment and intervention of SHS and the maintenance of population health.

With the progress of SHS study, the work on SHS assessment and prediction tools has been carried out constantly, which provides the possibility to reveal SHS and explore the occurrence and development mechanism of SHS from different levels: tissue, gene, molecule and human as a whole.

2 The Status Quo of Predictive Diagnostic Instrument for Suboptimal Health

At present, the research on the subjective and objective assessments and quantitative diagnosis of SHS is still in its infancy. The predictive diagnostic tools for SHS mainly include subjective measures, i.e., health questionnaires and scales, and objective measures: laboratory-based biological, biochemical and molecular biology tests and big data analysis.

2.1 Subjective Health Assessment Measures

2.1.1 Health-Related Quality of Life

Quality of life (QOL) has been widely used as a measure of health and functional status [3]. It includes many factors, such as individual's physical and psychological health status, independent levels, social relationships and so on [4]. The World Health Organisation (WHO) developed a questionnaire, named the WHO Quality of Life-100 (WHOQOL-100).

The WHOQOL-100 is a universal tool for assessing quality of life. It can be used for people with chronic diseases, people under stress and healthy people. It was developed in fifteen centers around the world [5]. It consists of six dimensions, including physiology, psychology, independence, social relations, environment and spiritual world, such as support, religion and personal belief [3]. After many verifications, the WHOQOL-100 showed enough reliability and is recognised by researchers. Facet reliability ranged from 0.43 for physical environment to 0.96 for activities of daily living [5]. The construct validity of the whole questionnaire and the dimensions was good. Reliability values for overall quality of life and overall health were 0.91 [5].

Based on WHOQOL-100, WHOQOL-Brief and WHOQOL-Old, special for health-related quality of life research of specific populations, are developed [6]. Because of its efficiency, WHOQOL-Brief is popular and has been applied in many researches. It consists of 26 items, which makes it convenient to use. Now, 15 international field centers have been committed to developing WHOQOL-Brief to obtain an effective tool to assess an individual's status cross-culturally [3]. The WHOQOL-Brief item scores for each dimension were very similar to the WHOQOL-100 scores, explaining approximately 95% of the variance in the total scores for the four domains (range 77–91%) [7]. Besides, the results of many studies show that the QOL of the elderly population has its own particularity and should be measured by a specific scale. For this reason, WHOQOL-OLD was developed by the WHOQOL group [8]. Questionnaires are available free to the community and researchers in the region. They are available in Portuguese at: *www.whoqolweb.com.br*. Previous research focused on generic quality-of-life issues has proven that WHOQOL-OLD has good psychometric properties [9]. Its reliability, validity and responsiveness make researchers confident that it can be widely used.

Health-related quality of life is a broad-ranging concept. This scale is applicable to a wide range of health-related states, and SHS is just one of them. In other words, this scale cannot accurately and adequately measure SHS. Therefore, research on suboptimal health needs specific tools.

2.2 Suboptimal Health Status

The suboptimal health status questionnaire-25 (SHSQ-25) has been developed to precisely measure suboptimal health status. The SHSQ-25 has been proven to be very effective in Africa, China and the Caucasus. It consists of 25 items in five dimensions: fatigue, cardiovascular, digestive, immune and mental status [10] (Fig. 1). A 5-point Likert scale is used to rate each item (from never or almost never to always). The total score ranges from 0 to 100, a high score indicating a poor health. Both healthcare and community settings can use the SHSQ-25. The SHSQ-25 could identify people who report being in poor health but who have not had a diagnosable illness in the last 3 months [11, 12]. The specific contents of SHSQ-25 are listed in Fig. 1.

The main advantage of the SHSQ-25 is that it is short and easy to answer. It is suitable not only for large population studies but also for routine health surveys [1]. To date, SHSQ-25 has been verified in a variety of populations, suggesting that it can be used as a practical SHS survey instrument for screening high-risk groups. Some previous studies found that SHS is a sensitive indicator for type 2 diabetes mellitus (T2DM) [13] and cardiovascular diseases [14].

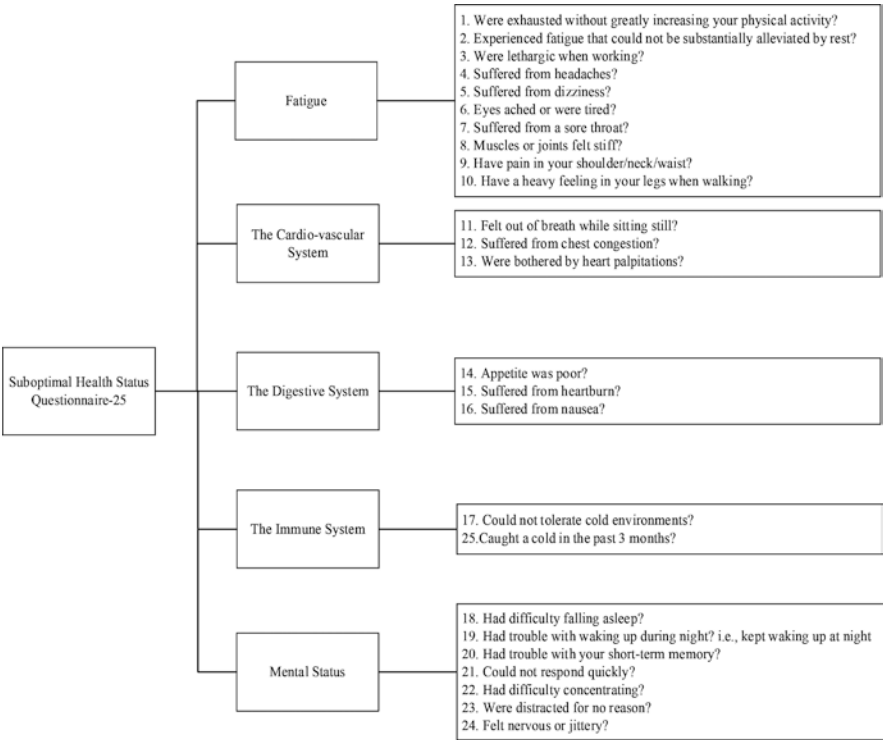

Fig. 1 Items of the Suboptimal Health Status Questionnaire-25 [1, 2]

The SHSQ-25 has been used in different population. In a cohort study of pregnant women in Ghana, Anto et al. found that a high SHS score was associated with an increased incidence of pre-eclampsia [12]. Studies conducted among adult community residents suggested that SHS was a new independent risk factor for T2DM and associated with endothelial dysfunction [15]. SHS was also proven to be related to psychological health among nurses and college students. A study conducted in Chinese college students demonstrated that SHS was associated with psychological symptoms (e.g., somatisation, obsessive-compulsive, interpersonal sensitivity and depression) [16]. In another study, the prevalence of SHS was higher among nurses who had psychological symptoms such as depression and anxiety [17].

Although it cannot be used to diagnose diseases, SHSQ-25 can ring the alarm for us before the outbreak of diseases to carry out health interventions for people as early as possible. This is therefore a contribution to the reduction of the burden of disease [18]. In addition to the SHSQ-25, there are other tools used to assess SHS. For example, the Sub-Health Self Assessment Scale (SSS) is currently used in the field of Chinese medicine. In China, the SSS is used to assess the SHS of undergraduate students [19]. This scale contains 3 symptom dimensions, with 58 items corresponding to 10 factors (Fig. 2). The current research suggests that SSS has satisfactory sensibility, representation and internal consistency [19]. However, it has

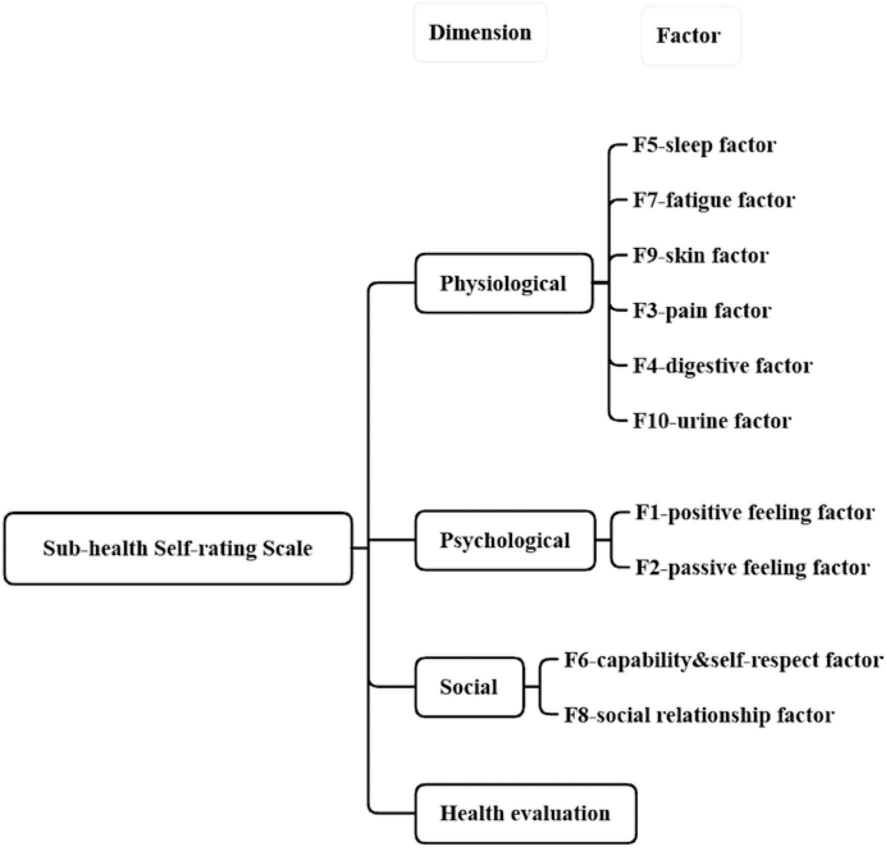

Fig. 2 Theoretical framework for the Sub-Health Self-rating Scale (SSS) [19]

a limited scope of application and must be tested and improved by more practice, because it is a self-assessment scale applied in groups of students, and the survey is only conducted among a few schools.

2.3 Sub-Health Measurement Scale V1.0

The Sub-Health Measurement Scale V1.0 (SHMS V1.0) is developed among Chinese adults aged 18 years and over. The SHMS V1.0 consists of three subscales (physical, mental and social domains) with a total of 35 items. Cut-offs for suboptimal health were established among Chinese urban residents by age group [20]. The study using the SHMS V1.0 for the estimation of suboptimal health status has mainly focused on the relationship between the lifestyle and the SHS, and participants are limited among Chinese [21–25]. It is unknown whether it has good reliability and validity to be applied in different populations or ethnicities.

2.4 The Multidimensional Sub-Health Questionnaire of Adolescent

The Multidimensional Sub-Health Questionnaire for Adolescents (MSQA) has been used on a large scale with Chinese students over the past few years. The MSQA is a multidimensional, self-reporting screening tool developed in China that examines physical and psychological symptoms in adolescents. It contains 71 items: physical symptoms (32 items) and psychological symptoms (39 items) [26].

3 Objective Measures for SHS

Aided by rapid advances in biotechnology and the availability of mega-health databases, health professionals are well placed to raise the issues of genetics, environment and behaviour and to motivate the introduction of predictive, preventive and personalised Medicine (PPPM) into routine medical care [11]. Modern biochemical and molecular biological research provides new ideas and tools for assessing health status and predicting disease progress, which is of great significance for SHS research. Traditional Chinese medicine and digital biomarkers might provide a new vision for evaluating SHS. However, owing to the complexity, diversity and non-specificity of SHS symptoms, an index system for biochemically assessing SHS is still lacking. The good news is that some achievements have been obtained in laboratory experiments.

3.1 Laboratory Examination

3.1.1 General Biological and Biochemical Indexes

Evidence from existing research showed that many biological and biochemical indexes have significant correlations with SHS, such as systolic blood pressure, diastolic blood pressure, total cholesterol and high-density lipoprotein cholesterol. In addition, studies have found that plasma glucose levels in men and triglyceride levels in women have an association with SHS [11]. SHS scores and serum cortisol levels were also significantly linearly correlated [11].

The SHSQ-25 has been found to be an accurate measure of chronic psychological distress. Plasma cortisol and glucocorticoid receptors are two important physiological mediators of psychological stress [27]. In this study, plasma cortisol levels and SHS score were significantly positively correlated, whereas glucocorticoid receptor mRNA expression in peripheral blood monocytes was negatively correlated with SHS score [27]. Another study also revealed that plasma cortisol detection played an important role in evaluating SHS [28].

A study of Ghanaian women found that oxidative stress was strongly associated with SHS. Endothelial dysfunction, a complication of oxidative stress, may also contribute to the development of SHS [29]. The association has also been verified in another Russian population-based study [14]. People scoring high on the SHS had significantly higher average levels of diastolic and systolic blood pressure, body mass index, triglycerides, total cholesterol and low-density lipoprotein cholesterol [14]. The combination of SHS and endothelial dysfunction provides a new opportunity to gain a comprehensive understanding of the relationship between subjective and objective health indicators. This suggests that SHS can be used to help screen for cardiovascular disease on a routine basis.

3.2 *Molecular Biological Measures*

The development of proteomics, glycogenomics and metabolomics makes it possible to research the physiological or pathological mechanism of SHS because SHS is a transitional stage from health to disease, which will inevitably be accompanied by changes at the biological and molecular level.

Proteomic studies have shown that many people with SHS have immune abnormalities that manifest clinically as cytokine-mediated immune responses with inflammatory consequences. In a controlled study, the Japanese patients, with chronic fatigue syndrome (CFS), were detected to reduce production of mRNA and transforming growth factor-β1 (TGF-B1) significantly [30]. Cytokine deficiency increases the risk of myalgia and muscle fatigue.

The analysis results using protein–protein interaction (PPI) network showed that10 hub genes (AMHR2, BMP10, BMPER, GJA1, KRT1, MT3, NTM, TWIST2, TUBB3 and TMEM98) were related to SHS. A transcriptomic prediction model can effectively discriminate SHS individuals from healthy individuals, its sensitivity was 83.3% with a 95% confidence interval (CI): 73.9–92.7%, and its specificity was 90.0% with 95% CI: 82.4–97.6%), and the area under the receiver operating characteristic curve (AUC) was 0.938 with 95% CI: 0.882–0.994 [31]. Therefore, two transcripts were selected in the model that was set up based on the candidate transcripts. It is shown below.

$$\text{Logit}\left(p = \text{SHS}\right) = 0.137 - 66.878 \times \left(\text{BMPER mRNA}\right) + 29.328 \times \left(\text{AMHR2 mRNA}\right)$$

The sensitivity of the model was 83.3% (95% CI: 73.9–92.7%). Its specificity was 90.0% (95% CI: 82.4–97.6%), and the AUC was 0.938 (95% CI: 0.882–0.994) [31].

In another report, SHS is positively correlated with the risk of developing metabolic syndrome. N-glycans have been found to be associated with the development

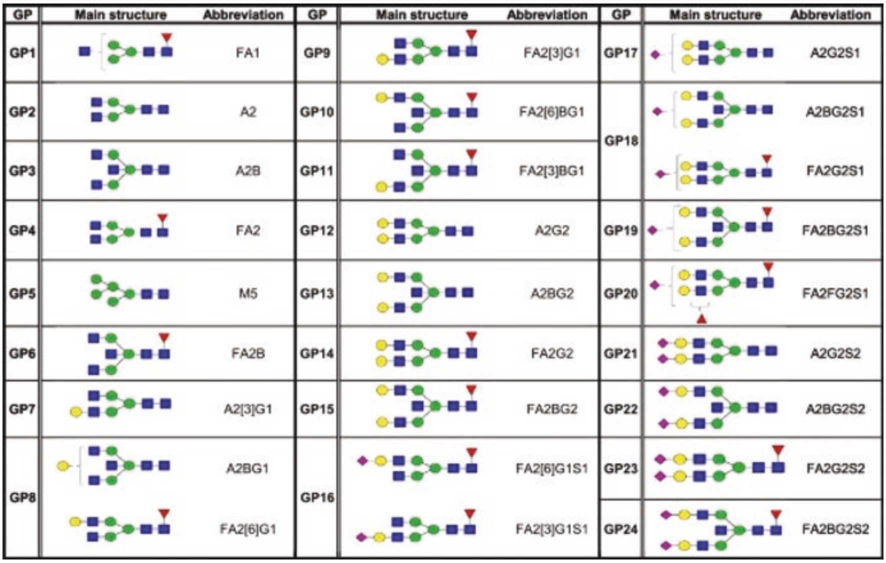

Fig. 3 The 24 IgG glycan peaks as measured with ultra-performance liquid chromatography [33]. Shown is the structure of the main IgG glycan component(s)

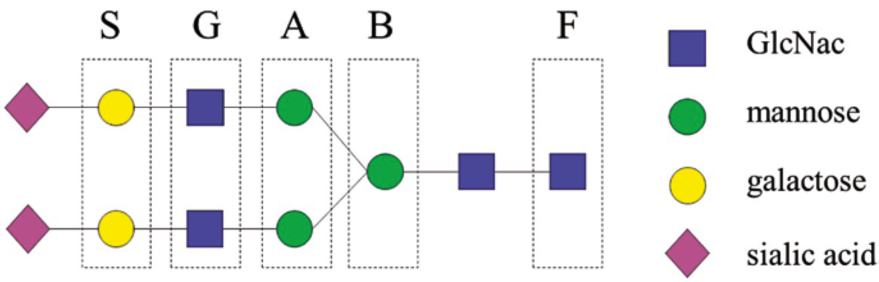

Fig. 4 Structural abbreviations and structural schemes

of metabolic syndrome in studies related to suboptimal health and glycosomics [32]. The glycan peaks (GPs) of GP8 (FA2[6]G1), GP18 (FA2G2S1), GP21(FA2G2S2) and GP34 (A4G4S[3,3,6,]3) could be used to predict SHS and metabolic syndrome [32].

Figure 3 highlights glycomics as a diagnostic tool for SHS. Figure 4 shows the structural abbreviations (a) and structural schemes (b).

Metabonomics studies have shown that the clinical manifestation of CFS represents a highly coordinated hypometabolic response, demonstrating that Metabonomics could be used as a powerful method for the identification of biochemical differences between health and disease [33]. An experimental method combining four metabolic biomarkers (sphingomyelin, progesterone, bovine heparan sulphate and cervinyl carnitine) is able to distinguish people with SHS from healthy people; its sensitivity was 94.0% and its specificity was 90.0%, and the AUC was 0.977 [34]. Existing research suggests that metabolic disorders associated with SHS can be identified at an early stage. Therefore, from a PPPM perspective, the ability to identify SHS-related metabolites early may represent a window of opportunity to manage chronic disease [34].

Studies have shown a high turnover of collagen and non-myofibrillar proteins in the amino acid composition of women's urine, suggesting that analysis of amino acids in female urine may be a useful tool for assessing fatigue and suboptimal health when administering amino acid supplementation to individuals [35].

In addition to physiological and biological measures, short relative telomere length (RTL) has been reported to have a significant association with SHS. This suggests that the combination of subjective (SHS) and objective (RTL) measures of subjects could provide a new and more practical tool for healthy ageing research [10].

3.3 Digital Biomarkers

A study of 200 Russian university students found that the vocal changes they made under stress could serve as an important biomarker for identifying SHS. Artificial intelligence using predictive machine learning models can automatically derive digital biomarkers based on the voice recordings of study participants, which could be a useful tool for identifying SHS [36]. This bodes well for the possibility of developing a method for the detection of SHS that is both convenient to use and non-invasive.

4 The Outlook of SHS Diagnostic Tools

The SHSQ-25 has been shown to have a wide range of applicability in previous studies, which means that the SHSQ-25 will be translated into other different languages and used by more researchers. To date, SHSQ-25 has had three language versions, Chinese, English and Russian. In the future, SHSQ-25 in more languages will be applied among different ethnic population.

Animal models are essential for SHS mechanistic studies. Although experiments have been performed on some animals, such as rats and mice, to establish animal models of SHS, they cannot completely simulate the human state [37, 38]. Even so, animal study provides more possibilities for us to deeply understand the mechanism of SHS, and it is helpful to establish an objective indicator system.

The current SHS evaluation criteria and thresholds are extrapolated from the range of clinical disease diagnoses. The reliability is uncertain and the scope of application is narrow. Therefore, only a single or a few indicators cannot reflect the real state of individual SHS. To solve this problem, we can carry out a large sample investigation or experiment, combine the scale investigation with experimental research, and find out the physiological and biochemical index spectrum corresponding to different subtypes of SHS, which might effectively improve the reliability and effectiveness of SHS diagnosis. In addition, according to the findings of our previous studies, the sensitive indicators might be different for people of different age and status, like pregnant women and general communities. The future studies could make an effort to explore the specific indicators in certain population to improve the recognising precision.

The molecular biology research on SHS has made remarkable achievements, but these researches rely heavily on laboratory detections, and some of them are not mature enough. Therefore, convenient, fast, efficient, sensitive and inexpensive practical tools need to be developed for future research and application [27, 28]. In the current diagnostic or screening technology, biodetection chips or kits have the advantages of high throughput, standardisation and practicality, and become the main development choice for SHS diagnosis in the future. N-glycans are involved in intracellular/extracellular interactions or signal transduction, cell adhesion, metastasis, cell–cell or molecular–cell interactions, inflammation and immune function, making them ideal dynamic biomarkers for monitoring physiological conditions. Thus, the N-glycan biochip can be used to help evaluate individual SHS. The advanced detection measurement based on glycomics is expected to develop into a powerful tool to evaluate objective indexes of SHS [39–43].

Based on the previous study, automated artificial intelligence (AI) analysis of voice recordings using predictive machine learning models can be effective in determining an individual's health status and can be used as potential digital biomarkers. In addition, analysis of disease-specific cell-free nucleic acid data (ccfDNA, ctDNA, mtDNA, miRNA) combined with metabolic patterns can be used for subsequent stratification and monitoring of individual SHS tests. This is a cost-effective application that allows for targeted prevention at the stage of reversible damage to health [36].

Future research on SHS needs to be conducted using a comprehensive paradigm with a large sample size. This should be a combination of qualitative and quantitative studies. As a consequence, massive data will be generated. If we include massive amounts of bioinformatics data, then the following requirement for technological development is that the revolutionary ability to process and analyse big data must be advanced (such as artificial intelligence).

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Risk Factors, Health Status, and Risk Groups in Suboptimal Health Condition

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Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular diseases
GBD	Global Burden of Diseases

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LMIC	Low- and Middle-income Countries
NCD	Non-communicable diseases
PPPM	Predictive, Preventive, and Personalised Medicine
SHS	Suboptimal Health Status
WHO	World Health Organisation

1 Intermediate State Between Health and Disease

A person's physical, psychological, and social stress can result in suboptimal health status, sometimes referred to as sub-health status (SHS), a transitional condition between health and illness with several adverse effects [1–3]. Its main underlying process is yet unknown [4]. However, physical, psychological, and social functions deteriorate due to the total coordination of the body's systems, including the neurological, endocrine, and immune systems, becoming unbalanced and dysfunctional, resulting in physical and psychological alterations. The body has not yet progressed to the illness stage [4–6].

Numerous chronic symptoms, including chronic fatigue, headaches, vertigo, unhappiness, anxiety, lack of hunger, sleeplessness, and functional problems, are experienced by people with SHS [3, 5, 7]. Similar to this, some organ systems, generalised discomfort, and functional abnormalities of many organ systems, such as the digestive, cardiovascular, pulmonary, and urinary systems, are connected to short- or long-term detrimental health effects [6, 7]. For instance, SHS contributes significantly to lower quality of life, frequent hospital visits, and expensive medical expenses [8, 9]. The afflicted continue to feel disappointed and unable to live normal lives because there are no obvious indications of any one disease [2–4]. Does the pathway to a chronic disease state appear to be shifting away from an optimal health status? Around the world, it is a difficult and real problem [10].

SHS seems to be common in China [6], and it has been steadily increasing in other nations [8, 11, 12]. The signs of SHS may be ignored worldwide, and many people are unaware that they have the condition [3]. SHS is displayed with various persons and organisations, including teachers, government employees, company owners, local citizens, healthcare professionals, and others [3, 5]. As a result, many academics and scientists worldwide have recently been concentrating on the age, sex, profession, topographical area, and behavior of people who are at higher threat of SHS. An individual health monitoring system inspired by the predictive, preventative, and personalised medicine (PPPM) technique, which is actively spreading throughout the world, is necessary to stop SHS from progressing to the state of chronic disease [13, 14].

2 Relationship Between SHS and Chronic Disorders

According to the WHO, non-communicable diseases (NCDs), often referred to as chronic disorders, kill 41 million people worldwide each year [15–19]. In addition, between the ages of 30 and 69, a productive age group, more than 15 million people die prematurely from NCD each year, with low- and middle-income countries (LMICs) accounting for 77% of deaths [15–19]. In addition, roughly 17.9 million people worldwide die each year from cardiovascular diseases (heart attacks and strokes), followed by cancer (9.3%), COPD (chronic obstructive pulmonary disease (COPD), and 1.5 million individuals with diabetes mellitus. Notably, these four illnesses account for more than 80% of NCD-related early mortality [15–19].

The risk factors for NCDs, like a bad diet, not being active, smoking, and drinking too much, are more common in young people, adults, and seniors [20, 21]. Similarly, young people, adults, and seniors are more susceptible to the influencing aspects leading to NCDs, such as poor diet, inactivity, smoking, and alcohol abuse [7, 9, 15–19]. On the other hand, SHS has been noted as a potential risk factor for various malignancies and metabolic diseases, as well as diabetes mellitus, heart disease, and stroke. It is recognised as a sub-clinical reversible stage of chronic diseases.

There is strong evidence that NCD risk factors include modifying personal behaviors like smoking, inactivity, poor diet, and excessive alcohol consumption. An estimated 7.2 million people die from smoking each year, followed by 4.1 million from eating too much salt, 3.3 million from drinking alcohol and developing cancer, and 1.6 million from not getting enough exercise [15–19]. As a result, WHO has set a target of reducing premature mortality brought on by NCDs by 2030 through a sustainable development agenda [15–19].

Examples of risk factors for chronic disease include socioeconomic status, degree of education, physical inactivity, salt consumption, blood pressure, cardiovascular indications, triglycerides, lipid, alcohol use, poor diet, etc. [2, 4, 22]. Similarly, SHS risk is directly correlated with smoking behaviors, physical activity, poor nutritional intake, insufficient sleep, and uncontrolled blood pressure [3, 4, 7, 23, 24]. These risk factors are connected to a person's lifestyle or behavior, and these unhealthy ways of living or behaviors significantly contribute to the rise in SHS [4, 20, 23].

The prevalence of chronic diseases such as cardiovascular diseases, hypertension, stroke, cancer, chronic obstructive pulmonary disease, and diabetes is rising as a result of modern lifestyles, higher work demands, and changes in diet and eating patterns [25]. Due to the preclinical and treatable stage of chronic diseases, SHS is crucial to the pathophysiology of these conditions [3]. SHS is diagnosed based on symptoms and biomarkers because the causes and mechanisms of the disease are yet unknown [26].

Along with the immune system [12, 27], neurological system [28], digestive system [29], and cardiovascular system [30], which are all parts of SHS [3, 7], intestinal microbiota also plays a crucial role in human health [31]. Emerging research supports the link between the intestinal microbiota and a number of disorders, including atherosclerosis [32], hypertension [33], diabetes [34], and immune deficiency syndromes [35].

3 Psychological Symptoms and Relationship with Chronic Diseases

Such professions affect SHS. Nursing is consistently regarded as one of the most stressful and demanding professions out of several. Working very long hours, work schedules, patient complaints, and low salaries are among the many workplace stressors that nurses frequently deal with [36]. Along with physical side-effects, including pain, weariness, reduced immunity, and other issues, such demanding work may severely influence mental health and quality of life, as well as physical side-effects, including pain, exhaustion, lowered immunity, and so forth [37].

There is evidence linking SHS to cognitive impairments [38], psychosocial stress [39], and mental health illnesses [40]. One of the four main elements impacting health, along with chemical, physical, and biological components, is referred to as a psychosocial or psychological factor(s) [41]. Health, both mental and physical, is getting more emphasis. According to recent epidemiological statistics [42, 43], between 35.8% and 61.7% of nurses experienced depressive symptoms. The two mental health conditions that are most common and have serious repercussions are depression and anxiety. As a result, it impacts how well society functions and how people live their lives and helps fuel social problems and economic losses [44–46].

Predictive, preventative, and customised medicine are replacing response treatment in the new, emerging medical paradigm (PPPM). It comprises medical care personalisation, preventive measures, and forecasting models for infectious diseases and catastrophic pandemics like COVID-19 [47]. It also covers chronic and noncommunicable diseases.

The ideal use of PPPM occupies a distinct market segment in healthcare. A few examples include a new level of professional interests, a new scale of knowledge integration, highly motivated technological innovation, highly motivated interdisciplinary and multidisciplinary cooperation, individualised care, predictive medicine, the new range of screening programs, targeted prevention, currently unmet needs of healthy subpopulations and patient cohorts, cost-effective medical services, and an optimised health care economy [48–50]. The ground-breaking PPPM is quickly becoming the focus of healthcare initiatives focused on reducing the prevalence of chronic diseases like cancer, diabetes, and cardiovascular disorders [51–53]. Cardiovascular illnesses, diabetes mellitus, oral drugs, lifelong health conditions, cancer therapy, and postoperative tumour assessment have all seen practical applications of PPPM ideas [54–56]. However, the study didn't fully explain how SHS affects nurses' mental health symptoms. Nursing staff's poor physical and mental health is caused by a long-term buildup of intangible workplace risks, even though it has a less immediate effect on their day-to-day work and activities. It affects people's general health [57]. Contrarily, good health makes it simpler to avoid errors in routine clinical practice because errors here can frustrate patients and possibly harm their prognosis.

In the framework of PPPM, the SHS concept is one of the creative alternatives [5, 57]. To stop or slow the progression of SHS before it reaches the disease level in nurses, targeted prevention and individualised treatment are needed. According to the PPPM model, screening the SHS population, figuring out disease risk forecasts, and then coming up with individualised interventions offer a window of opportunity to halt or delay the onset and progression of several diseases, significantly enhancing the model, which already has a medical component [58].

One of the unique solutions is the PPPM concept [5, 57]. To stop or slow down the progression of SHS into a disease state in nurses, it is important to use targeted preventive and specialist therapy. By screening the SHS population, figuring out who is most likely to get sick, and then making individualised interventions based on the PPPM model, there is a chance to avoid or delay the onset of several diseases. This significantly enhances the current medical model [58].

4 Lifestyle Factors and SHS

The most significant factor influencing human health is lifestyle [59–62]. Direct lifestyle factor correlations with physical, mental, and social SHS are weaker than indirect lifestyle factor correlations with physical, mental, and social SHS via health consciousness [6]. Furthermore, it has been demonstrated that physical, mental, and social SHS substantially correlate with health consciousness [63]. As a result, lifestyle variables such as drinking alcohol, skipping breakfast, eating an unbalanced diet, not exercising, and having sleep issues are significant risk factors for SHS [3, 64]. SHS is consistently linked to chronic disease risk factors and predisposed to the onset of these illnesses [53]. Therefore, people can be protected from chronic diseases by changing their bad lifestyle habits.

A person's capacity to sustain their energy balance over time is impacted by various lifestyle choices, such as how much sleep they get can affect their energy intake, energy output, or both [65, 66]. The amount of sleep that people get is crucial to their metabolism. Several causes include lifestyle decisions, work or family demands, and health or mental issues. In our fast-paced modern environment, chronic sleep deprivation is becoming more widespread [66]. An enormous section of the population suffers from chronic sleep deficits due to social transformation, such as increased TV viewing and internet usage [66]. Numerous chronic diseases are also directly linked to unhealthy lifestyles [67–70]. The main risk factors for the general population include poor stress management, self-actualisation, inactivity, and interpersonal relationships [8].

A healthy lifestyle is a multifaceted pattern of self-initiated views and behaviors that support and enhance one's health and well-being [8, 64]. These kinds of beliefs and behaviors can help to lessen illness occurrence, lower death rates, and improve the state of health. Bad lifestyle choices like smoking, drinking, eating poorly, and not exercising can lead to several chronic diseases and increase the risk of damage and illness [71]. According to the WHO, unhealthy behavior and lifestyle choices are among the top ten causes of death globally [15–19, 21, 72, 73].

5 Adolescent Period and SHS

The key adolescent years spanning from 10 to 24 years old are the time between childhood and adulthood [15–19]. Pubertal maturity, the transition to adult social roles, and the development of independence are characteristics of this time [74]. As a result, it is sometimes referred to as a time of "Stress and Storm" [75, 76]. Before a child becomes more focused on his or her peers, there is a small window of time when family health practices can be changed. Adolescents' physical activity is also influenced by their conception of the advantages of physical activity (beliefs), the social influences of family and friends on physical activity (social influences), and the growth of their self-efficacy (confidence in their own abilities to be physically active) [77]. During this period is more dangerous to be exposed to peer groups and engage in bad habits like drinking alcohol, smoking, eating poorly, etc. [74]. These effects have an impact on both present and future health status, yet, the adolescent stage offers plenty of opportunity for behavior to be positively influenced, leading to better long-term health outcomes [74].

According to epidemiological data, risky behaviors are the primary cause of adolescent illness and mortality worldwide [15–19]. Risk-taking is at its highest during adolescence, which shows that this is when people have a strong tendency or a natural desire to do so [21]. They frequently experience accidents or injuries due to their tendency to take high risks [78]. They are always at risk when engaging in this risk-taking activity during adolescence [76].

During adolescence, a person's body grows and changes their reproductive health, mental health, social life, and emotions. The most crucial time in one's life is when they are still young. Because of this, adulthood is a critical time for developing healthy or unhealthy behaviors, and those traits are linked to a higher chance of developing chronic diseases [79]. However, the increasing source of health hazards in old age may be determined by unhealthy practices and behavior and poor lifestyle choices made at a young age [64]. Adolescent harmful behavior can significantly impact the development of health issues later in life [80].

Risky behaviour among college and university students is also a big reason they get chronic diseases as they age [81]. The study showed that SHS was most common among high school students. Both physical and mental SHS were more often found in this age group [4]. Adolescence may be the best period to learn about health issues because of physical and psychological development. It would provide some proof of the degree of ill health. Health assessment data from a college or university may be more convincing if we want to explore how to avoid getting a chronic disease later in life [4].

It has been shown that SHS can be prevented if it is found and treated early. In predictive, preventive, and personalised medicine [5, 13, 14] (PPPM), a new therapeutic paradigm or mechanism has been made to give patients the power to treat diseases early [82].

In conclusion, SHS is a condition that comes from a person's physical, mental, and social stress between being healthy and being sick. Even though the body hasn't yet reached the disease stage, the general coordination of the body's systems gets out of whack and stops working. Physiological, psychological, and social functions are reduced as a result. SHS is linked to many long-term conditions, such as fatigue, headaches, dizziness, depression, anxiety, loss of appetite, trouble sleeping, and problems with functioning. Similar to this, several organ systems are linked to short- or long-term unfavourable health effects. SHS can affect people of any age, gender, job, or location and greatly affects the quality of life, leading to frequent visits and high treatment costs. Physical, mental, and social SHS strongly correlate with lifestyle variables. So, lifestyle factors are risk factors for SHS, and SHS is often linked to developing long-term illnesses. By screening the SHS in the community, figuring out how likely they are to get sick, and then making individualised interventions based on the PPPM model, there is a chance to avoid or delay many diseases. This significantly enhances the current medical model.

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Ethical Approval Each institution has granted ethical approval for the investigations covered in this book chapter. All procedures used in research involving human subjects complied with the 1964 Helsinki Statement and its later amendments, as well as the ethical guidelines established by institutional research committees.

Declarations of Interest Statement None.

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Treatment Algorithm Tailored to Individuals with Non-communicable Diseases: The Innovative Utility of Suboptimal Health Concept from the Predictive, Preventive and Personalised Medical Care Perspective

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Abbreviations

CVH	Cardiovascular Health
EPMA	European Association for Predictive, Preventive and Personalised Medicine
FS	Flammer syndrome
HCC	Hepatocellular carcinoma
NCDs	Non-communicable chronic diseases
PCa	Prostate cancer
PE	Preeclampsia
PPPM/3PM	Predictive, preventive, and personalised medicine
SHS	Suboptimal health status
SHSQ-25	Suboptimal Health Status Questionnaire-25
T2DM	Type II diabetes mellitus
VD	Vaginal dryness

1 Introduction

Worldwide, non-communicable disease (NCD) is one the leading cause of adverse health outcome and fatal rate. As such, several treatment strategies have evolved. Although most diseases are diagnosed before treatment, there are individuals who may experience poor health without a clear diagnosis but complain of general body weakness and vitality [1]. The latter group of individuals are termed to have suboptimal health, a physical stage between health and diseases. Nevertheless, these suboptimal health individuals can remain undiagnosed even for many decades of their life [1]. Individuals in pre-clinical phase of a health condition usually need to be treated with targeted drugs that help to avert or delay the development of a disease. However, suboptimal health individuals require no specific treatment and this increases their chances of poor health subsequent to a disease. Effective intervention tailored towards individuals with suboptimal health can only begin after the clinical manifestation of a disease. Thus, from the personalised medicine standpoint, this is a delayed intervention. Thus, identifying appropriate treatments tailored to individuals who suffer from NCDs is important in improving health and well-being.

2 The Healthcare System: PPPM as the Future Medicine?

Current healthcare systems practice more of a delayed treatment approach, which leads to several health complaints including drug resistance and reactions. The need to promote the paradigm change from the "wait-to-treat" approach to a more targeted predictive and personalisation of medical care is needed [2–5]. This concept has been coined as PPPM.

PPPM enables the early identification of individual's clinical signs prior to a clinical manifestation and thereby creates targeted preventive measures tailored to the affected individual. PPPM is more tailored to early prevention of childhood illness, general health screening, identification of high-risk population, categorisation of patients for the ideal regimen and reduction of adverse drug-to-disease or drug-to-drug interactions. PPPM concept utilises new technologies, including disease modelling, pathology-specific molecular patterns, pharmacogenetics, imaging techniques, and individual patient biochemical profiles to aid in disease prevention and treatment policies [5] making PPPM the precise future medicine [2, 3]. For decades, the concept of PPPM has contributed to health and policies on the treatment and management of diseases because of the all-inclusive approach it adopts in solving health problems [2, 5]. Global health organisations including the World Health Organisation and the European Union and the National Institutes of Health have recognised the concept of PPPM as a more cost-effective and economical in disease management [3, 4]. For several years, the European Association for Predictive, Preventive and Personalised Medicine (EPMA) has led the global effort to promote the concept of PPPM among patient organisations and in the communities, funding institutions, academic and research institutions, governmental institutions and healthcare stakeholders [3, 4].

3 Suboptimal Health Status Concept in the Perspective of Targeted Treatment Tailored to the Individual at Risk of NCDs

Over the past years, suboptimal health status (SHS) assessment has been considered as one of the public health concepts that explain the perspective of PPPM in that it recognises poor health in individual devoid of a diagnosable clinical condition and create the avenue for targeted personalisation of medical care [1, 6]. Even though the SHS evaluation using the SHS questionnaire-25 (SHSQ-25) is a cheap, reliable tool with a short turn-around processing time, and is readily available to both low- and high resource countries, it is a recognised measure that provides early phenotypic risk signs and predicts future NCD outcomes. Several researchers from across Africa, Asia, Australia and Europe who explored the SHSQ-25 as a screening tool found it to be suitable for patient's investigation, relative risk, prognosis, monitoring and targeted preventive therapeutic options that provide benefit to patients and the healthy population. Thus, the SHS concept is relevant and important for treatment algorithms tailored towards individuals at risk of developing a condition.

The ground-breaking evidence of PPPM via the use of SHS concept is the vital part of efforts in the healthcare treatment and management system aimed at preventing the occurrence of NCDs that include but are not limited to poor dental health, malignancies, hypertension, preeclampsia, mental disorders, cardiovascular diseases, diabetes mellitus and other familial pathologies.

3.1 Diabetes Mellitus and SHS Concept

PPPM plays a key role in the management of diabetes conditions by providing support on prediction of effective treatment dose, adequate patient stratification and lifestyle modification [3, 7–9]. Taken together, this has improved the quality of life, promoted longevity and delayed the onset of complications leading to a better health outcome. Like other chronic diseases, screening and beginning treatment at the suboptimal or prediabetic phase is pivotal in PPPM, and it provides the support for starting prophylaxis, which prevents the manifestation of diabetes mellitus and its complications. The pre-diabetes mellitus represent a suboptimal stage of the diabetes condition; hence, can be explained as a stage between non-diabetes and diabetes patients. Recent studies have found that SHS is a predictor for type 2 diabetes mellitus (T2DM) co-existing with poor lifestyle modifications and imbalance in biochemical concentrations [10, 11]. For instance, in a cohort study in a Ghanaian population, primarily sedentary lifestyle (AOR = 2.97), high triglyceride concentrations (AOR = 2.39) and high systolic blood pressure (AOR = 1.86-fold) were independent predictors of SHS [11]. Among the Chinese population, the fourth (AOR = 1.70), third (AOR = 1.60) and second quartiles (AOR = 1.50) of SHS scores

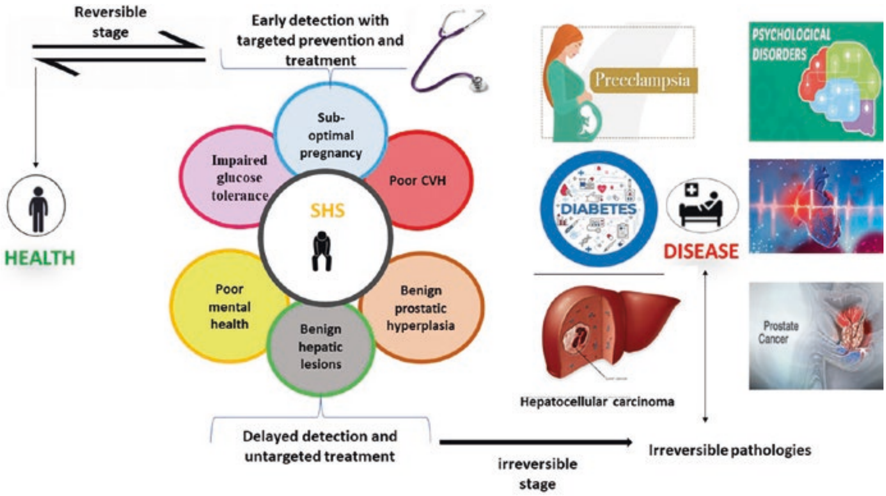

Fig. 1 Treatment algorithm at the suboptimal health stage is instrumental for reversing chronic conditions

were identified as a predictor of T2DM [10]. In addition to the study in China, the SHS score yielded a discriminating power of 84.8% for predicting the onset of T2DM, indicating that SHS evaluation can identify more than 80% of individuals in the pre-diabetics phase. The management of T2DM is thus suboptimal, even though a higher number of individuals may remain undiagnosed, leading to adverse diabetes events and complications. Identifying early individuals with combined risk of prediabetes, poor lifestyle modifications and cardiometabolic syndrome in suboptimal health individuals would inform health professionals to initiate targeted preventive measures to prevent the onset of T2DM [12]. In the current health system, it is therefore important to move from a more reactive medical approach to PPPM (Fig. 1).

3.2 SHS Screening Is Highly Recommended in Preeclampsia Management

The prediction of hypertensive disorder of pregnancy such as preeclampsia (PE) using SHS screening is highly recommended for maternal healthcare during pregnancy [13]. Particularly, a recent longitudinal cohort study in a Ghanaian population found that approximately 90% of suboptimal pregnant women who were between 10 and 20th weeks of gestation went on to develop preeclampsia [13]. In addition to this study, between 78.0% and 82.0% of the suboptimal pregnant women who developed were coexisting with dyslipidaemia, intrauterine growth restriction, stillbirth, HELLP (haemolysis elevated liver enzymes and low platelet count) syndrome and acute kidney injury in a prospective cohort study conducted in a Ghanaian population [13]. In our previous study, suboptimal health pregnant women who were normotensive were found to have imbalances in the concentrations of angiogenic growth mediators (AGMs) and oxidative stress (OS) biomarkers when measured at 10–20th weeks of gestation [14]. The first quartile for vascular endothelial growth factor-A (AOR = 5.35), and placental growth factor (AOR = 2.79), and the fourth quartile for soluble FMS-like tyrosine kinase receptor 1 (AOR = 1.84), soluble endoglins (AOR = 4.31), 8-hydroxydeoxyguanosine (AOR = 1.90) and 8-prostagliandinF2-alpha (AOR = 2.23) were independently predictors of suboptimal health [14] Even though OS and AGMs are significant factors in placental vascular development, an increased SHS score is an early sign of adverse pregnancy complication along with imbalance in OS and AGMs. SHS pregnancy is a call to start targeted treatment and monitoring tailored to prevent the clinical manifestation of preeclampsia (Fig. 1). From the prophylactic standpoint, targeted preventive approach and treatment options such as antioxidant and micronutrient supplementations tailored towards the suboptimal pregnant mothers are beneficial for alleviating new onset of preeclampsia [15]. The subjective measure, SHS along with objective biomarkers of OS and AGMs can be useful for the PPPM for pregnant women.

3.3 Suboptimal Health: The Link Between Vaginal Dryness and Flammer Syndrome

Suboptimal health condition is known to contribute to the development of vaginal dryness (VD) among pre- and post-menopausal women. Even though hormonal disturbances, which occurs among women during their climacteric period is the main cause, most of the affected individual tends to be suboptimal [16]. Other causes of VD such as Flammer syndrome (FS) are obviously avoidable and, therefore, if well managed, tend to reduce the occurrence of VD. Thus, to manage VD, it is important to prevent modifiable risk factors linked to FS phenotype at the primary prevention and treatment level while screening individuals at the suboptimal level. Thus, future studies are recommended to use SHS criterion as a health screening tool for both pre- and post-menopausal women for VD.

3.4 SHS Criterion in the Management of Cardiovascular Diseases

Maintaining optimal cardiovascular health (CVH) is a crucial component in the management of cardiovascular disease (CVD) [17]. The prevalence of SHS increased with increasing CVH metrics in a China suboptimal health cohort study

[17]. In the China study, SHS was associated with poor CVH metrics including dyslipidaemia, hypertension, hyperglycaemia and poor lifestyle characteristics (obesity, physical inactivity, cigarette smoking, and poor dietary habit). Early stratification of SHS individuals who have poor CVH metrics would create an avenue to initiate personalised medical care tailored to the affected individual [17]. Aside from poor CVH [11, 18], SHS has also been associated with behavioural factors [18, 19] and index of endothelial function, which the combined effect increases the individuals chances of cardiovascular disease [7]. From the personalised medical care perspective, it is imperative to monitor individuals at the suboptimal stage for poor CVH (Fig. 1).

3.5 SHS and Psychological Disorders

Mental health, which is among the SHS domains, is a public health challenge affecting both the young and adult. Previous studies in a Chinese population have found an association of SHS with mental health-related factors such as reduced cognitive function [8], psychological symptoms [9] and increased incidence of self-reported suicidal ideation [20]. The prevalence of SHS was 21.0% among China University College students in a cross-sectional study by Hou et al. [9]. In the Study by Hou and colleagues, SHS was independently associated with interpersonal sensitivity (AOR = 1.88), obsessive-compulsive (AOR = 3.52), depression (AOR = 1.85) and somatisation (AOR = 3.18) [9]. Another study among Chinese individuals reported that SHS was three-fold increased odds of developing cognitive impairment [8] and that early indication of poor health in relation with poor behavioural, cognitive, and emotional well-being would inform healthcare providers to initiate preventive measures and treatment options for mental health disorders (Fig. 1). Effective management of mental health disorders may lead to neurological complications [21–23].

3.6 Targeted Treatment and Preventive Measure in Prostate Cancer

Prostate cancer (PCa) is the one commonest cancer in men, globally. Although there are numerous causes of PCa, the need to improve the diagnosis and treatments is essential. The PCa management causes a remarkable divergence, i.e., permanently high prevalence of PCa cases on one hand and, stable or even slightly reducing fatal rates on the other hand [24]. In addition, there is always a delay in the time of prostate cancer diagnosis and therefore, to identify persons who may be at risk of developing prostate cancer, PPPM is the modern medical approach to use. Personalised treatment is beneficial for prostate cancer individuals since keeping urinary and sexual functions intact allows for a significantly higher quality of life for most PCa individuals without reducing the survival rates [24].

3.7 Hepatocellular Carcinomas Management: From the PPPM Perspective

Hepatocellular carcinoma (HCC) is the second leading cause of all cancer-related mortalities even though it is classified among the five top most common of all cancers [5]. This prevalence and mortality rate continues to increase due to inadequate facilities for effective screening programmes, tumour heterogeneity and late diagnosis. HCC is also multifactorial in origin and has erratic impacts of individual tumour growth and development. Thus the frequently untargeted treatment and its associated cancer resistance towards currently applied treatment approaches should be addressed [5]. The reactive medical approach is inappropriate in the management of hepatocellular carcinoma. A therapeutic system tailored towards HCC risk population would require an early evaluation of SHS. Early recognition of benign lesions at the suboptimal phase would create an opportunity for treatment options to reverse the growth of cancerous lesions (Fig. 1). Thus, there is an urgent need to change from reactive treatment toward predictive, preventive and personalised medicine.

4 Conclusion, Expert Recommendations and Future Perspective

Suboptimal health evaluation is recognised as an essential tool for PPPM. It is therefore important for healthcare to move from the reactive medical care to PPPM. Identifying persons at the suboptimal stage followed by an appropriate management strategy is essential for preventing the early onset of diseases and their adverse complications [13]. Implementing a targeted prophylactic therapeutic approach but not the 'wait' to 'treat' approach will create a window opportunity to prevent disease development and subsequent complications. The suboptimal stage, which is the flexible stage of chronic diseases, is the recommended stage to start a targeted treatment tailored to the individual. Evaluation of SHS using SHSQ-25 has become necessary and should be adapted as part of treatment strategies in monitoring and management of NCDs. As suggested in predictive, preventive and personalised medical care (PPPM), SHS-targeted treatment algorithms tailored towards persons are the future precision medicine for NCDs.

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Approaches for Measuring Reversible Damage to the Health

Yu-Xiang Yan and Wei Wang

Abbreviations

M-M	Multi-trait-multi-method
MMSE	Mini-Mental State Examination
MPQ	McGill pain questionnaire
SHS	Suboptimal health status
SHSQ-25	Suboptimal health status questionnaire-25

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1 Introduction

Health questionnaires and scales have become the dominant instruments to measure various health, such as the existence of different symptoms or specific characteristics [1, 2]. Multiple items are constructed for comprehensive assessment of subjective health complaints prior to organic lesions. Nowadays, there are a variety of health scales and questionnaires have been constructed for the detection of reversible health damages that could not be measured directly [3], such as the "Suboptimal Health Status Questionnaire-25 (SHSQ-25)" [3], "Mini-Mental State Examination (BMI) [4]" and "McGill Pain Questionnaire (MPQ) [5]."

The SHSQ-25 was established to evaluate suboptimal health status (SHS), which includes various health complaints. The SHSQ-25 consists of 25 items concerning a series of symptoms on five dimensions. Based on previous qualitative and quantitative analysis, work stress has been proven to be an important influencing factor of SHS. Chronic activation of the stress response is associated with a number of diseases, such as cardiovascular disease, gastrointestinal disease, immunological diseases and mental illness [3]. According to the impacts of mental stress on health, the preliminary SHSQ-25 was established based on a literature review and focus group discussions. The validity and reliability of the SHSQ-25 were evaluated in a large-scale investigation.

2 Major Procedures of Establishing a Health Instrument

Before establishing a questionnaire, it is necessary to determine the purpose and theoretical hypothesis of the investigation. The main contents of the questionnaire should be outlined and relevant data and information should be collected for the item pool.

2.1 Selection of Items

The individual questions of a new health instrument usually come from literature, existing questionnaires, expert opinions and focus group discussions [1, 2]. Exiting health questionnaires assessing a particular trait or disorder may be useful source of items. These instruments have been widely used and proved to be relevant, important and discriminating. So, some items of the newly developed questionnaire are derived from these widely used instruments.

It is a fact that potential subjects of a specific study are a good source of individual questions in establishing health instrument [1]. Focus group usually consisted of 5–10 individuals who have the disorder or health problem. The focus group discussion is led by a moderator, who adhered to a question guide with interesting theme. The discussions are conducted until no new items emerge. The opinions, experiences and perceived health were recorded, transcribed word for word, processed as text until no new themes appeared, and then analysed them by means of qualitative analysis [3]. Expert opinions are important to determine the most important characteristics of health complaints. The accumulated knowledge and experience of the experts, such as physicians, nurses and health managers, are necessary for the generation and choice of items [1].

2.2 Construction of Health Questionnaire

Once the individual questions have been selected, expert consults and focus groups will be performed again to evaluate whether these items are relevant, explicit, and whether they are written in a way that can be understood by interviewees. After that, a preliminary health instrument is developed according to the pool of questions. The researchers should consider the order of questions, logical structure of the questionnaire, convenience of the answers and potential psychological influence on the interviewees. For each question, we should pay attention to whether it is necessary and whether the answers are comprehensive and reasonable. Generally, a pilot survey will be conducted to evaluate whether the questions are feasible and relevant. According to the feedback of the interviewees, the instrument is then modified for formal investigation.

2.3 Measurement and Rating of Responses

To obtain effective answers, an appropriate scoring method to quantify the answers should be developed. A response of "yes/no" could not discriminate a person who has health problem from those who do not have. Rating scales are extensively utilised in the areas of health and social research for the measurement of characteristics that could not be evaluated directly [6–8]. Most of questionnaires have been constructed using thresholds of three or five classes with scores of "1, 2, 3" or "1, 2, 3, 4, 5," which correspond to the frequency or degree of health complaint suffered [6, 8]. For example, each item in the SHSQ-25 is evaluated using 5-point Likert-type scales anchored by 1 = "never or almost never," 2 = "now and then," 3 = "often," 4 = "very often," and 5 = "always" [3].

3 Assessment of Reliability

Reliability and validity are among the most important and fundamental characteristics in the assessment of any measuring methodology for data collection. They are important aspects in evaluating the accuracy and precision of an investigation.

Reliability refers to whether the same result can be attained consistently by applying the same methodology under similar conditions [9]. Reliability can be evaluated by the following methods:

3.1 Test–Retest Reliability

The test–retest reliability means whether the instrument produces stable scores over time. It is deemed an excellent test–retest reliability if the same instrument is repeated after a period of time and gives the same answers. The test–retest reliability is evaluated by correlation analysis between the first and second measurements by using the same instrument to the same subjects [10]. The environment should be as consistent as possible to minimise the external factors that may affect the measurements. The assumption of test–retest reliability is that the measured characteristic of the same subjects does not change over time.

3.2 Alternate Form Reliability

Alternate form reliability refers to equivalence between an alternate form of instrument and the original instrument. The alternate questionnaire has different items but equal means [11]. It is hypothesised that no significant differences should exist between the two forms of the instruments. Alternate form reliability is measured by the correlation coefficient between the scores of two parallel measurements administered in the same individuals or different group of individuals. Strong positive correlations between the two instruments indicate equivalent.

3.3 Split-Half Reliability

When alternate form of same measure is not available, split-half reliability can be used. The measurement is split into two half-tests that are as nearly parallel as possible, and the correlation between halves is calculated. The measurement can be split in ordered halves (first-half and second-half) or odd-even half. The correlation is likely to be an underestimate of the reliability coefficient for the full-length measurement instrument. To overcome this problem, the Spearman-Brown formula ($R = 2r/(1 + r)$, r indicates the correlation between halves, R indicates the split-half reliability) is then used for correction [12, 13].

3.4 Reliability of Internal Consistency

Internal consistency refers to whether the items correlate with each other within the instrument. Cronbach's alpha is a measure that assesses internal consistency reliability [14]. It can be used with both polytomous and dichotomous data. It is the average of all possible split-half reliabilities assuming the halves are parallel to each other. It is also the lowest bound of estimate of reliability. A Cronbach's alpha coefficient greater than 0.70 is generally considered acceptable for group comparisons, and 0.90 for person-level comparisons [15]. Cronbach's alpha can be affected by the length of the scale, the correlation coefficient between items and the dimension of measurement. With the increase of item numbers and correlation between items, Cronbach's alpha will also increase. However, Cronbach's alpha will decrease with increase of dimension number.

4 Assessment of Validity

Validity is defined as how accurately a methodology measures a variable that it intends to measure [9]. Validity is difficult to assess but can be evaluated by comparing the results with other relevant conception or theory. Validity can be evaluated by the following methods:

4.1 Content Validity

Content validity refers to the relevance and representativeness of the contents of the instrument, that is, whether the relevant aspects of the idea being measured are included in an instrument. In most cases, content validity is evaluated by panels of professionals [9]. Unlike with other types of validation, there is no correlation coefficient or some other statistic that can be used to measure content validation. Usually, experts review all of the items for readability, clarity and comprehensiveness and decide which items should be included in the final questionnaire [16]. Content validity is also called logical validity, intrinsic validity or circular validity.

4.2 Construct Validity

Construct validity reflects the compliance of a measurement to the existing concept and theory. To establish construct validity, researcher has to make predictions based on the assumed construct. The predictions will further be proved to support the validity of the instrument [17]. Evidence based on the internal structure of an instrument is used to determine whether the items measure unidimensional construct or a multidimensional one. In addition, it is used to ascertain whether internal relationships between the variables are consistent with the definition of the construct to be measured and the intended structure of the instrument. Exploratory or confirmatory factor analyses are usually used methods for the evaluation of construct validity [18, 19].

4.3 Criterion Validity

Criterion validity refers to the degree of association between the scores of a measurement instrument and a specific criterion, which can be measured by the correlation coefficient between the score of a measurement and a widely accepted measure of the same characteristics [20]. There are two types of criterion validity, including concurrent validity and predictive validity. Concurrent validity reflects the association between the new instrument and the current criterion. Predictive validity refers to the association between the new instrument and the future criterion (a criterion that is measured later), which reflects the accuracy of an instrument in predicting the individual's future performances. The more accurate an instrument predicts, the higher the predictive validity is.

4.4 Assessment of Discriminant and Convergent Validity

Discriminant validity means that the measurements of an instrument should be significantly less correlated with those of conceptually unrelated instruments than other measurements of that instrument [21]. Convergent validity refers to the degree of similarity of the results obtained when using different instruments to measure the same characteristics or conception. There should be a high correlation between two or more instruments of the same characteristics.

The discriminant validity and convergent validity are usually evaluated by the multi-trait-multi-method (M-M) proposed by Campbell and Fiske [22]. The M-M method requires multiple (at least two) instruments to measure multiple (more than two) characteristics, respectively, so that the correlation coefficient between the scores of any two instruments of the same characteristics and the correlation coefficient between the scores of any two different characteristics of the same instrument can be calculated. However, M-M analysis is relatively complex, it is not widely used in practice.

5 Conclusions

Health questionnaires and scales are important instruments in evaluating reversible damage to the health, which could not be measured directly. They have become a routine instrument for assessing subjective health complaints. A well-established health questionnaire is important for predictive, preventive and personalised medicine. Reliability and validity are important and fundamental aspects of health questionnaires and scales.Declarations of InterestNone.

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Leveraging Supervised Machine Learning for Determining the Link between Suboptimal Health Status and the Prognosis of Chronic Diseases

Eric Adua, Ebenezer Afrifa-Yamoah, and Emmanuel Awuni Kolog

Abbreviations

AI	Artificial intelligence
ANN	Artificial neural network
BMI	Body mass index
DT	Decision tree
HbA1c	Glycated haemoglobin
KNN	*k*-neural neighbour
ML	Machine learning
NB	Naïve Bayes
PCA	Principal component analysis
PPPM	Predictive, preventive and personalized medicine
RF	Random Forest
ROC	Receiver operating characteristic
SHS	Suboptimal Health Status

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SHSQ-25	Suboptimal Health Status Questionnaire-25
SVM	Support vector machine
T2DM	Type II diabetes mellitus
TC	Total cholesterol

1 Background

Advances in medical and health science research have informed a paradigm shift from reactive medicine to proactive approaches that personalise the prevention, stratification, diagnosis and treatment of a specific patient [1, 2]. This concept herein referred to as predictive, preventive and personalised medicine (PPPM) recognises individuals who are at risk of developing diseases by collecting and analysing large amounts of data including lifestyle, demographic, anthropometric and family history amongst others [3, 4]. With such information, tailored treatment can be administered to actualise optimal health outcomes for an individual. Moreover, PPPM is essential to allow the distinction between patients who are likely to respond to therapy, from those who would not and those likely to experience major side effects. Yet, the full potential of PPPM has not been realised as people have latent and varied subclinical presentations that are often missed. Suboptimal health status (SHS) is a concept that captures individuals with subclinical conditions and earmark them for treatment [2, 5]. Introduced in 2009, SHS identifies individuals who feel unwell, but their conditions cannot classify them as diseased. The concept is premised on the fact that the deterioration of health begins at least 30 years prior, with noticeable symptoms that range from general body weakness and vitality to loss of appetite, insomnia and recurring cold. Over time, these mild conditions progress into increased heart rate, weight gain, raised blood pressure and elevated plasma glucose until they worsen into cardiovascular diseases, metabolic syndrome [6], type II diabetes mellitus (T2DM) [6, 7], dyslipidaemia, amongst others. SHS is determined using validated subjective instrument, SHSQ-25 [4] that measures the health status of individuals from five domains including the immune system, cardiovascular, digestive, fatigue and mental system [5, 8, 9]. When combined with objective clinical makers, the link between SHS and diseases can be established (Fig. 1).

The implementation of PPPM requires massive research investment and innovations in biomedical, and social sciences, and health economics that inform the provision of equitable access to healthcare at the individual or population level. When implementing PPPM, it is important to consider the type of population and geographical location [10]. This is because, population subgroups have different genomic and environmental make-ups, which may affect their responses to therapy. For example, the implementation strategies for Africans, Caucasians and Asians are likely to differ because of the variations of climatic, demographic and socio-economic status. There is a need to perform analysis and construct models that contextually suit specific populations. Moreover, implementation based on biomarkers poses a formidable challenge because biomarkers change in response to

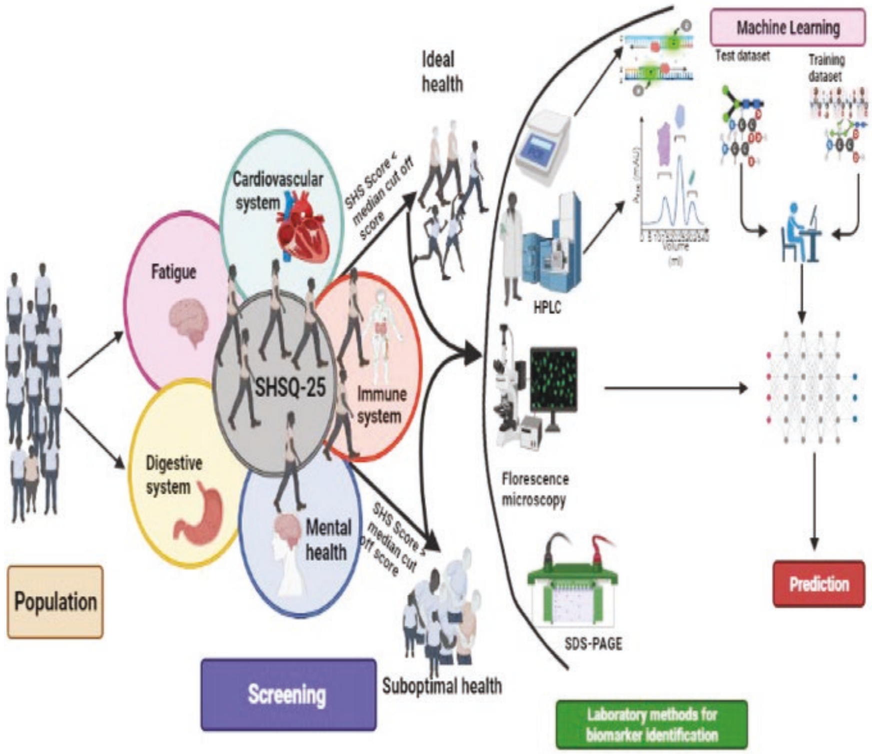

Fig. 1 The recognition of persons with suboptimal health status begins with screening with SHSQ-25. Responses are rated and individuals who score above a median cut-off value are classified as suboptimal health whereas those with scores below the median cut-off value have ideal health. Both groups undergo further testing, using analytical/molecular biology techniques to establish diagnosis and identify biomarkers. ML can transform data into clinically useful information, while enabling better health planning, assessment, management, disease forecasting and characterisation of disease risk

genetic, epigenetic and environmental perturbations. Thus, there is no one-size-fits-all approach for implementing PPPM. Furthermore, implementation of the PPPM requires a simultaneous application of public policy, legal ethics, medicine and science [10].

The SHSQ-25 can be central to PPPM implementation, as its application is seen worldwide. Among Ghanaians, SHS was linked with T2DM [3]. Yan et al. [5] associated SHS with cardiovascular risk factors in 2012 in a Chinese population, which was also confirmed by Wang et al. [11]. Moreover, SHS was associated with psychological syndromes such as depression and anxiety among Chinese nurses [12]. Hou et al. [13] also confirmed that SHS was associated with psychological symptoms such as interpersonal sensitivity, depression, obsessive-compulsive, sleep and diet problems and somatisation.

Anto et al. [8] indicated that SHS could lead to pre-eclampsia and oxidative stress [14] in Ghanaian pregnant women. Kupaev et al. [9] established an association of SHS and endothelial dysfunction in a Russian population. Sun et al. [15] also revealed that altered intestinal microbiota was associated with SHS. The ability to detect association between SHS and disease states has been possible because of technologies that allow the precise quantification of biomarkers and statistical methods that transform generated data into meaningful information (Fig. 1).

Univariate analysis (such as ANOVA and *t*-tests), traditional multivariate analysis, logistic regression and cox-regression approaches are only a few of the statistical techniques that have already been published [16] (Table 1). These techniques have uncovered biomarkers associated with illnesses, but their biological interactions are not made immediately apparent. This is partially due to the daunting challenges posed by the 'big data' produced by analytical technologies, which have

Table 1 Related studies on suboptimal health status

Population	Analytical tool	Statistical method	Biomarker measured
Chinese [17] Sample size 3635	Automatic clinical analyser	ANOVA, multivariable logistic regression, chi-square tests	BMI, BP, FPG TC, TG LDL-c, HDL-c
Ghanaians [3] Sample size 505	Cobas Integra chemistry analyser	Kolmogov–Smirnov test, linear regression and multiple logistic regression, ANOVA, Chi-Square	BMI, BP, FPG TC, TG, LDL-c and HDL-c, non-HDL-c, HbA1c
Ghanaians [8] Sample size 262	Cobas Integra chemistry analyser, haematology analyser	Kolmogov–Smirnov and multiple logistic regression, ANOVA, Chi-square	BMI, BP, FPG TC, TG, LDL-c and HDL-c, HbA1c, GGT, ALB, UA, Mg, Ca, Cl, K, LDH, ALP, Na, Urea, creatinine, AST, ALT
Russians [9] Sample size 459	Brachial plethysmography	Student's *t*-test, multiple linear regression, cluster analysis	BMI, BP, FPG TC, TG LDL-c and HDL-c
Chinese [5] Sample size 4881	Automatic clinical analyser radioimmunoassay	Univariate, multivariate analysis	BMI, BP, FPG TC, TG LDL-c and HDL-c, cortisol
Chinese Sample size 30	Agilent 2100 Bioanalyzer	Student/Mann–Whitney *U* test, Shapiro–Wilk test, Benjamini–Hochberg method, multivariate binary logistic regression	GJA1, TWIST2, KRT1, TUBB3, AMHR2, BMP10, MT3, BMPER, NTM and TMEM98
Chinese [18] Sample size 386	Radioimmunoassay, qPCR, capillary gel electrophoresis	Pearson's correlation analysis, multiple linear regression analysis, general linear model	Cortisol, mRNA

hampered the capacity of conventional statistical methodologies to thoroughly examine the data. These include, amongst others, over-fitting, curse of dimensionality, Simpson's paradox and multicollinearity [16, 19]. The limitations of the traditional statistical methods [20, 21] have ignited the need for more robust and advanced models from computational data analytical methods, such as machine learning (ML). The present study provides an overview of the ML process and algorithms and provides insights on their application in subclinical disease prediction based on SHSQ-25 data.

Machine learning (ML) has advanced the traditional approaches of artificial intelligence (AI) by capitalising on historical data to empower machines to make inform decisions. ML is defined as an application of algorithms that provides systems with the ability to automatically learn and improve from experience without being explicitly programmed [22]. The primary aim is to allow computers to learn automatically without or with minimal human intervention or assistance and adjust actions accordingly. The process of learning begins with observations or data, such as direct experience or instruction, to look for patterns in data and make better decisions in the future. The approach has widely been used to improve the landscape of data analysis and inference in many sectors, including health and medicine. Within the context of medicine,

ML can be used to transform medical data into clinically useful information, while enabling better health planning, assessment, management, disease forecasting and characterisation of disease risk. The application of ML in disease prediction has been mainly based on genotype data, which are generally expensive and time-consuming to collect and process. For instance, fasting plasma glucose, serum lipids, such as, total cholesterol, triglycerides, low-density lipoprotein cholesterols, resting pulse rate and high-density lipoprotein cholesterols have been identified as significant correlates for a range of cardiometabolic conditions. We hypothesise that suboptimal health status monitoring via SHSQ-25 could provide opportunity to gather worth of longitudinal data at a relatively cheaper cost, whose exploration could potentially confirm the SHSQ-25 as a 'pseudo' biomarker for cardiometabolic disease. However, the potential of ML methods to determine the trajectory from SHS to chronic diseases has not been previously investigated. Data-driven ML algorithms have improved disease prediction but there is limited evidence of their application in subclinical disease prediction. Recognition of SHS, prior to a cardiometabolic disease, is another area that ML can be leveraged. It can enable the identification of molecular intricacies that underpin the link between suboptimal health and metabolic disease.

ML can generally be classified into four: unsupervised, semi-supervised, supervised and reinforcement learning. For this study, we focused on supervised learning, as we presume that the ensuing SHSQ-25 datasets would be labelled, giving investigators some level of oversight in the implementation of the ML algorithms. Thus, the subsequent section delves deeper into the various supervised ML techniques for disease prediction (Fig. 2).

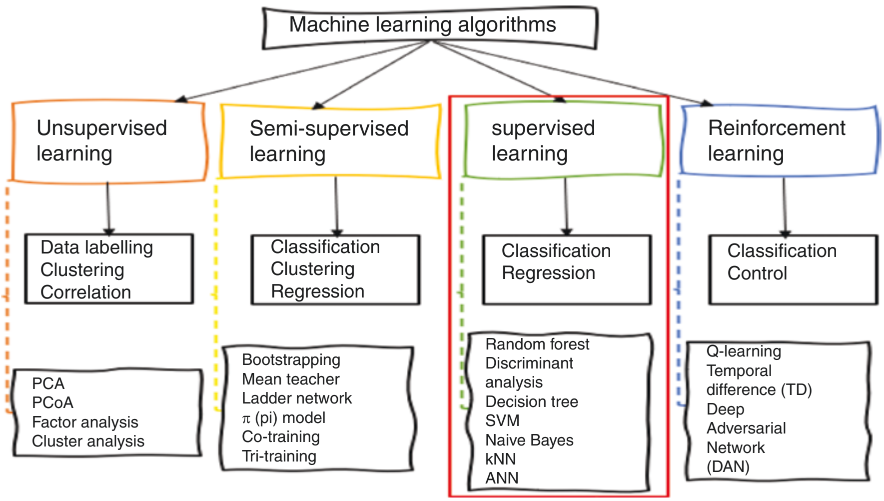

Fig. 2 Machine learning algorithms in brief: Types of machine learning algorithm, application and various types of techniques that fall under each type. *PCA* principal component analysis, *PCoA* principal coordinate analysis, *SVM* support vector machine, *kNN* *k*-nearest neighbour, *ANN* artificial neural network

2 Machine Learning Process

In this section, we describe the various categories of ML-based techniques by providing a systematic evaluation of their applications in disease prediction. For example, while each of the ML approaches has its own process, data preparation is a characteristic associated with all of them.

2.1 Data Sources and Preparation

Data from SHS and cardio-metabolic diseases are often generated in the health institutions and archive for possible exploration. In many cases, data can primarily be collected from the field depending on the intended purpose of the data. The type of data from SHS is numerical in nature. These data are usually managed structurally and archived in data warehouse. To pipeline data for classification and other ML techniques, it must be first pre-processed to improve the quality of the data. The accuracy of a predictive model largely depends on the quality of the data.

2.2 Feature Engineering

Feature engineering is the process of using domain knowledge to extract features from raw data. It forms one of the most important components of the ML pipeline. A robust predictive model does not only require clean and quality data but also the selection of features with high predictive strengths. The issues of curse of dimensionality and overfitting make this process very important in building models for prediction purposes. When there are several variables involved, it is necessary to target the most informative predictors. The technique can also be used to rank features based on their relevance. For example, Adua et al. [23] employed recursive feature elimination technique to rank predictive features of diabetes. In their study, glycated haemoglobin (HbA1c), total cholesterol (TC) and body mass index (BMI) were found as the most important features for predicting T2DM.

Feature selection methods are categorised according to filter methods, wrapper methods and embedded methods. The filter method applies a statistical measure to assign a score to each feature. Examples are the Chi-squared test, information gain and correlation coefficient. The wrapper feature selection methods consider the selection of a set of features as a search problem, where different combinations are prepared, evaluated and compared with other combinations. Examples are the use of feature elimination techniques and principal component analysis (PCA). Predominantly, PCA has been widely used to select features for ML. The embedded methods, on the other hand, learn which feature contributes to the best performance in the process of model building. Examples include elastic net, lasso and ridge regression.

SHS individuals generally suffer from a myriad of complaints including lethargy, physical exhaustion and mental fatigue. Association rules can be used to determine how the five health domains in the SHSQ-25 are connected. Subsequently, we can discover the relationships between SHS domains and clinical biomarkers of cardiometabolic health. For example, depending on how individuals rate their health status in each of the health domains, risk factors can be derived. In turn, the combination of variables or factors that lead to suboptimal health can be detected. We may detect that high SHS who frequently rate a question like "*How often were you bothered by heart palpitations?* (Subjective data) as 5 on the Likert scale also have raised blood pressure (objective data), and they can be said to be associated with each other. In addition, an improved version, called survival association rule mining that considers possible confounders and can be used to determine the interaction or interconnections between risk factors for high SHS and cardiometabolic disease. Undertaking these activities paves way for feature selection based on the SHSQ-25.

2.3 Supervised Learning

Supervised ML techniques have been widely used in the identification of clinical biomarkers for cardio-metabolic diseases. These techniques do lend themselves as suitable in studying the links between health status and cardio-metabolic diseases. Supervised learning aims at mapping input data to output data, thus, the input data (x) are tagged with the output (y) data, which yields a function $y = f(x)$. In supervised learning, a set of predictors is inputted and used to predict an outcome. For example, the ordinary least squares regression predicts an outcome based on the linear relationship between a continuous dependent variable and independent variables [24]. Broadly, supervised learning involves classification and regression processes. Hypothetically, clinical markers of patients could be used and mapped to their corresponding suboptimal health and cardio-metabolic health status. Such predictive models can be explored by training a supervised learning algorithm with labelled data.

2.3.1 Classification

Some supervised learning models, such as logistic regression are built for the classification purpose of predicting the response class based on some target attributes. Unlike traditional programming scenarios, both input and output (expected) variables/attributes are given to ML algorithms to learn. This implies that all instances of the input data (attributes) are given labels or come with its labels. Assume a diabetic dataset D, containing m instances/observations, where $x < m$ is explanatory attributes and $y < m$ categorical target attribute (diabetes status), for building a model such that $x + y = m$. The x attributes, also called predictive variables, may be numerical and/or categorical while the target attribute, y has class labels. The goal of the classification is to maximise the predictive relations of the function $y = f(x)$. Figure 3 shows a typical ML classification pipeline. The dataset undergoes a data preparation stage by cleaning. The cleaned data is scaled to ensure standardisation of the data attributes, thereby avoiding any possible estimation bias. Important features from the data are extracted to increase the strength of prediction. Training an ML algorithm requires efficient techniques. Among existing techniques for training an ML algorithm, test/train and cross-validation techniques are the most widely used. The test/train technique requires dividing the dataset into two where one part of the data is used for training while the remaining data is used for testing or validating the algorithm (classifiers). Often, the test data ranges from 10% to 30% while the training data ranges from 70% to 90%.

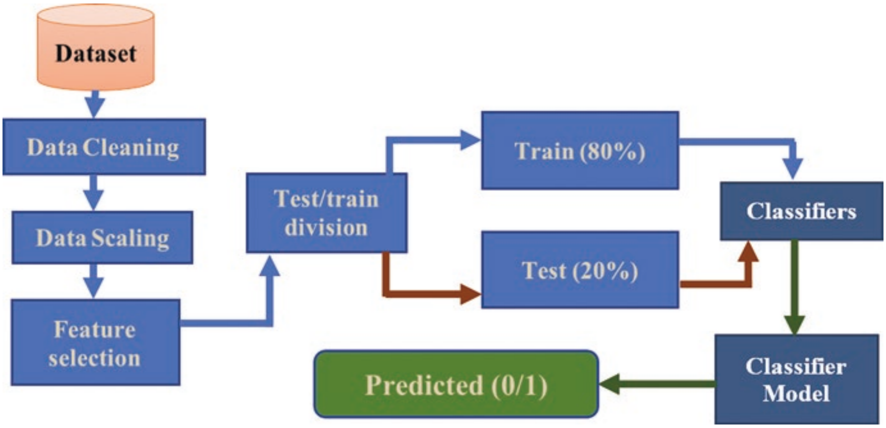

Fig. 3 Workflow of data classification process. A classification model where 1 represents suboptimal health and 0 is ideal health. Cleaning, scaling, feature selection, test/train validation, classifier model development and evaluation are among the steps in the process model

ML algorithms can suffer from overfitting issues, where the analysis or patterns produced are based on a subset of the data rather than being representative of the general dataset. Hence, the predicted outcomes may not be reliable. To mitigate this risk, cross-validation, such as leave-one-out and *k*-fold, is performed. In cross-validation, a random fraction, or a control dataset algorithm with known outcome (disease or no disease) is trained ("training set"), and the trained algorithm is then tested on the "test set" (validation set). The overall performance is then determined using the test sample [24]. The procedure has a single parameter, *k* that refers to the number of groups that a given data sample is to be split into. As such, the procedure is often called *k*-fold cross-validation. The widely used approach is the ten-fold cross-validation. There are various algorithms used in classification. These algorithms are also referred to as classifiers. Notable and most widely used classification algorithms are described as follows:

Random Forest

Random Forest (RF) comprises multiple regression trees with nodes at its base that resemble a forest and can be used for both classification and prediction purposes. A subset of the attributes is selected or evaluated at each split and trained separately on another dataset. The prediction is based on the mean of all trees under consideration. RF has been reported to be robust and computationally efficient because it selects complex and strong learners with low bias to reduce variance and error rates [25]. It ranks variables according to their importance. Random forest applies the Gini index that measures the frequency at which wrongly labelled element is chosen

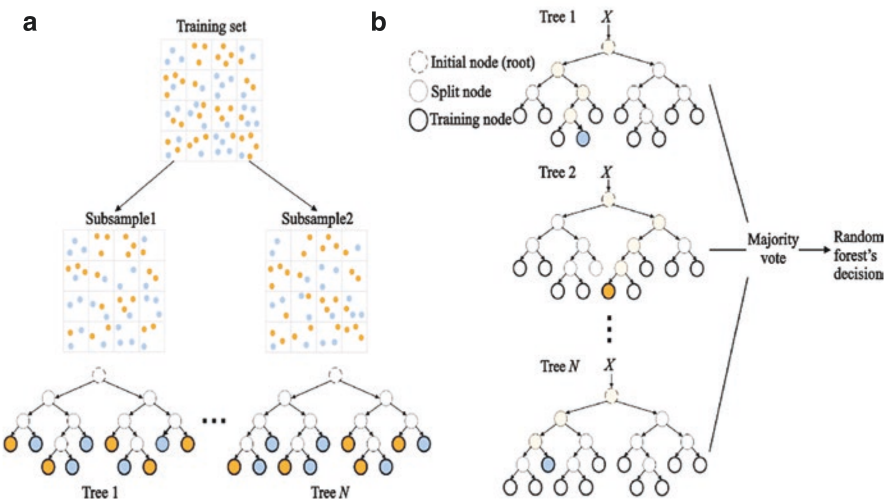

Fig. 4 Illustration of random forest model for training and classification processes. (**a**) *Training process*: A random bootstrap is used to build each decision tree in the ensemble from the original data, which contains positive (orange labels) and negative (blue labels) outcomes. (**b**) *Classification process*: A majority voting procedure is used for the class prediction among all individual trees. For each new data point (i.e., X) in each tree, the algorithm starts at the root node of a decision tree and traverses down the tree testing the variables' values in each of the visited split nodes, to decide the next branch to follow. This process is repeated until a leaf node is reached, which assigns a class. At the end of the process, each tree casts a vote for the preferred class label, and the mode of the outputs is chosen as the final prediction [26]

by chance in dataset (Fig. 4). In calculating this index, the probability of each class is summed up and subtracted from 1. This way, predictive power is enhanced while potential biases from decision tree (DT) on a system are removed [27]. Moreover, RF is appropriate for non-linear models and ideal for small datasets. However, analysing with RF can be time-consuming and may be subject to overfitting [28].

Decision Tree

Decision Tree (DT) is a tree-like structure comprising an internal node, root nodes and leaf nodes that form a hierarchy. The internal node stands for a test attribute, the test output is the branch, and the leaf node is a category [29, 30]. Decisions about an outcome variable are made in a hierarchical and sequential manner. Comparison of attributes is from the root to the leaves, and entropy assesses decisions at each internal node [27, 31]. Although the accuracy of prediction by DT may be affected by an overlap problem, its output is easy to visualise and interpret [28, 32].

Naïve Bayes

Naïve Bayes (NB) uses Bayes rules, and it is based on conditional probability that assumes that all features are unrelated and independent of each other. For a given outcome variable, Y and predictors, X, with realizations y_i and x_j respectively, the Bayes theorem is defined as:

$$(\forall i, j) P\left(Y = y_i \mid X = x_j\right) = \frac{P\left(X = x_j \mid Y = y_i\right)\left(P\left(Y = y_i\right)\right.}{\sum_k P\left(X = x_j \mid Y = y_k\right)\left(P\left(Y = y_k\right)\right.} \tag{1}$$

Naïve Bayes assumes conditional dependency between X and Y, defined as:

$$P\left(X_1, \cdots, X_n \mid Y\right) = \prod_i P\left(X_i \mid Y\right) \tag{2}$$

Prediction on Y is made based on the posterior distribution.

$$P\left(Y = y_k \mid X_1, \cdots, X_n\right) = \frac{P\left(Y = y_k\right) \prod_i P\left(X_i \mid Y = y_k\right)}{\sum_j P\left(Y = y_j\right) \prod_i P\left(X_i \mid Y = y_j\right)} \tag{3}$$

Decisions are made considering all possible information that reflects the way prognostic and diagnostic decisions are made by clinicians [33]. A posterior probability $P(Y = y_k| X_1, \cdots, X_n)$ of each class y given an object x is estimated from data after which further decisions are made based on the estimates. NB has been shown to be simple but computationally efficient, has low variance and is insensitive to noise and missing values in training data [34]. However, it is prone to skewed probabilities [28].

Support-Vector Machine (SVM)

In this algorithm, datasets are represented as points with the number of features in a dimensional space and classes are separated by vectors. A hyperplane, which must be at the utmost of the margin, separates the datasets into various sorts. SVM achieves robustness when the hyperplane's margin is high and the distance between each class and the nearest data point is maximised. SVM has been applied in handwriting interpretation, text and facial recognition. It is ideal for detecting both linear and non-linear relationships in variables even for small datasets but not favourable for multi-class classification problems and large datasets [28]. The objective of SVM algorithm is to maximise the margin between the data points and the hyperplane (Fig. 5), using the hinge loss function [35]. For a given observed outcome and predictor variables, y_i and x_j, respectively, a zero cost is observed when predicted

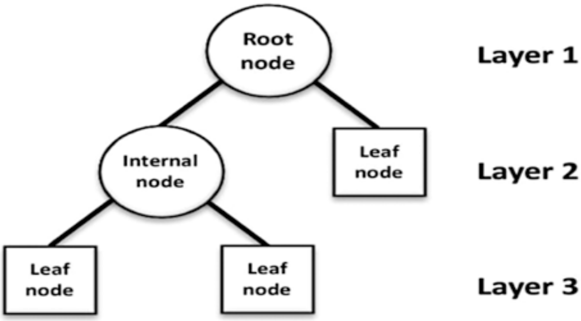

Fig. 5 Illustration of the decision tree's basic structure with three distinct hierarchical layers

value and the actual value have the same sign, otherwise a loss value is calculated incorporating appropriate regularization parameter expressed as:

$$\min_{w} \lambda w^2 + \sum_{n}^{i=1} \left(1 - y_i x_i, w\right)_+ \tag{4}$$

where w denotes the weights of the loss function. To find the gradient of the loss function, a partial derivative with respect to the weights is calculated, which can result in an iterative routine where the weights of our loss function can be updated as follows:

$$\frac{\delta}{\delta w_k} \lambda w^2 = 2\lambda w_k \tag{5}$$

$$\frac{\delta}{\delta w_k} \left(1 - y_i x_i, w\right)_+ = \{ \begin{matrix} 0, & \text{if } y_i x_i, w \geq 1 \\ -y_i x_{ik}, & \text{else} \end{matrix} \tag{6}$$

If the model predicts the class of the data point correctly, the gradient is updated from the regularization parameter as follows:

$$w = w - \alpha \cdot \left(2\lambda w\right) \tag{7}$$

otherwise

$$w = w + \alpha \cdot \left(y_i \cdot x_i - 2\lambda w\right) \tag{8}$$

The illustration in Fig. 6 presents the pictorial representation of the optimization outcome of the SVM algorithm for data classification.

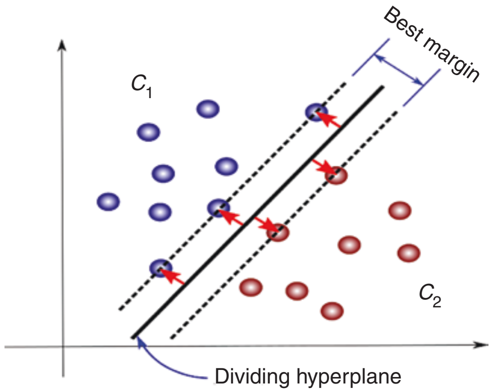

Fig. 6 SVM classification on datapoints in high dimensional vector space

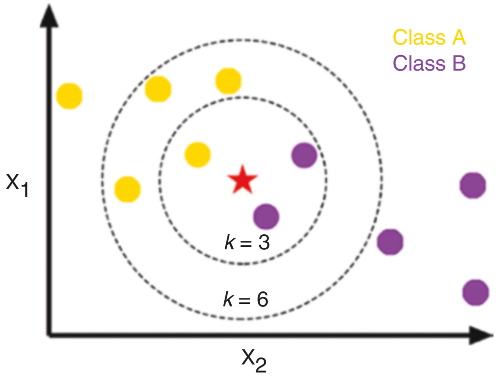

Fig. 7 *K*-Nearest neighbour classification on datapoints

K-Nearest Neighbour (KNN)

New objects are classified following data training and nearest neighbours to *K* forms the basis for classifying data. This is a memory-based classification that does not require a model [29]. Here, the minimum distance between the newly classified data and the *K*-nearest neighbours' Euclidean distance is calculated as follows:

$$d\left(x_i, x_j\right) = \sqrt{\left(x_{i1} - x_{j1}\right)^2 + \left(x_{i2} - x_{j2}\right)^2 + \ldots + \left(x_{ip} - x_{jp}\right)^{2.}} \tag{9}$$

The number of *k*-nearest neighbours obtained is used to predict the new data. In mathematical terms, x_i represents the input sample with p features (x_{i1}, x_{i2}, …, x_{ip}), n = total number of input samples ($i = 1, 2, \ldots, n$) and p the total number of features ($j = 1, 2, \ldots, p$). Euclidean distance and hamming distance are used for continuous and binary data, respectively [36]. KNN is useful for outlier detection, but interpretation of the results and the determination of the k can be challenging [28] (Fig. 7).

Artificial Neural Network (ANN)

ANN is a computational algorithm or classification method that mirrors the structure and function of neuronal cells in the human brain [37]. Here, nodes replace the neurons in the brain and are interconnected by weights that are automatically calculated during the training phase. It is made up of three entities. Information to be processed is received at the input unit; the results are displayed in the output unit and the hidden unit is sandwiched between the input and the output units. The input–output mapping can be determined after the network is trained on the dataset [38, 39]. This is followed by fixing the connections between the neurons and the classification of the new data is determined by the network. The output is the sum of the product of all the input layers and their associated weights through an activation function. The activation function in neurons of the hidden layer is often the same for those in the output layer [38]. The advantages of ANN include the ease of detection of relationship between variables, ease of visualisation and can be applied for non-linear modelling. However, it can be time-consuming and prone to overfitting [28].

Given a set of inputs ($x_1.x_2$, x_3), output (Y) and the corresponding synaptic weights (w_1, w_2, w_3) as shown in Fig. 8, the outputs in the network, either to the hidden layer or to the output layer, is defined by the activation function. An activation function controls the amplitude of the output. For example, an acceptable range of output is

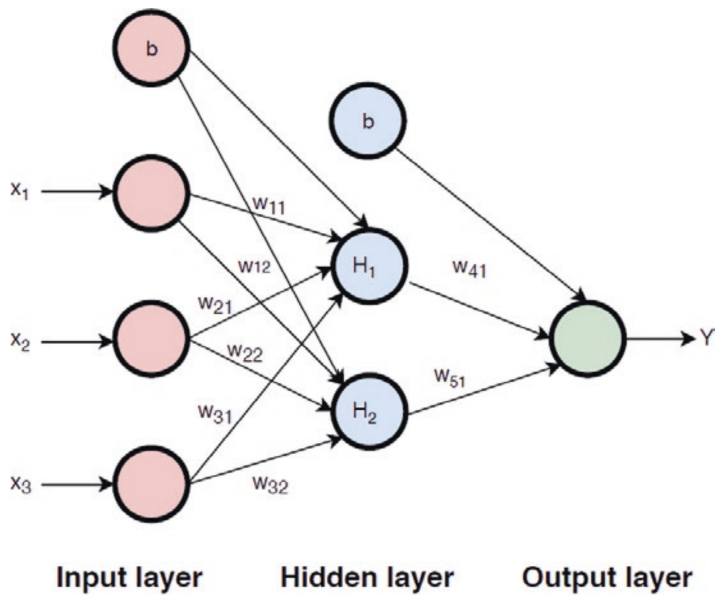

Fig. 8 Structure of an ANN for classification of suboptimal health status. It shows a three-layered feed-forward ANN with the hidden layer connected to the output layer via a connection weight and the input layer connected to both by a connection weight

usually between 0 and 1, or it could be −1 and 1. To deduce the output, then mapping function of the input and output data is given in Eq. (10):

$$Y = f(x) \tag{10}$$

From Fig. 8, the output for the hidden functions, shown in Eq. (11), are simplified in Eqs. 12 and 13, where *b* is bias or error.

$$\text{Hidden layers}(H1, H2) = \begin{bmatrix} w_{11} & w_{21} & w_{31} \\ w_{12} & w_{22} & w_{32} \end{bmatrix} \times \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} \tag{11}$$

$$H_1 = x_1 \cdot w_{11} + x_2 \cdot w_{21} + x_3 \cdot w_{31} + b \tag{12}$$

$$H_2 = x_1 \cdot w_{12} + x_2 \cdot w_{22} + x_3 \cdot w_{32} + b \tag{13}$$

Sigmoid function (*S*) given in Eq. 14, where *x* is an input variable and *e* is a mathematical exponent:

$$S(x) = \frac{1}{1 + e^{-x}} \tag{14}$$

Applying sigmoid function to the hidden layers in Eqs. 12 and 13:

$$H_1 = S(x_1 \cdot w_{11} + x_2 \cdot w_{21} + \cdot w_{31} + b) \tag{15}$$

$$H_2 = S(x_1 \cdot w_{12} + x_2 \cdot w_{22} + x_3 \cdot w_{32} + b) \tag{16}$$

From the hidden to the output nodes, with feed-forward algorithm, the final output by using sigmoid function is given in Eq. 17:

$$Y(\text{output}) = S(H_1 \cdot w_{41} + H_2 \cdot w_{51} + b) \tag{17}$$

2.4 Evaluation of Supervised Learning Models

Building a reliable model with a supervised learning technique requires a robust ML algorithm. ML models are expected to predict unseen data with a high level of performance. Thus, there is the need for ML models to be evaluated thereby ascertaining their efficacy in predicting unseen data such as data from optimal health status and cardio-metabolic diseases. ML models with high predictive relevance and accuracy levels are suitable for predicting unseen data, especially when it is concerned with predicting disease. Researchers often build models with competing ML algorithms and use various performance measures to select the best model. In the subsequent subsections, we discuss some existing ML performance measures. To improve the performance of the model, ensemble techniques have been developed to boost the accuracy of the training dataset. The most widely used ensemble for ML are Boosting, Bagging and Majority voting. The commonly used matrices for evaluating machine learning algorithms include classification accuracy (including Recall, Precision, F-Measure and Confusion Matrix), area under ROC curve, logarithmic loss, confusion matrix and root mean square error.

2.4.1 Recall, Precision, F-Measure and Confusion Matrix

Recall, Precision and F-Measure are widely used for evaluating the performance of ML algorithms. Precision estimates the number of positive class predictions that belong to the positive class. In Eq. (18), TP is true positive, and FP is false positive.

$$\text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FP}} \tag{18}$$

Recall quantifies the number of positive class predictions made from all positive examples in the dataset. It can also be described as the proportion of the data that an ML algorithm identifies. The Recall is represented in Eq. (19). In Eq. 19, TP is true positive, FN is false negative:

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{19}$$

F-Measure is the harmonic mean of the recall and F-measure. It is a representation of both the recall and Precision. Researchers often report and discuss the *F*-measure towards efficacy of machine learning algorithms because it offers the balance between the Precision and Recall.

$$F - \text{measure} = 2 \times \frac{\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \tag{20}$$

Confusion Matrix is a matrix that summarizes the prediction results of classification by taken. The results show the extent to which a classification model is confused. It gives insight not only into the errors being made by the classifier but more importantly the types of errors that are being made. Tables 2 and 3 are confusion matrices.

2.4.2 Receiver Operating Characteristics Curve (ROC)

Area under the curve-Receiver operating characteristics (AUC-ROC) is a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied. The curve serves as a performance indicator for

Table 2 Confusion matrix showing a recall

		Predicted	
		Negative	**Positive**
Actual	**Negative**	True Negative	False Positive
	Positive	False Negative	True Positive

True Positive + False Positive = Total Predicted Positive

Table 3 Confusion matrix showing precision

		Predicted	
		Negative	**Positive**
Actual	**Negative**	True Negative	False Positive
	Positive	False Negative	True Positive

True Positive + False Negative = Actual Positive

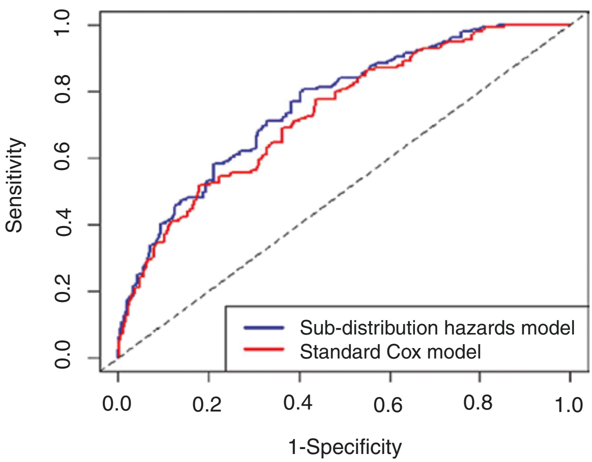

Fig. 9 ROC curves for diabetes risk prediction model showing sub-distribution hazards model and Standard Cox model. A study conducted on competing risk-based score for predicting twenty-year risk of incident diabetes in Beijing based on a Longitudinal Study of Ageing study [40]

categorisation issues at different threshold levels. AUC highlights the degree or measurement of separability, and ROC is a probability curve. It indicates the degree of class distinction the model is capable of. The model's accuracy in classifying 0 as 0 and 1 as 1 increases with the AUC score. Accordingly, the higher the AUC, the better the model's ability to differentiate between diseased and healthy people. In AUC-ROC, true positive rate (sensitivity) is plotted against the false positive rate (specificity). Figure 9 is an example of AUC-ROC showing sub-distribution hazards model and Standard Cox model. As indicated on the graph, the sensitivity is plotted at the *y*-axis against the specificity at the *x*-axis.

3 Unravelling the Link Between Suboptimal Health and Chronic Diseases Using Machine Learning

SHSQ-25 questionnaire is a diagnostic algorithm, which comprises 25 items that multidimensionally capture health constructs of individuals from five health domains: immune system (3 items), mental health (7 items), fatigue (9 items), digestive system (3 items) and cardiovascular system (3 items) (Fig. 1). Participants rate how they feel in the previous 3 months by providing the following responses on a Likert type scale: (1) never or almost never, (2) occasionally, 3) often, (4) very often and (5) always. The discriminatory ability of the SHSQ-25 for diseased and non-diseased individuals has been reported for multiple chronic conditions [3, 4, 6, 8, 9, 14]. This screening is not only non-invasive, but it also provides a cheaper means of building a large database for an individual.

A lack of lifestyle modification of SHS may manifest as a life-threatening clinical condition in the future, with multiple studies already associating it with cardiometabolic diseases [3, 6], endothelial dysfunction [9], psychological stress [18] and digestive disorders [15]. Unfortunately, these studies have been cross-sectional, providing limited evidence to support the cause–effect relationships. Longitudinal studies will provide the opportunity for researchers to access big data that are scalable, and analysable to obtain more robust cause–effect outcomes that would inform effective and efficient practices. Thus far, the only study that has attempted to investigate the progression from SHS to a chronic disease was by Ge et al. [17]. In this study, authors analysed multiple clinical biomarkers and showed that SHS individuals developed T2DM in 3.1 years. Although the connection between SHS and T2DM was established, the period of investigation was short to concretise this link.

Serial SHS screening, conducted over an extended period will enable a comprehensive exploration of human health, while highlighting the interaction between multiple factors in disease progression. Indeed, each subscale of the SHSQ-25 represents an aspect of a person's health status, which could be explored in the disease continuum. For example, symptoms of fatigue may progress into myalgic encephalomyelitis/chronic fatigue syndrome, cardiovascular system domain may be indicative of heart diseases (e.g., cardiomyopathy, pericarditis, arrhythmia etc.), mental health complaints may indicate depression, schizophrenia, psychosis, complains in the digestion system can precede digestive disorders (gastroesophageal, reflux disease, ulcerative colitis amongst others) while immune system decline may result in coeliac disease, lupus, type 1 diabetes and rheumatoid arthritis. Each of these diseases are diagnosed based on the elevation or aberration of objective biomarkers (Fig. 10). When these biomarkers are matched with the responses on SHSQ-25, the path to and the pattern to developing chronic diseases can be revealed. This is where ML becomes valuable, as it can train models on database to understand patterns and relationships through a hierarchical learning process [22].

In ML applications, the SHS data observed longitudinally will enable the accurate generalisation of patterns for future unseen data. The diverse range of methods

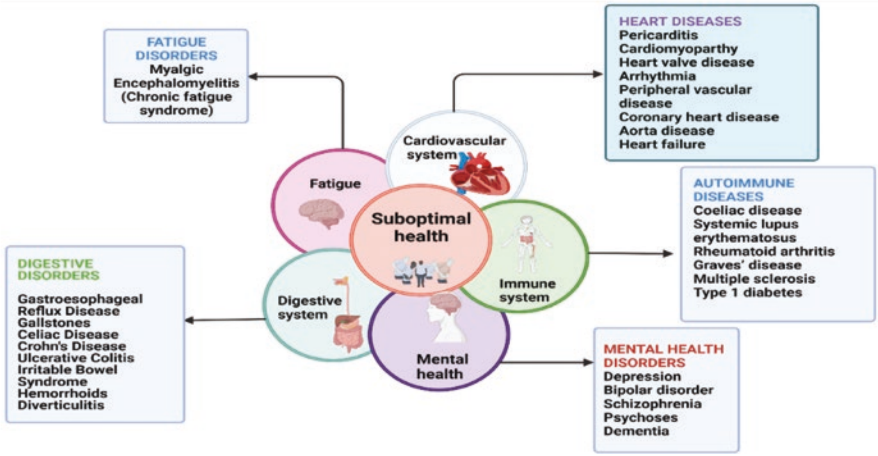

Fig. 10 The association between SHSQ-25 domains and chronic disease development. Longitudinal and repeated screening with the SHSQ-25 can reveal how each subscale correlates with chronic diseases. Poor ratings in each of the domains can be indicative of future cardiovascular, immune system, digestive, fatigue and mental disorders

in ML underpins its broad applications in classification, clustering, regression, features, and neural networks, depending on the type of the data system. For example, for a given data obtained from the administration of the SHS questionnaire over time, ANN can be applied to stimulate the working function of the five thematic connections of the scale, to achieve a massive parallel distributed process [41] that predicts likely chronic conditions. The process of chronic disease development and progression can be explained by the activations flowing through networks that link together nodes. In this process, new events will lead to changes in the strength of connections among relevant units in the database, by altering the connection weights for the nodes. Consequently, units in the database developing different chronic conditions are likely to respond based on their experiences. Most ML algorithms have adaptive-learning and fault-tolerance capabilities, making them highly suitable for pattern recognition applications, which is fundamental in the diagnosis of chronic conditions.

The integration of ML in suboptimal health studies is vital in the pursuit of PPPM, as confirmed chronic diseases among population in the database over time can be traced to the responses provided for the domains of SHSQ-25. This will offer opportunities to establish robust thresholds for the domains and their alignment to known chronic conditions. The thresholds will become standardized benchmarks for highlighting predisposed domains of SHSQ-25, to inform targeted lifestyle changes and healthcare to prevent and/or effectively manage chronic diseases. Targeted personalised lifestyle changes, such as diet and exercise [40], stimulate varying molecular pathways that can greatly influence the functioning of the human body in building resistance against chronic diseases. For example, diet and regular exercise have been identified as key regulating risk factors for T2DM, and interventions targeting these behaviours can help to prevent or postpone this disease [42, 43]. With the standardized benchmarks for the domains of SHSQ-25, patient-centred medicine will be promoted, ultimately complementing, and reducing the burden of care in our healthcare systems and institutions.

4 Outlook

Data-driven ML algorithms have improved chronic disease prediction [44, 45], but there is limited evidence of its application in subclinical disease prediction. Recognition of SHS, before chronic diseases, is another area in that ML can be leveraged. It can enable the identification of molecular intricacies that underpin the link between suboptimal health and metabolic disease. ML develops models from a dataset, cross-validate, test, and evaluate the models and detect the best correlative or associative features. Thus, ML can optimise the accuracy of predictive models for suboptimal health. The application of ML approaches on longitudinal data will be more valuable in the prediction of chronic diseases compared to approaches that rely on conventional risk factors and cross-sectional data [46]. Over time, confirmed chronic diseases among population in the database can be linked to the responses to the domains of SHSQ-25. This will provide opportunities to establish robust thresholds for the domains and their alignment to known chronic conditions.

ML learning encompasses supervised learning, semi-supervised learning, unsupervised learning, and reinforcement learning. These areas have attracted diverse interest depending on the type of knowledge and data within the health ecosystem. While we aim to explore all these areas in the health ecosystem in the future, this study only focused on the application of supervised learning in disease detection. We envision that this study will provide the needed foundation for practitioners who aim to establish the association between SHS and cardio-metabolic diseases.

5 Conclusion

One could argue that modern society takes medical knowledge and technological progress for granted. In this chapter, several ML algorithms including random forest, Naïve Bayes, *k*-neural network, and support vector machine have been discussed. ML can make it easier to analyse data of individuals and discover disease patterns that would support early detection of chronic diseases. In the context of PPPM, ML can pinpoint the intricate molecular processes that underlie the connection between poor health and cardiometabolic diseases, enabling accurate precision to be brought to medicine.

Author Contributions EA[1,2], EA-Y[3] and EA[4] conceived the study and wrote the manuscript. All authors edited the ideas and concepts presented. All authors read and approved the final manuscript.

Competing Interests Authors have no competing interest to declare.

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Integrative Approach to Investigate Suboptimal Health Status and Endothelial Dysfunction

Vitalii Kupaev, Madina Zhalbinova, and Wei Zhang

Abbreviations

BMI	Body mass index
DBP	Diastolic blood pressure
ET-1	Enddothelin-1
GLU	Plasma glucose
IEF	Index of the endothelial function
IR	Index of reflection at the baseline
IR2	Index of reflection of the second measure
IS	Stiffness index at the baseline
IS2	Stiffness index of the second measure
NO	Nitric oxide
PPPM/3 PM	Predictive, preventive, and personalised medicine
SBP	Systolic blood pressure
SHS	Suboptimal health status
SHSQ-25	Suboptimal health status-25 questionnaire
TCH	Total cholesterol

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1 Introduction

There have been many significant changes occurred in Russia in the past decades. The rapid economic growth and socio-demographic changes caused the increased risk for people to suffer from chronic diseases with increased morbidity and mortality [1]. The early detection of cardiovascular diseases at their preclinical status is one of the important parts in the promotion of the essential medical services at the primary healthcare setting. There has been a demand in screening the risks of the development of the chronic diseases, which should be cost-effective and time-efficient. For instance, the SHSQ-25 is a tool designed for screening the early stages of chronic diseases [2]. Initially, this method was developed and validated in a Chinese population [2]. SHSQ-25 gives a new opportunity for primary health workers to identify the risk factors that are associated with cardiovascular diseases [3].

SHS is characterised by the feelings of health complaints, chronic fatigue and complex of physical symptoms and lack of strength, a preclinical illness stage [3]. The previous studies showed that SHS has a significant contribution to the identification of the progression or development of the chronic disease among the people who have continued exposure to the risk factors [4]. The linear relationship between SHS and cardiovascular risk factors, as well as a decrease of cholesterol shows clear association of SHS with cardiovascular health [3].

The intervention of the pathological processes in patients with cardiovascular diseases is related to the assessment of their endothelium function. Endothelial dysfunction and vascular stiffness are the integral indicators, reflecting the structural function of vascular wall and blood pressure [5–7].

1.1 Endothelial Dysfunction

1.1.1 Current View of the Endothelial Dysfunction

The vascular endothelium carries on many important functions as it is an active receptor-effector organ with a dynamic structure. It releases substances during exposure to a chemical or physical stimulus. In normal case, vascular endothelium maintains vascular-tissue homeostasis and vasomotor balance [8–10].

Endothelial dysfunction could be considered as an imbalance between the production of the prothrombotic, vasoconstrictive and proliferative endothelial factors. The loss of homeostasis of angioprotective, antiproliferative and vasodilating factors occurs during endothelial dysfunction [11]. Progression of the vascular lesions is caused by the imbalance between vasoconstrictors and vasodilators, which forms vasospasm [12]. Thus, the endothelium is a selective barrier for the various substances that penetrate from the bloodstream into tissues. This is a central link in the regulation of vasomotor tone [13].

The most damaging element in the endothelium is the endothelial factor known as nitric oxide (NO). The basal release of NO from the vascular endothelium reduces the tone of the muscular arteries and the resistant vasculature [14]. NO is responsible for the vasodilative effect of the relaxing factor, which is secreted by the endothelium. A number of aminopeptidases and endothelins are produced when the vascular endothelium is damaged. Investigations show that the vasodilative effect of NO counteracts the vasoconstrictor effect of endothelins [15, 16].

Endothelins are a family of the biologically active peptides with a wide spectrum of the effects. They are one of the most important regulators of the functional conditions of the endothelium. Violations in systemic and regional hemodynamics are observed as a result of their vasoconstrictor action. Endothelin-1 is currently considered as a biomarker for assessing the severity of the coronary heart disease. The normal concentration of endothelin-1 in the healthy human blood plasma is 0.1–1 fmol/mL or undetectable at all. The half-life of the endothelin-1 is not more than 4–7 min. There are about 80–90% of the endothelin-1 inactivated during their passage through the lungs' blood vessels. It revealed that the level of endothelin-1 in the blood plasma is significantly higher in individuals at the initial stage of hypertension compared to healthy individuals [17]. Based on this, it is evident that endothelins play a role in the pathogenesis of cardiovascular disease during the early stages. Endothelial dysfunction is considered the primary triggering mechanism in the development of cardiovascular pathology [18, 19].

1.1.2 New Methods of Determination of Endothelial Dysfunction

Currently, mechanical properties of the arteries are being actively studied due to their high clinical and prognostic significance. Extensibility, compliance and rigidity are important determinants of the elastic properties of the vascular wall. Elongation is determined by the ratio of the compliance to the initial volume of the artery. Arterial stiffness is the value reciprocal to the tensile.

Non-invasive methods are widely recommended, for example, ultrasound examination of the vascular wall, magnetic resonance imaging, the method of volumetric sphygmography with the determination of PWV in the area from the brachial artery to the ankle, rheovasography of the forearm and laser Doppler flowmetry.

One of the most accessible methods for the determination of vascular stiffness is the method of computer photoplethysmography that estimates the shape of the peripheral pulse wave [20]. Registration of the peripheral pulse wave is based on the passage of the infrared radiation through the finger vessels. The amount of the light is directly proportional to the volume of the blood pulsing in the finger. The pulse curve is recorded by photoplethysmography, which consists of two components: a direct wave that goes to the periphery and a vessel wave. Reflection index and stiffness index are determined. A clear parameter that measures vascular tone and allows assessing vascular endothelial function, calculated as the ratio of the amplitude of the diastolic and systolic peaks, is the reflection index (RI). Investigations revealed a correlation between the RI and vascular tone (diameter of the large vessels) [21].

In addition, the stiffness index (IS) is a measurement that associates with the pulse wave speed (in seconds). Furthermore, the index of the endothelial function (IEF) is the index value that reflects changes during reactive hyperemia at the third minute of the post-occlusive blood flow (RI-3 min) in comparison to the pre-test baseline measure. It is defined as the ratio of growth to the pulse wave's spread time from the lower part of the body to the finger. The advantage of the computed photoplethysmography is the availability of the method as the pulse wave of the finger could be obtained very easily. This fact makes possible the usage of this method in real-world population-based epidemiological health surveys.

The results were compared with the flow on the other arm. Furthermore, the following parameters of the photoplethysmogram were analysed: reflection index, stiffness index (IS) and the index of the endothelial function (IEF).

2 Comparison of the Correlation Between Vascular Endothelial Function Parameters with Indicators of Suboptimal Health Status and the Factors of Cardiovascular Risk

2.1 Investigation of Suboptimal Health Status in a Russian Population

The cross-sectional study was performed on 459 patients. Most of them were Russian residents aged 18–40 years (34.01 ± 14.; male 41.4%). Participants had no diseases and any prescribed treatments within the last 2 weeks. The study was conducted in the health centers at the medical clinics in Samara city with a population of more than one million. We used SHSQ-25 to assess SHS, along with family history, sedentary lifestyle, smoking, alcohol consumption and unhealthy diet. Specially trained doctors examined participants to ensure quality control of results. The study was approved by the scientific and ethical committees of Samara State Medical University and the medical institution of Samara region of the Russian Federation.

The arterial blood pressure was measured three times using standard methods. The average of the second and third measurements was used to estimate the systolic blood pressure (SBP) and diastolic blood pressure (DBP). Venous blood samples were obtained from the overnight fasting for the measurement of the plasma glucose and serum lipids. Plasma glucose, high-density lipoprotein, cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were measured using the enzyme-linked immunosorbent assay (ELISA), a commonly employed analytical biochemistry technique ("Biomedica," Austria). During the interview, our specialists measured the body weight and height of the participants two times.

Indicators of the arterial stiffness and endothelial dysfunction were determined using the standard method of the shoulder plethysmography technique "Eldar" [22].

The index of endothelial function (IEF) was determined in two stages, before and after the reactive hyperemia test. By occlusion of the brachial artery, reactive hyperemia was created. For occlusion, a cuff was used to measure blood pressure, which was applied at the level of the upper third of the shoulder, where pressure was gained above the systolic pressure by 30 mm Hg. This pressure was maintained for 5 min and then quickly vented. Then, a photoplethysmogram was recorded and analysed at the third minute of post-occlusive blood flow.

We used the SHSQ-25 for measurement of the SHS [2]. The SHS score was calculated for each participant by summarising the 25-item scores. The high score represented a high level of SHS (poor health). The total score of more than 35 points indicates a suboptimal condition that requires more examination according to five scales [23, 24].

2.2 Statistical Analysis

Continues variables were reported as mean ± standard deviation. Categorical variables were presented as frequency. Participants were divided into two groups: Group 1—healthy ($n = 295$), and Group 2—participants with risk factors of cardiovascular diseases ($n = 164$). Participants of Group 2 were with higher levels of blood pressure (>140/90 mmHg), glucose (>6.1 mmol/L), lipids (TCP > 5 mmol/L) and BMI (>24.5 kg/m^2). The difference of the SHSQ-25 scores between the two groups was performed by Student's *t*-test. According to the Pearson's correlation analysis and linear regression analysis, the relationship between SHS and endothelial dysfunction was identified by using the score of the SHSQ as dependent and endothelial dysfunction as independent. Cluster analysis was carried out to identify systemic patterns resulting from exposure to various risk factors. Subjects were identified as separate local subsets (clusters), according to the grouping attributes with k-means clustering. The statistical analysis was performed in SPSS program version 10.0.

2.3 Results

All participants completed a questionnaire, along with laboratory and instrumental measurements. Their mean age was 34.01 ± 14.10 years (males = 41.4%). The cardiovascular risk group was dominated by men (51.2%), older age (74.4% against) and labour workers (51.83%) (Table 1).

Although there was no statistically significant difference in the incidences of individuals with suboptimal health status between the healthy and cardiovascular risk groups (7.8% vs. 8.8%, $p > 0.05$), the SHSQ-25 scores showed differences between the two groups on three SHS subscales: (1) fatigue, (2) cardiovascular and 3) immune ($p < 0.05$). The largest discrepancy was concentrated in the cardiovascular and fatigue subscales. The average score of the cardiovascular system according

Table 1 Characteristics of the studied groups

Variables	Group 1 $n = 295$	Group 2 $n = 164$	χ^2	*P*
Gender				
Male	106 (35.9%)	84 (51.2%)	10.15	<0.01
Female	189 (64.1%)	80 (48.8%)		
Age				
18–40 years	256 (86.8%)	42 (25.6%)	173.19	<0.01
41–60 years	39 (13.2%)	122 (74.4%)		
Occupation				
Labour workers	28 (8.5%)	86 (51.83%)		
Office workers	267 (90.5%)	79 (48.17%)	103.16	<0.01
Suboptimal health status	23 (7.8%)	14 (8.8%)	0.029	>0.05

Note: *Group 1* healthy group, *Group 2* cardiovascular risk group

Table 2 Comparison of the cardiovascular risk factors between the healthy and cardiovascular risk groups

Variables	Group 1	Group 2	*t*	*P*
BMI (kg/m^2)	22.1 ± 4.2	28.55 ± 5.0	14.12	<0.001
Index smoker	1.66 ± 10.2	7.9 ± 15.5	4.801	<0.001
SBP (mmHg)	111.73 ± 12.7	129.5 ± 11.9	13.611	<0.001
DBP (mmHg)	73.86 ± 8.2	80.86 ± 8.3	8.803	<0.001
GLU (mmol/L)	4.03 ± 0.86	4.67 ± 0.96	6.403	<0.001
TCH (mmol/L)	4.28 ± 0.8	5.6 ± 0.96	6.441	<0.001
TG (mmol/L)	1.11 ± 0.57	1.56 ± 0.87	2.801	0.010
LDL (mmol/L)	2.85 ± 0.17	3.01 ± 0.37	2.562	0.006
Endothelin-1, (fmol/L)	2.3 ± 2.2	6.1 ± 5.42	3.3	<0.01

Note: Continuous variables are presented as mean ± SD; The statistical significance: $p < 0.05$
Abbreviations: *Group 1* healthy group, *Group 2* cardiovascular risk group, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *GLU* plasma glucose, *TCH* total cholesterol, *TG* triglyceride, *LDLC* low-density lipoprotein cholesterol

to the scale was 1.95 ± 1.81 in patients with cardiovascular risk, which is significantly higher than that in the control group ($p < 0.001$).

The group with risk factors for cardiovascular disease is presented in Table 2. Group 2 with cardiovascular risk had significantly higher levels of BMI, smoker index, SBP, DBP, GLU, TCH, TG, LDL and endothelin-1 ($p < 0.01$).

The method of computer photoplethysmography was used for assessment of the endothelial function. The higher the index of endothelial function (IEF), the less the exhibition of endothelial dysfunction. The endothelial function parameters are presented in Table 3.

Some important differences were revealed according to the index of the endothelial function by age: for people 41–50 years old, the index of endothelial function –(IEF) value was 9.4 ± 9.3%; for over 50 years old, IEF value was 6.4 ± 9.0% which were significantly lower than in people aged 18–40 years who had

Table 3 Index of endothelial function

Characteristics	IEF (%)	*t*	*P*
18–40 years	16.5 ± 8.4	4.97	0.0001
41–60 years	9.4 ± 9.3		
Males	14.3 ± 9.7	0.15	0.88
Females	14.5 ± 9.2		
Smokers	6.4 ± 8.1	−6.4	<0.0001
Non-smokers	15.1 ± 9.9		
Office workers	16.4 ± 9.5	−2.17	0.03
Labour workers	12.0 ± 9.0		
BMI < 25	16.6 ± 8.6	8.19	<0.0001
BMI ≥ 25	7.8 ± 9.6		

Note: Continuous variables are presented as mean ± SD; Significant *p* value: <0.05
Abbreviations: *BMI* body mass index

Table 4 Index of endothelial function in comparison groups

Groups	IEF (%)	IR (%)	IR-2 2 (%)	IS (m/s)	IS-2 m/s
Group 1- SHS < 14, *n* = 181	16.4 ± 8.6	68.1 ± 12.2	59.1 ± 11.3	11.3 ± 4.3	8.2 ± 4.1
Group 2- SHS ≥ 14, *n* = 146	6.6 ± 10.5	71.8 ± 12.4	63.3 ± 10.7	12.3 ± 8	9.3 ± 3.3
P	<0.0001	0.01	0.001	0.22	0.01

Notes: *IEF* index of endothelial function, *IR* index of reflection at the baseline, *IR2* index of reflection of the second measure, *IS* stiffness index at the baseline, *IS2* stiffness index of the second measure

IEF value at 16.5 ± 8.4%, $p = 0.0001$. IEF value was significantly higher in the office workers than that in the labour workers (16.4 ± 9.5% vs. 12.0 ± 9.0%, $p = 0.03$); while IEF value was significantly lower in the individuals with overweight than that in the individuals with normal body weight who had higher IEF value (7.8 ± 9.6% vs. 16.6 ± 8.6%, $p < 0.0001$).

In our investigation, we also identified a significant difference of IEF value ($r = -0.43$, $p < 0.05$), between smokers and non-smokers. IEF value was significantly higher in the non-smoker individuals than that in the smokers (15.1 ± 9.9% vs. 6.4 ± 8.1%, $p < 0.0001$). An inverse relationship was also found with the level of blood pressure ($r = -0.44$, $p < 0.05$) and total cholesterol ($r = -0.23$, $p < 0.05$).

The comparison groups that were divided according to the average score of SHS had significant differences of characteristics such as: IEF (Group 1, 16.4 ± 8.6%; Group 2, 6.6 ± 10.5%, $p < 0.0001$), index reflections outgoing (IR) (Group 1, 68.1 ± 12.2%, Group 2, 71.7 ± 12.4%; $p < 0.01$), IR after the test (IR2) (Group 1, 59.1 ± 11.3%; Group 2, 63.3 ± 10.7%, $p < 0.001$) and stiffness index after the test (SI 2) (Group 1, 8.2 ± 4.1 m/s; Group 2, 9.3 ± 3.3 m/s, $p = 0.01$) (Table 4). This indicated higher vascular tone and stiffness in individuals with suboptimal health status.

Furthermore, we studied the indicators of endothelial function in participants as we divided them for comparison into two groups according to their average score of

SHS. There were significant differences in the group of participants with SHS score > 14 on IEF, reflection of index outgoing before the sample (IR 1) and after the sample (IR 2), and index of stiffness after the sample (S 2) (Table 4). This indicates higher vascular tone and stiffness in participants with higher suboptimal health status score.

2.4 Discussion

Our research confirmed about the importance of the measurement of the wall stiffness by using photoplethysmography assessment. Thus, our investigation revealed a significant correlation between the index of endothelial function and general indicators of the suboptimal health status (SHS) (Table 5).

Changes in the lipid level affect the state of the vascular wall of the endothelium. We assessed vascular wall health using photoplethysmography to measure the IEF. Among the variables, SHS score and IEF value ($p = 0.0001$) and also age ($p = 0.013$) showed a significant association, respectively, by linear regression analysis respectively (Table 5).

The endothelin-1 index had a significant connection with index of endothelial function ($r = -0.72$, $p < 0.05$), SHS-total ($r = 0.62$, $p < 0.05$), with an indicator of sub-optimal status by scale “cardiovascular system” ($r = 0.79$, $p < 0.05$). Association of suboptimal health status with endothelin-1 index ($r = 0.62$, $p < 0.05$) once again provided a potential sensitivity method for assessing suboptimal health status tests for predicting the risk of cardiovascular diseases.

We further examined the integral relationship between endothelial dysfunction scores and CVD risk factors according to the correlation analysis between endothelial dysfunction and SHSQ-25 scores. A multivariate statistical analysis of the following parameters was used: “ the total score of SHSQ-25, the respective subscale scores of the SHSQ-25 (fatigue, mental state, cardiovascular system, digestive system, immune system”), smoker index, BMI, SBP, DBP and endothelial function

Table 5 The results of the regression analysis (dependent variable SHSQ-25 total score)

	Unstandardised coefficients		Standardised coefficients		
Variables	Beta	Std. error	Beta	*t*	*P*
Age	−0.132	0.053	−0.209	−2.491	0.013
BMI	0.139	0.145	0.079	0.958	0.339
Index smoker	0.034	0.085	0.026	0.398	0.691
SBP	0.069	0.054	0.102	1.288	0.199
DBP	−0.040	0.049	0.052	−0.815	0.416
IEF	−0.248	0.068	−0.284	−3.679	0.0001

Note: The significant p value is <0.05

Abbreviations: *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IEF* index of endothelial function indices, vascular stiffness index, pulse wave reflectance index, blood glucose and total cholesterol (Fig. 1).

According to the cluster analysis of cardiovascular risk factors and indicators of SHS, all participants were divided into five clusters (Fig. 1) [25]. The first cluster included $n = 99$ young people with lower total index of SHSQ-25, normal body weight, normal blood pressure, absence of the endothelial dysfunction and lower level of glucose and cholesterol. These individuals were rated with optimal health. The second cluster contained 121 cases. This cluster was characterised by the young age of the participants with average value of the total SHSQ-25 index, abnormalities in the mental status and immune system, normal weight, blood pressure, absence of the endothelial dysfunction, and reduced level of the glucose and cholesterol. This cluster was described with low risk of SHS cluster. The third cluster ($n = 91$ cases) differs from the other two with high values of the cumulative index of SHSQ-25, especially on the scale of the mental status, digestive system and immune system. This cluster was described as an SHS cluster with a high risk of a non-cardiac pathology profile. The fourth cluster included $n = 94$ participants with a higher age of 35 years, with average values of the total SHSQ-25 index, but with at least 1–2 risk factors for cardiovascular diseases. This cluster primarily consisted of overweight participants with a long history of smoking. We designated this cluster as a low-risk cardiovascular syndrome phenotype. The fifth cluster ($n = 54$ cases) was characterised with significant variations in the total SHSQ-25 score, the cardiovascular disease scale, the presence of the risk factors for cardiovascular diseases and endothelial dysfunction. These participants were assigned to our SHS cardiovascular phenotype with a high risk of suffering from cardiovascular disease.

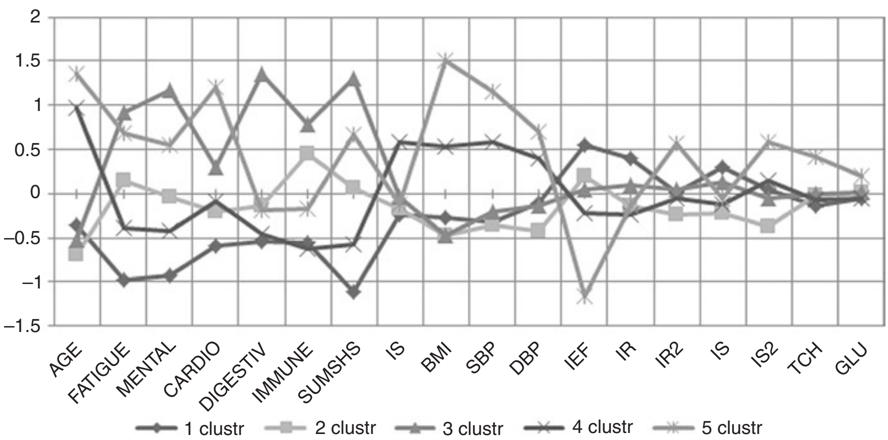

Fig. 1 Cluster analysis of integration of the suboptimal health status, cardiovascular risk and endothelial dysfunction. **SUMSHS* the total amount of SHS:25, *IS* index smoker, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IEF* index of endothelial function, *IR* index of reflection before the sample, *IR2* index of reflection after the sample, *IS* stiffness index before the sample, *IS2* stiffness index after the sample, *TCH* total cholesterol, *GLU* glucose. Figure source: Kupaev et al. The EPMA Journal (2016)

We saw a strong association between SHS scores and cardiovascular risk factors by using cluster analysis. We noted the largest distance and significant dependence between the clusters, which indicates the presence of the relationship between health conditions and vascular wall rigidity. Cluster analysis showed the association between SHS scores, risk factors of cardiovascular disease and endothelial dysfunction scores ($p < 0.001$). Among the risk factors for cardiovascular diseases, the largest distance was mentioned between clusters 1, 2, 3, and between 4 and 5 clusters. The most significant dependencies were found in age, body mass index, and blood pressure, indicating the presence of a relationship between vascular wall rigidity and several traditional determinants of cardiovascular pathology at a suboptimal stage of health.

In the present study, the assessment of SHS was combined with analysis of the endothelial dysfunction condition, which allowed to identify the risks of the development of the cardiovascular diseases and to interfere early in the framework of predictive, preventive and personalised medicine (PPPM) [26, 27].

However, the present study had limitations: information on the physical activity habits, dietary profile, frequency of the meal intake and sleeping habits that were not able to be collected for assessment [28]. All these parameters are also important for the measurement of the suboptimal health status [29–31].

3 Conclusions and Recommendations

1. Suboptimal health status has a significant relationship with risk factors for cardiovascular disease. SHSQ-25 could be used as a useful predictor for the cardiovascular diseases for community-based population surveys at a primary care setting.
2. This study identified the association of endothelial dysfunction with age, blood glucose levels and systolic blood pressure and also relationships with SHS index and metabolic factors such as body mass index and total cholesterol levels.
3. SHSQ-25 can be used as a tool for health measures following the context of PPPM concept.

The assessment of the SHS index, combined with the analysis of the state of the endothelial dysfunction, allows to identify the risk of the developing cardiovascular diseases at the early stage and gives an example of early intervention from the perspective of PPPM in a Russian population.

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Individualised Preventive Measurements of Suboptimal Health

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Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
BMI	Body mass index
CH2	Constant heavy 2
E2	Estradiol
Fc	Fragment crystallisable
FcγRIIB	Fc gamma receptor type IIB
FSH	Follicle-stimulating hormone
GlcNAc	N-acetylglucosamine
IgG	Immunoglobulin G
LH	Luteinising hormone
MBL	Mannose-binding lectin
NCDs	Non-communicable chronic diseases
PPPM/3PM	Predictive, preventive, and personalised medicine
PTM	Post-translational modification
RCT	Randomised controlled trial
SHS	Suboptimal health status
SHSQ-25	Suboptimal Health Status Questionnaire-25
TNF-α	Tumour necrosis factor alpha
WHO	World Health Organization

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1 Disease Prevention

Phases of the disease's natural history include the underlying, susceptible, subclinical, clinical, and recovery/disability/death stages [1]. According to the guidelines from the World Health Organization, health prevention is classified into primary, secondary, and tertiary prevention [2]. Comprehensive preventive strategies can prevent diseases by reducing the risk of morbidity and the subsequent complications of overt disease [1].

Primary prevention also called aetiology prevention is the fundamental action to prevent, control, and eliminate diseases. From both individual and population levels, it focuses on actions that endeavour to control the effects of risk factors [3]; thus, the target population of primary prevention is those whose diseases have not yet occurred [1, 4]. Primary prevention consists of two components: health promotion and health protection. Health promotion aims to reduce an individual's exposure to the causes (risk factors) of diseases by creating a health-promoting environment. In such case, the susceptibility can be altered, and the individual can be protected from disease, thus the morbidity rate can be reduced [2]. Health protection is a measure taken for diseases with clear causes (risk factors) or specific ways of prevention, for example, the vaccination against *hepatitis B* to prevent *hepatitis B* [5]. The two-pronged strategy is often employed for primary prevention, combining universal prevention for the whole population and focused prevention for high-risk population. Both components complement each other to improve efficiency [3].

Secondary prevention also known as preclinical prevention aiming to control the development and deterioration of the disease and prevent the disease from recurring or turning into chronic status [2]. The core of secondary prevention is early diagnosis, with its premise being early detection and early diagnosis, which can contribute to early treatment and thus improve the prognosis [1]. An ideal secondary prevention requires the dissemination of disease prevention knowledge to the public, the improvement of clinicians' diagnosis, and the establishment of a reliable and an accurate disease surveillance system [6]. Due to the long period of the occurrence and the development of chronic diseases, it is feasible to achieve early detection and early treatment of those diseases, such as cervical cancer, coronary heart disease, and hypertension. Activities for early detection include census, screening, regular medical examinations, and establishment of specialist clinics [3, 4].

Tertiary prevention also termed as clinical prevention refers to taking timely and effective treatment for those who have already suffered from the disease [2]. It aims to prevent deterioration, complications, and disability for those who have already diagnosed with diseases. It mainly promotes functional recovery, psychological rehabilitation, and home care guidance [7–9]. In that case, patients can restore their living and working abilities as far as possible and can participate in social activities and prolong their life. Symptomatic treatment, which can relieve pain, reduces the adverse effects of the disease, and prevents complications and disability, and rehabilitation, which mainly involves functional, psychological, social and vocational rehabilitation, are the primary tertiary preventive strategies [9].

Individualised prevention also refers to personalised prevention, [10, 11]. It cannot be separated from the development of precision medicine, which is an innovation and development based on traditional medicine. Related fields including medical informatics, molecular medicine, health economics, and medical sociology [11, 12]. The individualised medicine is relied on the development of molecular diagnostics and molecular pharmacodynamics [2]. Progresses in genomics and proteomics have greatly contributed to the development of molecular medicine [11]. The application of high-throughput gene microarrays and protein microarrays has made molecular typing of various diseases possible [11]. The molecular spectrum of specific patients has gradually become a very important basis and evidence in clinical diagnosis and treatment [12]. From the concept of predictive, preventive, and personalised medicine (PPPM), the present assessment applications for human health status involved both subjective and objective measurements. With regard to subjective measurements, they are typically referred to self-reported questionnaires, contingent on subjects' feelings, opinions, and general impressions. In preventive medicine, the subjective tool Suboptimal Health Status Questionnaire-25 (SHSQ-25), which has been coined and validated as a reliable and robust health measurement, is employed to evaluate Suboptimal Health Status (SHS) in five domains: cardiovascular system, digestive system, fatigue immune system, and mental status [13]. SHS is defined as an intermediate physical state between health and disease [13]. Additionally, it is reversible and helps predicted or prevented non-communicable diseases (NCDs) before the onset of diseases [14–16]. While objective measurements are more impartial compared with subjective measurements. One of the most prevalent methods to objectively quantifying outcome of interest is the application of biomarkers, such as classical inflammatory biomarkers, such as tumour necrosis factor alpha [TNF-α], and multi-omics molecular biomarkers, such as analyses in genome, transcriptome, epigenome, proteome, metabolome, and glycome. Of note, glycosylation is the most common and diverse form of post-translational modification (PTM) of protein. N-glycosylation, the binding of a glycan to an asparagine residue of a protein, is the most common and best understood. A variety of biological processing (such as protein folding, cell adhesion, and receptor activation) can be affected by glycosylation. Immunoglobulin G (IgG) is the most abundant antibody in human blood circulation, accounting for about 80% of the antibodies. The alterations in IgG N-glycans have been associated with SHS (PMID: 35719133). Moreover, IgG N-glycosylation have linked to SHS-related diseases or disorders, such as cardiovascular diseases [17] and type 2 diabetes mellitus [18]. This connection may offer insights and strategies for reversing SHS.

On one hand, the objective of individualised prevention is to supplant current traditional, community- or population-based public health efforts. On the other hand, individualised prevention also strives to ensure that individuals have access to the appropriate preventative measures at the right dose and timing in order to maximise the effectiveness and safety of all interventions and optimise the benefit-risk ratio [19]. Thus, the cost-effective, time-efficient, and tailored prevention programmes for reversing SHS can be provided from the precise application of primary and secondary prevention [12, 19].

2 Prevention of SHS Defined by Subjective Measurements

The timely screening for SHS has the potential for early prediction and prevention of non-communicable diseases (NCDs), and effective SHS prevention may be an effective and economical way to prevent NCDs [16]. To assess the SHS efficiently and economically, our team developed and validated the innovative and robust health assessment tool, SHSQ-25. This is in line with the conceptualisation of PPPM/3PM [20].

Disease prevention, especially for chronic NCDs, requires an emphasis on SHS according to PPPM/3PM strategies to prevent the development of diseases in advance (Fig. 1). Ideally, interventions should be delivered when a person presents with symptoms that suggest a non-healthy state but does not yet meet existing diagnostic criteria for the disease. When it comes to SHS prevention, it is important to pay attention to identifying physical health conditions, as well as mental and emotional states. In summary, it is essential to implement people-oriented interventions based on the comprehensive concept of PPPM/3PM and to provide rapid, economical, and targeted preventive measures. In this chapter, we demonstrated the effectiveness of preventive measurements of SHS through cases studies.

Case Study 1: Examine the Effect of Baduanjin Exercise on SHS Individuals
There is increasing proof exercise or physical activity can help to improve one's physical and mental condition [21]. Additionally, traditional Chinese exercises, such as Baduanjin exercise, have proven to be successful workout regimens for promoting both physical and mental health, as well as improving body composition [22–24]. There are eight separate, delicate, and smooth exercise movements in

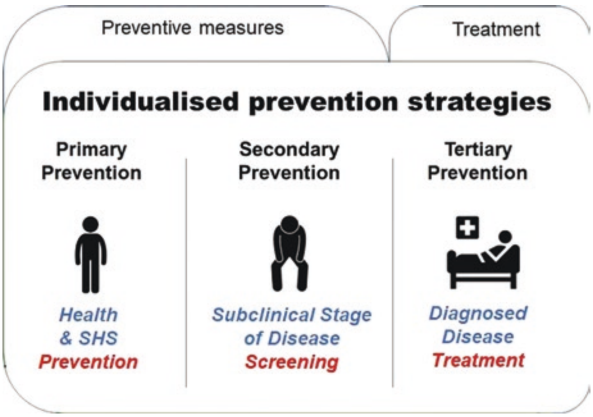

Fig. 1 Strategies in accordance with the individualised prevention. Primary prevention focuses on actions that endeavour to control the effects of risk factors of disease at both individual and population levels. Secondary prevention refers to early detection of diseases. Tertiary prevention represents taking timely and effective treatment for those who have already suffered from the disease

Baduanjin exercise (1 raise hands to hold up the sky; 2 draw two bows to shoot vultures; 3 raise one arm to control the stomach and spleen; 4 turn head to eliminate fatigue; 5 lean forwards and backwards to release heart fire; 6 pull your toes together with both hands to support your waist and kidneys; 7 clench the fists and glare fiercely; 8 tiptoe up and down), and each movement helps certain body parts or organs by improving their capacity for function [25].

A clinical trial was carried out to examine the impact of Baduanjin exercise on the symptom of fatigue in SHS participants [26].

To determine the long-lasting impact of Baduanjin exercise on SHS, participants were monitored for a period of 12 weeks after the intervention. Statistical comparisons of the SHS score were carried out at several time points, including preintervention, the fourth and sixth week following the intervention, and the 12th and 18th week during the post-intervention follow-ups. The findings revealed the Baduanjin exercise group had substantially decreased SHS scores ($P < 0.05$). The study suggests that Baduanjin exercise has an effect on relieving fatigue in people with SHS [26].

Case Study 2: Effectiveness of Mild Moxibustion for SHS in Pre- and Post-menopausal Women

Women, who are at the peri-menopausal stage of life, would frequently experience SHS, which is characterised by uncomfortable symptoms such as difficulty concentrating, fatigue, headache, hot flashes, insomnia, irritability, and mental confusion [27]. Chinese and other Asian people have been reported to use moxibustion, which is a kind of heat treatment in dried "moxa" burned on acupoints, as a way of clinical therapy and for self-healthcare [28]. A randomised controlled study (RCT) with 60 participants randomised to the intervention (moxibustion) and control groups was carried out to examine the safety and effectiveness of moxibustion for improving SHS in peri-menopausal women. Mild moxibustion was administered to the moxibustion group, and vitamin E soft capsules were given to the control group as a placebo [29]. According to the results in the study, the intervention in the (moxibustion) group dramatically improved SHS when compared to the control group. Pre-menopausal women had more pronounced improvements in SHS compared to post-menopausal women. Additionally, after treatment, the moxibustion group had substantially higher estradiol (E2) levels than the control group, and pre-menopausal women in the moxibustion group had higher E2 levels than post-menopausal women. Pre-menopausal women had considerably greater levels of E2, prolactin (PBL), and progesterone, while post-menopausal women had significantly higher levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH).

Case Study 3: Effects of Pulsatile Cupping on Body Pain and Quality of Life in People with SHS

A traditional medical practice known as cupping therapy uses heated cups to apply pressure to the skin in order to clear blockages and promote "Qi" flow [30]. Cupping has been widely employed in China and other Asian populations because of its non-invasive nature, straightforward procedure, and quick results [31]. Cupping was identified as a primary clinical treating way to relieve SHS and improve patients' overall well-being in clinical practice [32].

The effects of pneumatic pulsatile cupping on pain and life quality in SHS patients were examined in a four-arm randomised clinical experiment [33]. In this study, 96 SHS patients were recruited and assigned to receive low-frequency (LF) or high-frequency (HF) pulsating cupping, traditional cupping (TC), or wait-list (WL) therapy.

Compared to the TC group, pain symptoms dramatically declined in both LF and HF groups, whereas the life quality was significantly improved in both the LF and HF groups. Additionally, compared to the WL group, the quality of life was significantly improved in both LF and HF groups and pain symptoms were significantly reduced. However, there was no statistically significant difference between the LF and HF groups.

3 Prevention of SHS Defined by Objective Measurements

While no statement meets the clinical diagnostic criteria for health declines (i.e. in SHS), the molecular processes are already measurably perturbed.

Glycans are thought of as one of the ideal objective measures for detecting SHS as glycosylation plays a crucial role in the inflammatory processing at the molecular level (42). Immunoglobulin G (IgG) is one of the most thoroughly studied glycoproteins overall, connecting the innate and adaptive immune system branches [34]. Conserved N-glycans linked to the constant heavy 2 (CH2) region of the IgG fragment crystallisable (Fc) domain mediate downstream immunological responses in addition to directly influencing the conformation of the fragment crystallisable (Fc) region (Fig. 2) [35, 36]. In addition, alternations of the IgG N-glycosylation can elicit inflammageing, which is a generalised term describing the process of ageing at the molecular level through inflammation [37]. IgG N-glycans can serve as a

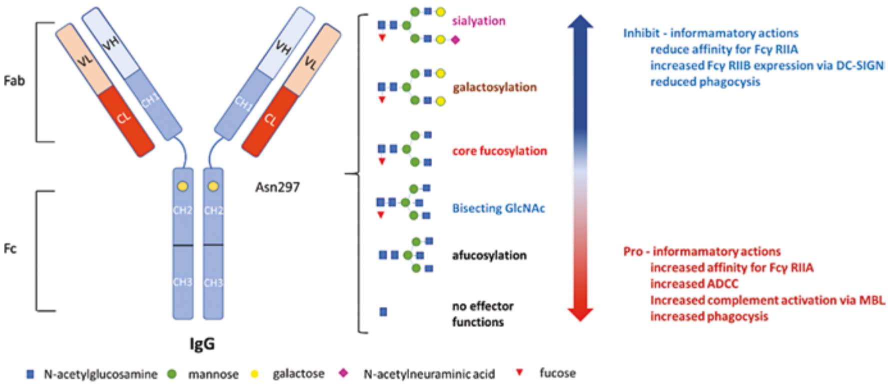

Fig. 2 Fc-bound N-glycans modulate IgG effector functions, adapted from [35, 36]. *ADCC* antibody-dependent cellular cytotoxicity; *FcγRIIB* Fc gamma receptor type IIB; *GlcNAc* N-acetylglucosamine; *MBL* mannose-binding lectin

molecular parameter for individualised monitoring and prevention of SHS, as they are important dynamic biomarkers for identifying SHS and offer a window opportunity for its management.

SHS is on the rise, posing a new threat to both societal and individual health due to the epidemics of poor lifestyle such as physical inactivity. The cost of managing non-communicable diseases is increasing, placing growing pressure on healthcare budgets. Shifting the emphasis on SHS prevention can effectively address this issue. It is feasible to track the impact of the outcomes of helpful interventions because IgG N-glycome can be utilised as a biomarker for SHS and interventions can influence IgG N-glycome compositions.

Case Study 1: Intense Physical Exercise Induces an Anti-inflammatory Change in IgG N-glycosylation Profile

A longitudinal intervention research involving 29 males was carried out to demonstrate the impact of high intensity physical exercise programme on the IgG N-glycosylation profile [38]. IgG N-glycosylation profiling was assessed from blood samples at three time points: (1) baseline, (2) post-intervention (EXC), and (3) recovery period (REC). The outcomes from the baseline, EXC, and REC time periods were compared after the IgG N-glycosylation study. Analysis was conducted on the following derived glycan characteristics: agalactosylation (G0), monogalactosylation (G1), digalactosylation (G2), monosialylation (S1), disialylation (S2), bisection (B), and core fucosylation (CF). IgG N-glycome compositions at the REC time point were significantly different from the baseline due to the effects of exercise (Table 1).

Case Study 2: Effects of Estradiol on Biological Age Measured Using the Glycan Age Index

A randomised controlled trial (RCT) was carried out to estimate the effects of estradiol supplementation on glycan age [39]. This research involved 36 healthy young women in total and underwent 5 months treatment of gonadotropin-releasing hormone agonist (GnRHAG) to suppress ovarian gonadal hormones. Participants were

Table 1 Effects of intense physical exercise on levels of IgG N-glycosylation [38]

Structural feature	Estimate EXC	*P*-value EXC	Adj. *P*-value EXC	Estimate REC	*P*-value REC	Adj. *P*-value REC
Agalactosylation (G0)	−0.2009	0.5394	0.6152	−0.8080	0.0190	**0.0473**
Monogalactosylation (G1)	−0.1040	0.5388	0.6152	−0.1710	0.3149	0.4409
Digalactosylation (G2)	0.3049	0.4554	0.6152	0.9950	0.0203	**0.0473**
Monosialylation (S1)	0.2688	0.1283	0.6152	0.5270	0.0048	**0.0339**
Disialylation (S2)	0.1430	0.2206	0.6152	0.2465	0.0399	0.0698
Bisection (B)	0.0901	0.5807	0.6152	0.1095	0.5030	0.5868
Core fucosylation (CF)	−0.0373	0.6152	0.6152	−0.0339	0.6479	0.6479

then randomly assigned to estradiol (E2) intervention (GnRHAG + E2, $n = 15$) and placebo control group (GnRHAG + PL, $n = 21$) [40].

IgG N-glycosylation profiling was assessed from blood samples at three time points: (1) baseline, (2) post-intervention, and (3) recovery period (Fig. 3). Estradiol supplementation significantly reduced glycan age (−0.23 years), which was significantly increased by 9.1 years when gonadal hormones were suppressed. Glycan age in both groups returned to baseline levels following the recovery period.

Case Study 3: Extensive Weight Loss Reduces Glycan Age by Altering IgG N-glycosylation

Bariatric surgery is considered as one of the most effective methods to treat severe obesity [41]. To explore if weight loss can improve glycan age, 37 obese patients were recruited in an exploratory cohort from Oxford University Hospitals and 2146 participants were included in a replication cohort from the Twins UK cohort. Participants recruited from the exploratory cohort underwent bariatric surgery after low-calorie diet for 3 weeks.

The IgG N-glycome compositions were assessed at three time points: (1) baseline, (2) the day of the bariatric surgery, and (3) the day of 20% of weight loss. Subsequently, the replication cohort longitudinally monitored IgG N-glycome of 3742 participants with information on body mass index (BMI) [42]. The results indicated that low-calorie diet causes a decrease in bisecting GlcNAc that reflected a decreased pro-inflammatory trend (Fig. 4). During the one year follow-up after the bariatric surgery, an increase in digalactosylation and sialylation was observed, while agalactosylation and core fucosylation was decreased.

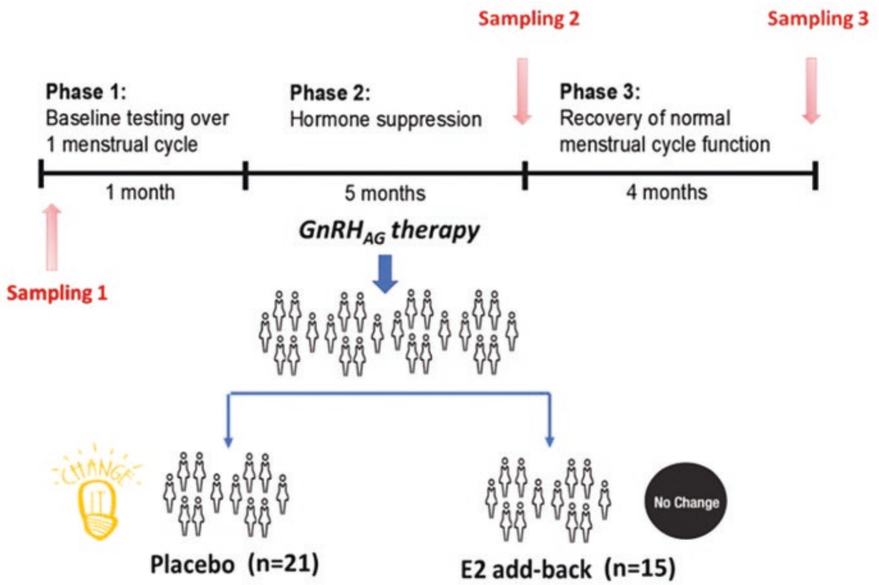

Fig. 3 Flowchart of the study design

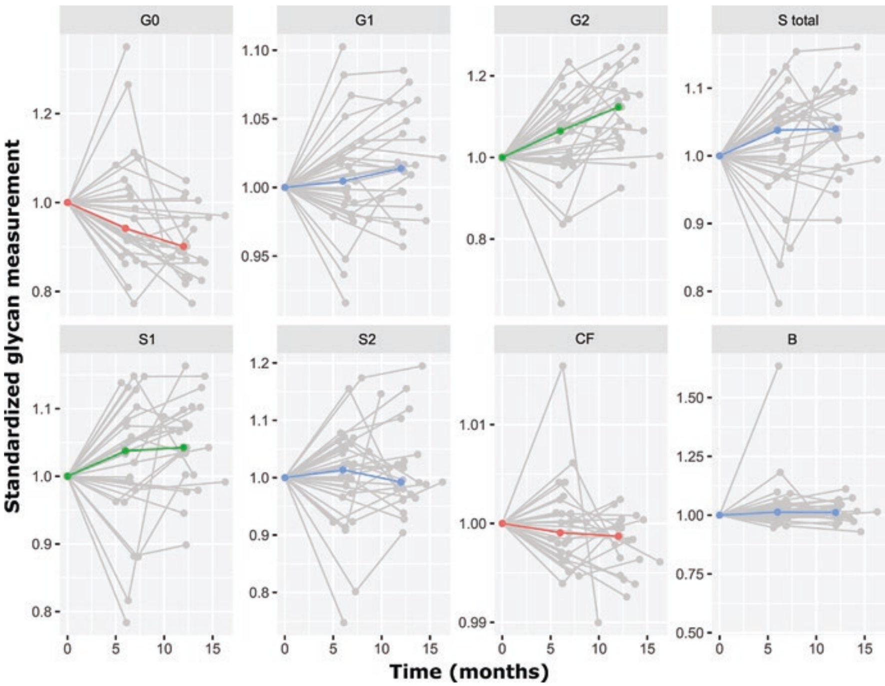

Fig. 4 Effect of Bariatric surgery on IgG N-glycosylation [41]. *G0* agalactosylation; *G1* monogalactosylation; *G2* digalactosylation; *S total* total sialylation; *S1* monosialylation; *S2* disialylation; *CF* core fucosylation; *B* bisecting N-acetylglucosamine

4 Conclusion, Expert Recommendations, and Future Perspective

In conclusion, personalised SHS measurements provide a reliable and robust platform for effective prevention measures. The established SHS assessments, such as SHSQ-25 and IgG N-glycosylation profile, should thus serve as the foundation for individualised preventative strategies for SHS. The examples of targeted interventions for prevention aforementioned showed how the combination of subjective and objective SHS assessments has a positive impact on health improvement. From the perspectives of PPPM, it provided a thorough strategy for the individualised prevention of SHS from progressing into the disease phase.

Declaration of Interest Statement Declarations of interest: none.

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Early Vascular Aging in Young Adults Is Instrumental as the Screening Tool to Combat CVD Epidemics in the Population

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Abbreviations

ABI	Ankle-brachial index
AC	Atherogenic coefficient
AGEs	Advanced glycation end products
AH	Arterial hypertension
BH	Burdened heredity
BM	Body mass
BMI	Body mass index
BP	Blood pressure
CAVI	Cardio-ankle vascular index
CR	Calorie restriction
CV	Cardiovascular
CVD	Cardiovascular diseases
CVRF	Cardiovascular risk factors
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DSR	Dietary sodium restriction

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EDD	Endothelium-dependent dilation
eNOS	Endothelial nitric oxide-synthase
ET-1	Endothelin-1
EVA	Early vascular aging
HDL	High-density lipoproteins
HR	Heart rate
LDL	Low-density lipoproteins
MitoQ	Mitochondria-targeted antioxidant
MMPs	Matrix metalloproteinases
MnSOD	Manganese superoxide dismutase
mTOR	Mammalian target of rapamycin
NAD	Nicotinamide adenine dinucleotide
NMN	Nicotinamide mononucleotide
NO	Nitric oxide
NR	Nicotinamide riboside
PH	Prehypertension
PWV	Pulse wave velocity
RF	Risk factors
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SIRT-1	Sirtuin 1
TC	Total cholesterol
TG	Triglycerides
VA	Vascular age
VS	Vascular stiffness
YP	Young people

1 Preamble

Although modern cardiology is characterized by a high level of implementation of innovative therapeutic and diagnostic technologies, cardiovascular diseases (CVD) still remain the leading causes of death worldwide [1]. The problem is aggravated by the fact that the process of rejuvenation of morbidity and mortality from these diseases is widely reported [2]. Contextually, more attention should be paid to studying early preclinical stages of CVD pathogenetic continuum, in particular at young age [3–5], in order to cost-effectively protect populations against health-to-disease transition and vascular aging at the stage of suboptimal health [6, 7]. To this end, specifically stroke of unclear etiology affects a big portion of altogether over 101.5 million individuals diagnosed with stroke worldwide including patients at teenager age. The World Stroke Organization prognosed 1 in 4 adults over the age of 25 getting a stroke in their lifetime with associated global costs estimated at 721 billion US dollars annually. The overall number of affected individuals is assumed to be about 14-times greater than clinically recorded, due to undiagnosed “silent” brain infarction related to early and unpredictable vascular aging [8].

The key point is to change the paradigm from reactive medical services (applied to patients affected by downstream pathologies such as clinically manifested myocardial infarction and ischemic stroke, among others) to a predictive approach applied to individuals in suboptimal health conditions, in order to protect them against the health-to-disease transition based on a multi-parametric health risk assessment and application of artificial intelligence in medicine [8].

2 Vascular Stiffness as an Early Stratification Indicator for 3PM Approach

A number of authors believe that preventive CV technologies should be based on the concept of vascular aging, the main determinant of which is arterial stiffness [9, 10]. Increased vascular stiffness (VS), meaning the loss of elastic properties of the medial layer of the wall of large-caliber arteries, is a highly significant predictor of total and CV mortality [11, 12], as is a decrease in the ankle-brachial index (ABI), which reflects abnormalities mainly in the inner layer of the arterial wall [13]. In the case of increased stiffness of the vascular wall, large arteries lose their ability to damping, due to which the impact of the energy of shock blood ejection on internal organs is reduced. For this reason, conditions are created for realization of the damaging effect of excessive pulse wave on target organs, and also the load on myocardium increases, its blood supply is disturbed and the risk of development of major CVD increases [14].

The assessment of vascular stiffness indices allows differentiating young people from their elastic potential of the arterial wall into certain phenotypes. However, until now, young people as carriers of preclinical athero- and arteriosclerosis have not been studied, and these phenotypes have not been investigated in terms of their relationship with major risk factors, including AH, which in turn is considered a leading cardiovascular risk factor (CVRF). Some experts believe that VS and AH are in a continuous bidirectional mutual influence with each other [15].

We are about to develop an approach aimed at identifying carriers of premature vascular aging or EVA (Early Vascular Aging) syndrome among young people in order to include them in the CV risk group as soon as possible and to initiate individualized and targeted preventive programs under control of not only BP and other traditional RF but also VS indices [16]. The goal of such preventive interventions, according to leading experts, should be the restoration of healthy vascular aging and its maintenance on the basis of differentiated preventive interventions under dynamic control of arterial stiffness parameters—in the form of pulse wave velocity (PWV) or cardio-ankle vascular index CAVI (cardio-ankle vascular index). The prognostic significance of VS has been confirmed both in relation to the development of CV complications in mature and elderly individuals [11, 17], and in the aspect of the occurrence of CVD in 35–45 years old individuals, in whom EVA syndrome was detected in childhood and adolescence according to the results of angiological instrumental screening [18].

Interval division of samples homogeneous by sex and age by this index allowed P. Nilsson and his colleagues to substantiate the doctrine of vascular aging phenotypes [10]. In accordance with this approach, three main variants of vascular aging are distinguished: premature (or EVA syndrome), normal, and favorable. This approach creates a prospect for improving the existing dispensary models, as well as for creating a system of effective monitoring of arterial biological age parameters and real management of it in each person starting from the early stages of its pathogenetic CV continuum [19]. Young people are of particular importance in the discussed aspect since it has already been shown that the main behavioral stereotypes, which then act as the main RF, are finally formed exactly at this age [15]. However, the youth features of vascular aging are still poorly studied.

3 Complexity of Mechanisms of Premature Vascular Aging

In the process of vascular aging, mechanisms of functional and structural damaging synergistically form arteriosclerosis as a pathology of predominantly (1) middle sheath of arteries and (2) media [15]. Risk factors of the first include increased blood plasma levels of endothelin-1, insufficient NO bioavailability, impaired balance of sympatho-adrenal, immune, renin-angiotensin-aldosterone systems resulting in non-compensated oxidative stress by excessive formation of ROS.

Structural damage to the media side includes the shifted ratio of proteins of the medial membrane such as collagen and elastin, due to the altered activity of metalloproteinases and formation of glycation end products (AGEs). The latter create conditions for "piercing" of proteins promoting arterial stiffness. The functional component of arterial stiffness depends on vasoconstrictor tone, which, in turn, increases the tone of smooth muscle of blood vessels [20]. Age-related neurohumoral dysfunction resulting from a decrease in the baroreflex combined with an increased sympathetic activation also contributes to inadequately enhanced arterial stiffness [21]. Systemic inflammation, which increases with age, may predispose to increased arterial stiffness through immune activation pathways and the development of hypertension. Age-related endothelial dysfunction also interacts closely with arterial stiffness, as it is favored by dissociation of endothelial NO synthase (eNOS) resulting in significantly decreased NO bioavailability, which may be further exacerbated by non-compensated oxidative stress. Age-related structural remodeling of the extracellular matrix of the middle layer is accompanied by pathological changes in the composition and ratio of elastin and collagen in the wall of large elastic arteries. Extended fragmentation and degradation of elastin, which are largely mediated by the activation of matrix metalloproteinases (MMPs) followed by collagen deposition replacing the loss of elastin molecules have been observed [22]. Accelerated formation of glycation end products (AGEs) strongly contributing to the "cross-linking" of protein structures further exacerbate increased arterial stiffness. Oxidative stress and inflammation synergistically lead to proliferation of smooth muscle cells, their transformation, collagen deposition, and remodeling associated with AH. Angiotensin II may also modulate the structural contribution to arterial stiffness by stimulating the formation of collagen, reducing elastin synthesis, and promoting remodeling of the vascular matrix.

Regarding the functional interrelationship between AH and VS, there is still an uncertainty on what is primary and what is secondary in the development of vascular aging, namely an increase BP or vascular stiffness. However, accumulated data indicate that not only AH predisposes to increased vascular stiffness, but also a systematic increase in arterial stiffness may significantly contribute to BP increase with the systolic hypertension as a consequence [23, 24].

Arterial hypertension may contribute to aortic stiffness, and increased stiffness of large elastic arteries may precede and contribute to SBP increase. Rigidity of large elastic arteries is an independent predictor of arterial hypertension in many longitudinal cohorts [25]. Experimental data are consistent with such clinical findings—in rodents fed a diet high in fat and sucrose, an increase in aortic pulse wave velocity was found before an increase in systolic AH [26].

As large elastic arteries become stiffer with age, systolic BP increases while diastolic BP decreases due to decreased elastic recoil of the aorta; as a result, pulse pressure increases with age [8]. Isolated systolic hypertension is the most common form of arterial hypertension in individuals aged 50 years and older. Increased stiffness of large elastic arteries is the main cause of AH changes with age, ultimately contributing to the development of systolic hypertension [27]. Age-related endothelial dysfunction, characterized by decreased nitric oxide (NO) bioavailability and increased endothelin-1 production, also contributes to both increased SBP levels and impaired regulation of vascular tone [21]. These phenomena are partially mediated by increased oxidative stress associated with excessive superoxide production. There may also be an interaction between the immune system and hypertension, as immune activation and inflammation induced by oxidative stress are involved in the development of hypertension [28]. As already indicated, the activity of the sympathetic nervous system increases with age and the association between it and BP levels becomes stronger, especially in women [29]. In addition, chronic activation of the renin-angiotensin system contributes to damage to target organs, including the kidneys and heart, because angiotensin II promotes both BP and the production of reactive oxygen species [15, 30].

4 Vascular Stiffness as an Early Indicator of the EVA Syndrome in Youth

According to the recommendations of international experts, in order to determine whether a particular person belongs to one or another variant or phenotype of vascular aging, a sample homogeneous by sex and age should be subjected to interval analysis within its various variants [10, 31]. This approach makes it possible to determine the quantitative criteria of each phenotype by one or another VS indicator—PWV, CAVI, and others.

We examined 346 students (young adults) of the Stavropol State Medical University (131 males and 215 females) to evaluate such VS index as cardio-ankle vascular index or CAVI (cardio-ankle vascular index) on the VaSera device (model VS-1500N, Fukuda Denshi, Japan). Unlike the used PWV, the CAVI index does not depend on the level of current BP stretching the arterial wall at the moment of its measurement [32]. Elevated VS in young adults has already demonstrated its potential to detect an increased risk of CV events later in life [33, 34].

All young adults were divided into tertile groups according to a sex-specific measure of vascular stiffness, the CAVI index. Consideration of biological sex is considered necessary because it has already been established that CAVI index values are on average 0.2 higher in men than in women in all age groups [32]. It was found that male sex is an independent factor determining a higher CAVI level.

With the proposed approach we succeeded with phenotyping of premature aging—see Figs. 1 and 2. To this end, CAVI-R levels correlated well with BP values on the right hand, as well as CAVI-L levels correlated well with BP on the left hand. The system works well for screening and phenotyping of affected individuals and allows for individualized diagnostics and follow-up recommendations. For the EVA syndrome carriers, CAVI-R values ≥6.10 and ≥5.87 are characteristic for young males and females, respectively; CAVI-L values ≥6.16 and ≥6.08 are characteristic for them (see Figs. 1 and 2).

Particular accents should be put to the upper tertile (the group at highest risk) for the targeted disease prevention and treatments tailored to the individualized patient profile [14]. This is the key point for changing the paradigm from reactive medical

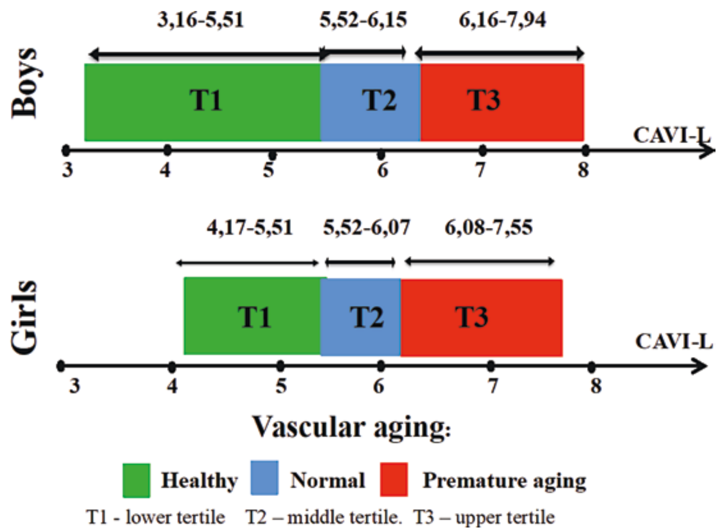

Fig. 1 Tertile distribution of young people taking into account CAVI-L (n = 346)

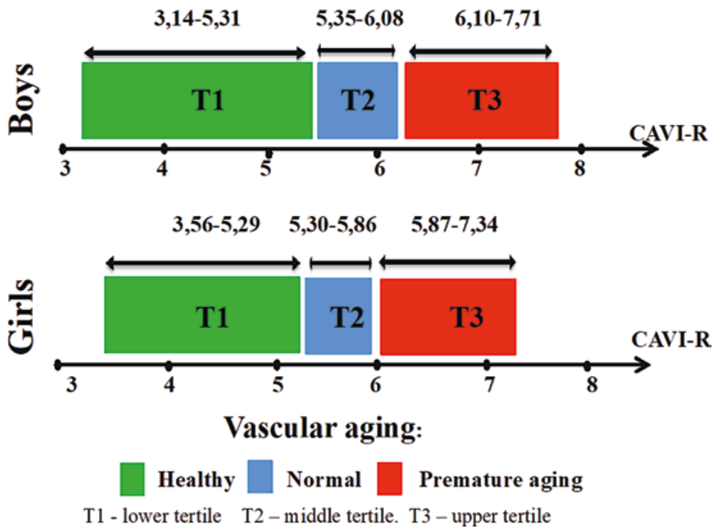

Fig. 2 Tertile distribution of young adults under consideration stratified by CAVI-R ($n = 346$)

services (applied to patients affected by downstream pathologies such as sudden heart attack, clinically manifested myocardial infarction and ischemic stroke, among others) to healthy individuals in suboptimal conditions to protect them against the transition from health-to-disease based on a multi-parametric analysis (including VS and BP) and application of artificial intelligence in medicine [8].

5 Phenotyping of Vascular Aging in Youth Correlated with Blood Pressure

Because of the continuing uncertainty as to whether EVA or arterial hypertension is primary or secondary in the development of the pathogenetic CV continuum, it was important to study BP levels in young adults with different variants of vascular aging.

Table 1 shows that among young males and females from the first to the third group SBP did not increase as expected, but, on the contrary, even slightly decreased. Moreover, the differences in this indicator between the extreme groups in both groups reached a reliable level ($P_{1-3} = 0.048$; $P_{1-3} = 0.037$). No particularly clear trends were found in DBP in either young males or females between the groups. HR was higher in males with favorable phenotype of vascular aging compared with carriers of phenotypes of normal and especially early vascular aging, but the differences between the groups were not significant. In young females, there were no particular differences in HR between groups.

Table 1 Hemodynamic parameters of young people by phenotyping of vascular aging

Parameters	First group Healthy aging	Second group Normal aging	Third group Early aging	*p*	ANOVA
Young males, *n* = 131					
n	42	44	45		
SBP, mmHg	134.6 ± 1.8	135.1 ± 2.2	129.8 ± 1.6	$P_{1-2} = 0.872$ $P_{2-3} = 0.051$ $P_{1-3} = 0.048$	0.084
DBP, mmHg	77.4 ± 1.2	79.3 ± 1.5	77.7 ± 0.9	$P_{1-2} = 0.861$ $P_{2-3} = 0.364$ $P_{1-3} = 0.330$	0.504
HR, beats/min	79.2 ± 2.2	74.3 ± 2.1	72.9 ± 2.3	$P_{1-2} = 0.109$ $P_{2-3} = 0.636$ $P_{1-3} = 0.050$	0.110
Young females, *n* = 215					
n	73	71	71		
SBP, mmHg	119.8 ± 1.2	116.9 ± 1.3	116.3 ± 1.1	$P_{1-2} = 0.109$ $P_{2-3} = 0.735$ $P_{1-3} = 0.037$	0.097
DBP, mmHg	71.9 ± 0.9	72.3 ± 0.9	71.8 ± 0.7	$P_{1-2} = 0.819$ $P_{2-3} = 0.677$ $P_{1-3} = 0.865$	0.921
HR, beats/min	73.9 ± 1.2	74.6 ± 1.3	71.6 ± 1.2	$P_{1-2} = 0.705$ $P_{2-3} = 0.104$ $P_{1-3} = 0.192$	0.225

SBP systolic blood pressure; *DBP* diastolic blood pressure; *HR* heart rate

Having received the presented data on the absence of association of AN/PH with CAVI-phenotypes reflecting the level of arterial wall remodeling relative to the middle muscular sheath in young people, we decided to study the peculiarities of occurrence of various hemodynamic variants in the aspect of isolated EVA syndrome, isolated BP increase and their combination. It is equally important to determine among young people the representation of carriers of a favorable combination, including the presence of normotonia with good vascular elasticity. This approach to the analysis of the obtained data allows us to understand how the process of development of the main cardiovascular pathology starts long before its clinical manifestation, as young people correspond to the very beginning of the pathogenetic CV continuum.

The data of another analysis (Fig. 3) show that a certain part of the examined young people are carriers of isolated VS increase, i.e., they have increased VS combined with office normotension and even with hypotension. This phenomenon is somewhat more frequent among young females, but the differences with young men in terms of VS do not reach a significant level. There is also an isolated presence of office BP increase in conditions of preserved elastic potential of the vascular wall. This variant of hemodynamic status is observed three times more often among young men compared to their female counterparts ($p = 0.000$). The combined variant of increased VS together with increased BP was also registered 2.6 times more often ($p = 0.024$) in the representatives of the stronger sex. More than a half of

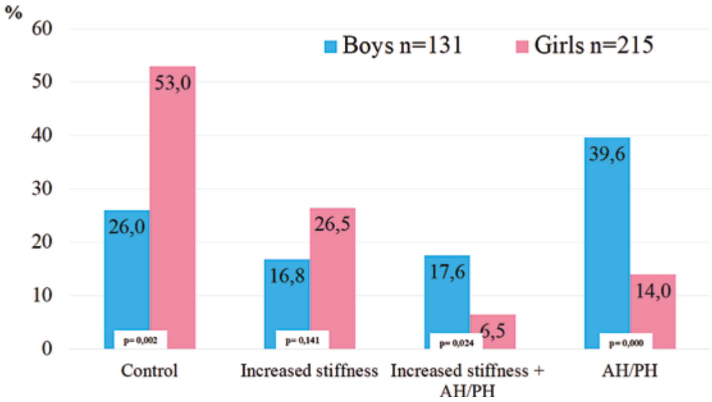

Fig. 3 Hemodynamic variants in young people according to the CAVI-L index (n = 346)

young females and only a quarter of young males ($p = 0.02$) were carriers of favorable hemodynamic status, which in the discussed aspect means a combined presence of non-elevated BP and sufficiently preserved elastic status of arteries within the framework of untimely vascular aging, which corresponds to the first and third CAVI-tertiles.

In other words, the obtained data clearly show that both EVA syndrome and increased BP can act as the primary event at the early preclinical stage of the development of major CVD in young people. At the same time, there are clear sex differences in young people with respect to the presence of the hemodynamic variants we have identified, associated with two important CV parameters such as BP and arterial stiffness. Such subdivision of the youth population according to the presented variants of hemodynamic status based on the results of preventive angio-screening may provide very effective tools for preclinical diagnosis of the features of vascular remodeling at the very beginning of the pathogenetic cardiovascular continuum.

Follow-up studies are required to elucidate both the causes of the identified differences and the peculiarities of further clinical course of these hemodynamic variants. Their identification also dictates the need to study the possibilities of differentiated approaches to preventive interventions aimed at restoration and maintenance of healthy vascular aging in EVA syndrome depending on the level of background BP.

6 Phenotyping of Vascular Aging Correlated with BMI: The Youth Obesity Paradox

The study of vascular stiffness (VS) in young people from the point of view of the peculiarities of the correlation of its index such as CAVI with the main RF (Table 2) allowed us to find out that the most significant correlation of this index was with body weight and BMI. The correlation between these parameters in young men and

Table 2 Correlation of the indicator CAVI with the main risk factors in investigated groups of young males and females

Parameters	Statistical significance	Age	Height	Weight	BMI	TC	HDL	TG	LDL	AC	Glucose
Young males, *n* = 93											
CAVI-R	Pearson correlation coefficient	0.193	−0.145	−0.428[b]	−0.417[b]	−0.054	0.091	−0.017	−0.084	−0.013	−0.058
	p	0.064	0.165	0.000	0.000	0.666	0.466	0.895	0.505	0.920	0.647
CAVI-L	Pearson correlation coefficient	0.210[a]	−0.124	−0.453[b]	−0.456[b]	−0.048	0.131	−0.006	−0.091	−0.022	−0.043
	p	0.044	0.237	0.000	0.000	0.699	0.294	0.960	0.465	0.867	0.739
Young females, *n* = 171											
CAVI-R	Pearson correlation coefficient	0.152[a]	−0.058	−0.108	−0.109	0.002	0.020	−0.128	0.025	−0.086	−0.067
	p	0.047	0.454	0.160	0.157	0.982	0.830	0.178	0.796	0.380	0.487
CAVI-L	Pearson correlation coefficient	0.135	−0.046	−0.112	−0.122	0.017	0.030	−0.153	0.039	−0.105	−0.036
	p	0.079	0.548	0.143	0.111	0.860	0.750	0.105	0.681	0.281	0.707

CAVI-R cardio-ankle vascular index right; *CAVI-L* cardio-ankle vascular index left; *BMI* body mass index; *TC* total cholesterol; *HDL* high-density lipoproteins; *TG* triglycerides; *LDL* low-density lipoproteins; *AC* atherogenicity coefficient

[a] The significance of the connection at the level of 0.05 (*p*)

[b] The significance of the connection at the level of 0.01 (*p*)

young females is negative and moderate, and in the former it was also highly significant.

We also studied the features of VS association with weight, BMI, and waist from the standpoint of the above-described phenotypes of vascular aging, which we determined by CAVI-tertile groups presented above (Table 2). It turned out that body weight, BMI, and waist volume in both—young males and females from the first to the third group, i.e., as the arterial aging phenotype worsened, the differences between the groups of comparison for the first two parameters reached a significant level among young males. Table 3 summarizes selected cardio-metabolic RF in groups of comparison stratified by phenotypes of corresponding vascular aging.

The results of analyzing the parameters of vascular status and basic RF in three groups formed according to BMI level (Table 4) demonstrated that as BMI increases, the CAVI index in both young males and females steadily decreases. We called the phenomenon we have identified "the youth obesity paradox." An analysis of the current literature has shown the absence of such a phenomenon in older individuals [35]. At the same time, similar results have been recorded in children [36].

The "youth obesity paradox" described by us demonstrates clear sex differences. The described trend is particularly clear among young men—the difference in mean CAVI values between the extreme groups on both sides is 1.4, while in young

Table 3 Selected cardio-metabolic RF in groups of comparison stratified by phenotypes of corresponding vascular aging

Parameters	1 g Healthy aging	2 g Normal aging	3 g Early aging	*p*	ANOVA
Young males, *n* = 131					
n	42	44	45		
Body weight, kg	81.8 ± 1.8	75.4 ± 2.2	71.4 ± 2.1	$P_{1–2}$ = 0.026 $P_{2–3}$ = 0.205 $P_{1–3}$ = 0.000	0.002
BMI, kg/m^2	25.2 ± 0.5	23.6 ± 0.6	22.1 ± 0.6	$P_{1–2}$ = 0.052 $P_{2–3}$ = 0.087 $P_{1–3}$ = 0.000	0.001
Waist, cm	86.3 ± 1.7	82.3 ± 1.8	81.3 ± 2.0	$P_{1–2}$ = 0.110 $P_{2–3}$ = 0.710 $P_{1–3}$ = 0.062	0.139
Young females, *n* = 215					
n	73	71	71		
Body weight, kg	62.1 ± 1.2	59.3 ± 1.2	57.8 ± 1.1	$P_{1–2}$ = 0.111 $P_{2–3}$ = 0.376 $P_{1–3}$ = 0.011	0.038
BMI, kg/m^2	22.5 ± 0.5	21.3 ± 0.4	20.9 ± 0.4	$P_{1–2}$ = 0.043 $P_{2–3}$ = 0.569 $P_{1–3}$ = 0.010	0.019
Waist, cm	70.9 ± 0.9	70.0 ± 1.3	69.0 ± 0.9	$P_{1–2}$ = 0.594 $P_{2–3}$ = 0.529 $P_{1–3}$ = 0.174	0.460

BMI body mass index

Table 4 CAVI values and the main risk factors in groups of comparison stratified by BMI

Parameters	Young males, $n = 93$			p_{1-2} p_{2-3} p_{1-3}	Young females, $n = 171$			p_{1-2} p_{2-3} p_{1-3}
	Group 1 Insufficient BW $n = 12$	Group 2 Normal BW $n = 56$	Group 3 Excess BW $n = 25$		Group 1 Insufficient BW $n = 32$	Group 2 Normal BW $n = 119$	Group 3 Excess BW $n = 20$	
CAVI-R	6.7 ± 0.2	5.7 ± 0.1	5.3 ± 0.1	$P_{1-2 = 0.000}$ $P_{2-3 = 0.008}$ $P_{1-3 = 0.000}$	5.8 ± 0.14	5.6 ± 0.06	5.5 ± 0.13	$P_{1-2 = 0.141}$ $P_{2-3 = 0.286}$ $P_{1-3 = 0.091}$
CAVI-L	6.8 ± 0.2	5.9 ± 0.1	5.4 ± 0.1	$P_{1-2 = 0.000}$ $P_{2-3 = 0.002}$ $P_{1-3 = 0.000}$	6.1 ± 0.11	5.9 ± 0.05	5.7 ± 0.13	$P_{1-2 = 0.298}$ $P_{2-3 = 0.134}$ $P_{1-3 = 0.053}$
SBP, mmHg	127.8 ± 3.2	131.9 ± 1.3	136.04 ± 3.5	$P_{1-2 = 0.211}$ $P_{2-3 = 0.183}$ $P_{1-3 = 0.145}$	114 ± 1.2	117 ± 0.86	125.15 ± 2.0	$P_{1-2 = 0.091}$ $P_{2-3 = 0.000}$ $P_{1-3 = 0.000}$
DBP, mmHg	74.6 ± 1.5	77.8 ± 1.02	77.72 ± 1.9	$P_{1-2 = 0.174}$ $P_{2-3 = 0.983}$ $P_{1-3 = 0.314}$	70.8 ± 1.01	70.9 ± 0.6	74.65 ± 1.5	$P_{1-2 = 0.925}$ $P_{2-3 = 0.030}$ $P_{1-3 = 0.031}$
HR, beats/min	81.9 ± 6.3	74.3 ± 1.5	73.96 ± 2.7	$P_{1-2 = 0.087}$ $P_{2-3 = 0.907}$ $P_{1-3 = 0.177}$	76.5 ± 1.6	72.1 ± 1.1	74.6 ± 2.5	$P_{1-2 = 0.056}$ $P_{2-3 = 0.369}$ $P_{1-3 = 0.514}$
TC, mmol/L	3.5 ± 0.2	3.5 ± 0.1	4 ± 0.2	$P_{1-2 = 0.904}$ $P_{2-3 = 0.038}$ $P_{1-3 = 0.097}$	4.02 ± 0.2	3.94 ± 0.08	4.6 ± 0.16	$P_{1-2 = 0.652}$ $P_{2-3 = 0.003}$ $P_{1-3 = 0.033}$
HDL, mmol/L	1.02 ± 0.08	0.99 ± 0.04	0.95 ± 0.06	$P_{1-2 = 0.776}$ $P_{2-3 = 0.538}$ $P_{1-3 = 0.502}$	1.5 ± 0.08	1.35 ± 0.03	1.13 ± 0.13	$P_{1-2 = 0.028}$ $P_{2-3 = 0.014}$ $P_{1-3 = 0.013}$

TG, mmol/L	1.1 ± 0.3	1.04 ± 0.1	1.6 ± 0.2	$P_{1-2=0.821}$ $P_{2-3=0.020}$ $P_{1-3=0.218}$	0.7 ± 0.04	0.82 ± 0.04	1.35 ± 0.2	$P_{1-2=0.417}$ $P_{2-3=0.000}$ $P_{1-3=0.006}$
LDL, mmol/L	1.9 ± 0.3	2.1 ± 0.1	2.32 ± 0.14	$P_{1-2=0.688}$ $P_{2-3=0.188}$ $P_{1-3=0.198}$	2.1 ± 0.2	2.21 ± 0.08	2.8 ± 0.2	$P_{1-2=0.620}$ $P_{2-3=0.006}$ $P_{1-3=0.011}$
AC	3.5 ± 0.2	3.7 ± 0.2	4.23 ± 0.3	$P_{1-2=0.731}$ $P_{2-3=0.131}$ $P_{1-3=0.094}$	2.75 ± 0.2	2.9 ± 0.09	4.38 ± 0.37	$P_{1-2=0.422}$ $P_{2-3=0.000}$ $P_{1-3=0.000}$
Glucose, mmol/L	4.9 ± 0.05	4.99 ± 0.1	5.02 ± 0.15	$P_{1-2=0.830}$ $P_{2-3=0.877}$ $P_{1-3=0.671}$	4.75 ± 0.1	5.1 ± 0.07	4.89 ± 0.2	$P_{1-2=0.065}$ $P_{2-3=0.373}$ $P_{1-3=0.499}$

AH arterial hypertension; *BW* body weight; *TC* total cholesterol; *HDL* high-density lipoproteins; *TG* triglycerides; *LDL* low-density lipoproteins; *AC* atherogenicity coefficient, *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *HR* heart rate, *CAVI-L* cardio-ankle vascular index left; *CAVI-R* cardio-ankle vascular index right females it is only 0.3 for CAVI-R and 0.4 for CAVI-L. At the same time, thin young males have markedly higher values than thin young females, and in contrast, obese young males have lower values than obese young females. At the same time, the differences between the groups reach significant differences. It is noteworthy that this trend on the part of VS indicator is observed despite the increase in both SBP and DBP from group 1 to group 3. An unfavorable tendency was also revealed in the above groups on the side of lipidogram parameters, and it was especially strong in young females.

The data presented in the tables in their totality characterize the age specificity of vascular aging at the young stage of the life cycle. It is shown that there is no special influence of the main RF on VS and its, in fact, paradoxical reaction to the increase in BM. Moreover, this seemingly positive rearrangement of the arterial wall occurs in young individuals despite the obvious deterioration of hemodynamics and lipid status associated with overweight and/or obesity.

According to the current literature [37, 38], the correlation between VS and overweight and/or obesity in older age groups is quite different—in adulthood the correlation between these parameters is close to zero, and in old age it becomes positive. At the same time, our data coincide with the results of pediatric studies indicating a lower level of VS in obese children compared to their normal-weight peers [39, 40]. The authors explain this phenomenon in children by the inclusion of a peculiar adaptation mechanism as a consequence of the training effect of excessive BM on the activity of their CV system by analogy with physical exercise. This adaptation moment is limited in time and therefore some researchers call it a "honeymoon period" [41].

Summarizing these data with our results on young people, we can conclude that the directionality of the effect of the above RF on the arterial wall in terms of its stiffness has clear age-specific features that should be taken into account when planning preventive interventions for individuals of different ages. We believe that despite the youthful "obesity paradox" described by us, the correction of metabolic and hemodynamic disorders should be started in youth, even in the presence of seemingly different rejuvenating effect of obesity on the vascular wall, which we described above. Only from such long-term positions in the planning and implementation of preventive interventions can we expect to slow down vascular aging in mature and elderly people in full compliance with the principles of 3P-medicine.

7 Arterial Hypertension in Young Adults: Particularities of Metabolic and Hemodynamic Status

Since elevated BP of all RF makes the most significant contribution to CV mortality of the adult population, we believe that the study of AH features at the beginning of the pathogenetic continuum, to which young people correspond, deserve special attention.

The data in Table 5 show that in young males the index of vascular stiffness CAVI on both sides of its registration slightly decreases with increasing BP although the differences between the groups do not reach a significant level ($p = 0.099$ on the left and $p = 0.105$ on the right). It should be reminded that this index characterizes the state of the middle shell of the arterial wall and its increase indicates an increase in arterial stiffness due to the development of arteriosclerosis and loss of its elastic potential. Therefore, the data obtained in young males with AH on the decrease of CAVI index indicate the improvement of elastic properties of arteries, which we can explain by the higher BMI in this group and for this reason associated with the previously described youth obesity paradox. At the same time, the ankle-brachial index (ABI), which reflects, with its decrease, the impairment of mainly the internal arterial sheath due to atherosclerosis, also slightly decreases and for this parameter the differences between the groups reach significant values for both sides of the registration ($p = 0.000$ on the left and $p = 0.004$ on the right). BMI and waist score show an increase in the presence of AN/PH, but it is not significant ($p = 0.074$) and ($p = 0.103$), respectively. Most of the atherogenic lipid status parameters tend to be increased, anti-atherogenic HDL tend to be decreased, but the differences between normo- and hypertensive young males are not significant. Fasting blood glucose is unchanged. The incidence of aggravated heredity (BH) for the development of early

Table 5 Selected hemodynamic, metabolic, and other parameters at AH/PH in young males ($n = 131$)

Parameters	Normotension $n = 58$	AH/PH $n = 73$	p
Young males			
HR, beats/min	74.7 ± 15.2	75.9 ± 13.9	0.630
CAVI-R	5.83 ± 0.8	5.60 ± 0.74	0.105
CAVI-L	5.98 ± 0.8	5.76 ± 0.73	0.099
ABI on the right	1.07 ± 0.1	1.02 ± 0.08	0.004
ABI on the left	1.08 ± 0.08	1.02 ± 0.08	0.000
BMI, kg/m^2	22.89 ± 4.4	24.2 ± 3.7	0.074
Waist, cm	81.4 ± 8.9	84.8 ± 11.5	0.103
TC, mmol/L	3.58 ± 0.76	3.70 ± 0.86	0.552
HDL, mmol/L	1.03 ± 0.21	1.01 ± 0.29	0.805
TG, mmol/L	1.13 ± 0.64	1.25 ± 0.91	0.532
LDL, mmol/L	2.06 ± 0.7	2.16 ± 0.68	0.559
AC	3.56 ± 0.88	3.77 ± 1.30	0.464
Glucose, mmol/L	5.03 ± 0.68	5.03 ± 0.73	0.992
Smoking, *n* (%)	6 (10.3)	9 (12.3)	0.674
BH, *n* (%)	17 (29.3)	30 (41.1)	0.160

Note: *AH* arterial hypertension; *PH* prehypertension; *HR* heart rate; *CAVI-R* cardio-ankle vascular index right; *CAVI-L* cardio-ankle vascular index left; *ABI* ankle-shoulder index; *BMI* body mass index; *TC* total cholesterol; *TG* triglycerides; *HDL* high-density lipoproteins; *LDL* low lipoproteins; *AC* atherogenicity coefficient; *BH* burdened heredity

CVD in families among young hypertensive males reached 41% versus almost 30% in normotensive males, but the difference is not significant ($p = 0.160$). The number of smokers in the compared groups is almost the same, but it is slightly higher in the group with AN/PH. Table 6 summarizes selected hemodynamic, metabolic, and other parameters at AH/PH in investigated young females.

Among the examined young females (Table 6), the changes in the vascular stiffness index CAVI on the left and right sides show a similar tendency to its decrease with increasing BP. Moreover, on one side the differences between the groups reach quite a significant level ($p = 0.012$ on the left and $p = 0.133$ on the right). The ABI in young females also showed a similar trend to that of young males, with a significant decrease in ABI in AN/PH carriers compared to normotensive peers ($p = 0.003$ on the left and $p = 0.007$ on the right). In young females, BMI and waist also showed an increase in the presence of AH/PH, with the former parameter showing significant differences between groups ($p = 0.000$). As in young males, most atherogenic lipid status indicators in the weaker sex tend to increase, anti-atherogenic HDL—to decrease, but the differences between normo- and hypertensive young females are not significant. Fasting blood glucose in young females does not show a significant increase with increasing BP ($p = 0.174$), and its mean values do not exceed the acceptable norm. BH on early CVD among hypertensive young females was

Table 6 Selected hemodynamic, metabolic, and other parameters at AH/PH in investigated young females ($n = 215$)

Parameters	Normotension $n = 168$	AH/PH $n = 47$	p
Young females			
HR, beats/min	72.0 ± 10.1	78.3 ± 11.8	0.002
CAVI-R	5.62 ± 0.7	5.46 ± 0.6	0.133
CAVI-L	5.87 ± 0.64	5.63 ± 0.5	0.012
ABI on the right	1.08 ± 0.08	1.04 ± 0.08	0.007
ABI on the left	1.07 ± 0.07	1.03 ± 0.07	0.003
BMI, kg/m^2	20.99 ± 2.7	23.82 ± 4.6	0.000
Waist, cm	69.5 ± 7.4	72.11 ± 8.5	0.132
TC, mmol/L	4.00 ± 0.8	3.99 ± 0.8	0.920
HDL, mmol/L	1.39 ± 0.3	1.25 ± 0.35	0.129
TG, mmol/L	0.85 ± 0.5	0.89 ± 0.49	0.702
LDL, mmol/L	2.27 ± 0.7	2.28 ± 0.78	0.944
AC	3.02 ± 0.8	3.33 ± 1.26	0.298
Glucose, mmol/L	4.91 ± 0.5	5.22 ± 0.96	0.174
Smoking, *n* (%)	2 (1.2)	1 (2.1)	0.620
BH, *n* (%)	55 (32.7)	21 (44.7)	0.173

AH arterial hypertension; *PH* prehypertension; *HR* heart rate; *CAVI-R* cardio-ankle vascular index right; *CAVI-L* cardio-ankle vascular index left; *ABI* ankle-shoulder index; *BMI* body mass index; *TC* total cholesterol; *TG* triglycerides; *HDL* high-density lipoproteins; *LDL* low lipoproteins; *AC* atherogenicity coefficient; *BH* burdened heredity detected in almost every second, while in the normotensive group only in every third. The number of young females who smoked did not exceed 1.5% of all those examined in the two groups.

In general, the materials presented in this subchapter once again show the presence of specific associations between arterial stiffness and BP at young age, which predetermine the possibility of AH development in young people at overweight despite the presence of a favorable vascular status in the form of a reduced VS indicating a good elastic status of the arteries. Usually in the literature, when describing the relationship between AH and VS in the traditional mature population, it is stated that there is a direct relationship between these parameters of hemodynamic status [42]. The favorable variant of AH presented by us was practically not described. Meanwhile, based on our own results, carriers of this form of elevated BP among young males are almost 40%, and among young females—14%. Taken together, our data indicate the need to use in the practice of dispensary measures among young people the method of angiological screening to assess the VS index and identify vascular phenotypes with mandatory and timely consideration of BP level in each young person.

8 3PM-Related Concepts to Maintain Vascular Health in the Population

Vascular aging phenotypes can be determined at both clinical and preclinical stages of the CV continuum. In patients with overt CV pathology, assessment of vascular age (VA) can be used to improve compliance with treatment and to assess the effect of therapy on VS as one important indicator of its efficacy. These are technologies within the framework of reactive or disease-oriented medicine. In the case of young students, we should talk about preclinical diagnostics, which in essence corresponds to health-oriented medicine and aims to inhibit or even stop the process of initial development of CV pathology, which, in turn, is the most effective way to reduce CVD and mortality. This approach is fully consistent with the principles of 3P-medicine. The main stake in this contingent is made not on traditional pharmaceutical therapy, but on preventive interventions aimed not only at correction of traditional RF, but at restoration of favorable vascular aging or its maintenance. For this reason, we advocate the introduction of instrumental assessment of VS, which is the main determinant of vascular age, and its further correction as the main technologies of the youth dispensary system.

What are the main principles of corrective measures after determination of VA phenotype in young people? Of course, first and foremost, these should be strategies based on a rational lifestyle.

In this section, we focus on the mechanisms by which lifestyle-based strategies can modulate arterial stiffness without much effect on BP [43]. The authors suggest that lifestyle-based strategies designed to maintain or restore healthy vascular aging appear more likely to influence the functional components of arterial stiffness. After all, it is difficult to identify any structural changes that might occur during the time period that is usually assessed in traditional prospective studies [21].

8.1 Physical Activity

The results of studies aimed at investigating the cellular and molecular mechanisms of the positive effects of aerobic exercise on cardiovascular function in aging have shown the important role of inhibition of oxidative stress and inflammation during such exercise [44]. In an experiment on mice, it has been shown that aerobic exercise can improve the status of vascular mitochondria in elderly animals [45], and lifelong exercise can prevent age-related decline in the functional status of mitochondria in the vascular wall [46]. Older adults who engage in aerobic exercise have also been found to have lower markers of endothelial cell senescence compared to their sedentary peers [47]. These markers include, for example, less blood flow-mediated dilatation of the brachial artery. The authors conclude that the described effect of aerobic exercise on vascular function is to inhibit various signs of aging in arterial wall structures through suppression of oxidative stress and inflammation or both simultaneously. To this end, starting with early age, for example, in subpopulations of school children, personalized couching of body exercises is essential to meet individual needs and effectively promote health conditions [48].

8.2 Impacts by Healthy Dietary Patterns

8.2.1 Calorie Restriction (CR)

Reducing total caloric intake (by approximately 30–40%) while maintaining adequate micronutrient intake is one of the most well-studied and documented methods of beneficial effects on the CV system [49]. In an experiment, it has been shown that lifelong CR in mice can prevent endothelial dysfunction, arterial stiffness and increased SBP by partially preventing excess oxidative stress, as well as preserving NO bioavailability and the balance of arterial wall structural proteins (collagen and elastin). It was still found that lifelong CR could preserve the abundance and/or activity of SIRT-1 and mTOR (with no differences compared to young control groups), which allowed the authors to suggest that CR contributes to the preservation of vascular function throughout life, partially affecting a hallmark of aging such as “unregulated nutrient uptake” [50]. CR may also improve CV system health during aging by enhancing autophagy, suggesting that CR may also affect another hallmark of aging, “impaired proteostasis” [51].

Diet-induced weight loss (consumption of a diet designed to reduce body weight by 10%) in young and elderly people with overweight and/or obesity has also been shown to improve vascular endothelial function and arterial stiffness [52]. Moreover, the improvement in endothelial function was associated with a reduction in oxidative stress as assessed by circulating oxidized low-density lipoprotein cholesterol. It has also been demonstrated that diet-induced weight loss in overweight and obese adults can reduce arterial stiffness and SBP by 7–8 mmHg [53, 54]. Taken together, these results suggest that CR-mediated weight loss may be an effective dietary approach to improve cardiovascular health at different ages.

8.2.2 Limiting Dietary Sodium Intake

Given the clear association between excessive dietary sodium intake and cardiovascular dysfunction [55], reducing sodium intake is recommended as a lifestyle/nutritional strategy for individuals at increased risk of CVD (e.g., adults with overweight and/or obesity). Historically, dietary sodium restriction (DSR) has been promoted as a therapeutic strategy to reduce BP—for example, the DASH diet is an important component of the dietary approach to the treatment of hypertension [56]; however, excessive dietary sodium intake has adverse effects independent of BP. It has been found that DSR can improve endothelial function in arteries by increasing NO bioavailability secondary to a reduction in excess suppression of endothelial function associated with oxidative stress [57]. DSR has also been found to be associated with reduced aortic stiffness in adults with overweight and/or obesity [58, 59]. Some investigators suggest that DSR may improve endothelial function by altering arteriolar deoxyribonucleic acid methylation patterns (i.e., through epigenetics) [60]. In other words, DSR may be a safe and effective dietary strategy to improve CV health in adults with overweight and/or obesity.

8.2.3 Relevant Dietary Models

As mentioned earlier, the DASH diet was specifically designed to reduce BP, and its efficacy for reducing BP in adults with overweight and/or obesity has already been established. Data from a large cohort longitudinal study also suggest that the DASH diet independently inhibits the increase in arterial stiffness between the ages of 36 and 64 years [61]. However, the effect of the DASH diet on endothelial function is equivocal [62, 63].

The Mediterranean diet is defined as a diet rich in whole grains, vegetables, legumes, fruits, seeds, herbs, spices, olive oil and, in moderation, seafood, dairy products and poultry. It has demonstrated clear efficacy to improve arterial stiffness, endothelial function, normalize SBP [64, 65] and prevent CVD [66]. In the elderly, effects on arterial stiffness and SBP levels have been found [67]. The cardiovascular function-promoting effects of both the DASH and Mediterranean diets are thought to be due in part to the high intake of soluble fiber that accompanies these diets. Numerous epidemiological and intervention studies involving large cohorts have shown that high-fiber diets reduce CVD-related morbidity and mortality [68–71].

Unfortunately, a low percentage of individuals with overweight and/or obesity follow the recommended daily intake of total dietary fiber (25–30 g/day) [71]. The DASH diet and Mediterranean diet as a dietary style may represent effective approaches to increase fiber intake in adults with overweight and/or obesity. Recently, a group of researchers from Colorado conducted a controlled nutrition study in children and adolescents under 18 years of age to determine the effects of dietary fiber on arterial function, in which one part of the study included a short-term (7-day) high-fiber diet. The results of this study showed that increasing dietary fiber in this population was a safe and effective strategy to improve endothelial function and SBP (4 mmHg reduction in 7 days), and that these improvements may be due to a reduction in vascular oxidative stress [72]. However, more work is required to determine whether high-fiber diets directly affect vascular function in aging and to explore the potential mechanisms underlying these effects.

The European Association of Preventive Cardiology (EAPC) in the latest version of its recommendations for the prevention of major CVD [73] presents for practical use the following positions of the formation of a rational diet, which in general coincide with the principles of the above-described diets.

Characteristics of a healthy diet (EARS, 2021):

1. The basis of the diet is predominantly plant foods rather than animal foods.
2. Saturated fatty acids account for <10% of daily calories and are replaced by polyunsaturated fatty acids, monounsaturated fatty acids, and whole-grain carbohydrates
3. Trans-unsaturated fatty acids should be minimized where possible, eliminating their intake from processed foods.
4. <5 g of table salt per day.
5. 30–45 g dietary fiber per day, preferably from whole-grain products.
6. ≥200 g of fruit per day (≥2–3 servings).
7. ≥200 g of vegetables per day (≥2–3 servings).
8. Limiting red meat intake to 350–500 g/week, especially processed meat should be minimized.
9. Consumption of fish one to two times per week, especially oily fish is recommended.
10. 30 g of unsalted nuts per day.
11. Limit alcohol consumption to 100 g/week.
12. Avoid sugary drinks such as soft drinks and fruit juices.

8.3 Dietary Supplements

Regular aerobic exercise, a healthy diet, reducing caloric intake (if necessary) and restricting certain nutrients (e.g., DSRs) are likely to be the most effective approaches to promote healthy aging of the CV system. From a public health perspective, these interventions should be considered first-line strategies [74, 75]. A complementary approach could be the use of "natural" therapies such as nutraceuticals, defined as dietary supplements that may benefit human health in the aspect of inhibition of premature aging [76, 77] or certain synthetic pharmacological agents based on consideration of physiological functions and with favorable safety profiles. In this aspect, it is worth highlighting the long-term research data of the already mentioned group from Colorado [15, 21], as such an approach to influence the primary mechanisms of age-related vascular dysfunction is particularly relevant for the young population in accordance with the principles of 3P medicine. Their research concerns compounds that target: (1) nitric oxide (NO) bioavailability; (2) mitochondrial health and mitophagy involvement; (3) inflammation; (4) energy perception and NAD+ homeostasis; (5) cellular senescence.

8.4 Bioavailability of Nitric Oxide (NO)

NO bioavailability decreases with age and can be increased with certain lifestyle modifications [78]. Therefore, NO represents a therapeutic target for the correction and/or prevention of CV aging [79]. Supplementation of inorganic nitrite to old and young mice in their diet has been shown to completely reverse age-related endothelial dysfunction by increasing NO bioavailability secondary to a reduction in oxidative stress, as well as reducing arterial stiffness [80]. Similar changes have been described in adult subjects by sodium nitrite administration [78, 81]. The mechanism of such anti-aging effects has been deciphered. It has been shown that sodium nitrite supplementation leads to a decrease in free oxygen radical (ROS) levels in the mitochondria of the vascular wall and thereby contributes to mitochondrial stress resistance [81]. Research is now ongoing with inorganic nitrate supplementation using nitrate-rich beetroot juice to increase NO bioavailability to improve vascular function and normalize BP in patients with chronic kidney disease. If beetroot juice is shown to be safe and effective, it could be a very useful nutraceutical to improve vascular function and reduce the risk of CVD in chronic kidney disease, as these diseases are the leading cause of death in these patients [82].

8.5 Mitochondrial Health as the Target for Anti-aging Strategies

Mitochondria are frequently the major source of excessive oxidative stress in aging. Therefore, targeting the mitochondrial health becomes an effective therapeutic approach for preventing and treating age-related vascular dysfunction [83]. It was found that the addition of the mitochondria-targeted antioxidant MitoQ to the diet of aged mice completely restores (returns to youthful levels) endothelial function by increasing NO bioavailability, reducing ROS in mitochondria and, in part, by increasing mitochondrial resistance to stress [84]. The same effect was obtained in adults with overweight and/or obesity [85].

It has been shown that the disaccharide and natural autophagy enhancer trehalose can reverse age-related endothelial dysfunction by increasing NO bioavailability and reducing ROS-related EDD over-suppression and may also reduce age-related arterial stiffness. These changes have been associated with reduced inflammation and increased activation of mitochondrial quality control and autophagy pathways in the vascular network [86, 87]. In addition, trehalose reduced vascular mitochondrial oxidative stress, suggesting an improvement in mitochondrial status [87]. In adults with overweight and/or obesity, it was found that trehalose supplementation could improve arterial resistance to EDD by increasing NO bioavailability and reducing excess oxidative stress; however, trehalose had no effect on arterial stiffness in this cohort [88]. As trehalose is a disaccharide (carbohydrate), long-term administration requires body weight control [88]. The natural polyamine spermidine has also been studied in terms of its effect on autophagy, and it was found that spermidine is generally safe and can restore age-related impairment of NO-mediated endothelial function and reverse aortic stiffness in mice [89]. The improvement in arterial function was mediated by a reduction in vascular oxidative stress and was associated with increased activation of autophagic pathways [89]. Clinical studies showed that dietary spermidine intake is inversely associated with BP and cardiovascular disease risk [90]. More information about the mitochondrial health—associated medical conditions is provided in the chapter "*Mitochondrion: The Subordinated Partner Who Agreed to Come Short but Insists in Healthy Life*" by Golubnitschaja O.

8.6 Adverse Effects by Inflammation

Inflammation is a well-known mechanism of CV system aging [91, 92]. A study of the anti-inflammatory nutraceutical curcumin (the main polyphenol contained in turmeric) in an experiment showed that its administration could restore NO-mediated endothelial function and normalize arterial stiffness in old mice by reducing excess oxidative stress [93]. In humans, curcumin supplementation was able to improve NO-mediated resistance and arterial endothelial function by reducing excess oxidative stress, but had no effect on arterial stiffness [94]. Curcumin may be a promising nutraceutical for the treatment of vascular dysfunction in different groups of patients with accelerated vascular aging, but further studies are required.

8.7 Bioavailability of NAD+

Decreased NAD+ bioavailability is thought to be an important mechanism for age-related decline in physiological functions, in part because of NAD+'s role as a substrate for SIRT-1 and its association with unregulated nutrient uptake. NAD+ is also an important coenzyme for various cellular reactions that regulate DNA repair, inflammation, metabolism, and other processes [95]. Consequently, the addition of a precursor for NAD+ biosynthesis has become one of the most popular ways to increase NAD+ levels and promote healthy aging. Increasing NAD+ bioavailability is a compelling therapeutic approach to treat and/or prevent vascular dysfunction in aging, given that increasing the amount/activity of SIRT-1 is an effective strategy to improve vascular function in aging [96]. The administration of the NAD+ precursor, nicotinamide mononucleotide (NMN) in the diet of aged experimental animals can restore NO-mediated endothelial function by reducing excessive ROS bioactivity and reverse arterial stiffness, favorably modulating the intrinsic mechanical stiffness of the aortic wall and structural protein levels (more elastin and less collagen) [97]. The use of another NAD+ precursor, nicotinamide-riboside (NR) increases NAD+ bioavailability, that is evidenced by an increase in NAD+ metabolites in peripheral blood mononuclear cells. It was also found that NR could reduce SBP by 4 mmHg and reduce arterial stiffness with particular efficacy (SBP reduction by 9 mmHg) in patients with baseline SBP above normal (i.e., CAD ≥120 mmHg) [98].

8.8 Cellular Senescence

Different effects on cellular senescence to improve various age-related conditions are now being intensively studied [99]. Given that cellular senescence is among the fundamental mechanisms underlying vascular aging, targeting cellular senescence to treat CV aging is very promising [100–102]. Currently, the most widely accepted approach to reduce the burden of senescent cells is treatment with compounds that selectively clear/kill senescent cells and are therefore called senolytics. Typically, senolytic compounds are administered intermittently, with the aim of removing excess senescent cells in a single step, while maintaining basal cellular senescence levels and not interfering with processes such as wound healing [103] and cancer suppression [104]. Currently, synthetic pharmacological senolytics (e.g., dasatinib + quercetin) are undergoing clinical trials in various pathological conditions [105, 106] for their side effects, making it very difficult to introduce this senolytic strategy to adults without clinical disease. Accordingly, there is great interest in studying natural senolytics to improve age-related vascular dysfunction, as experts believe that these compounds have the greatest potential to restore and maintain a healthy aging CV system. A candidate natural senolytic is the flavonoid fisetin, which has been shown to exert senolytic effects in vivo and increase longevity and health markers in mouse models of both chronological and accelerated aging [107]. Experiments in aged mice show that administration of fisetin markedly increases NO-mediated endothelial function and reduces arterial stiffness, and that these improvements result from suppression of excess cellular senescence in the vascular wall [108]. However, further studies in adults with overweight and/or obesity are needed.

9 Conclusions and Expert Recommendations in the Framework of 3PM

Above presented data motivate follow-up research on EVA syndrome and application of innovative screening programs to the needs of young populations following the paradigm change from reactive medical services (clinically manifested disorders) to 3PM approach based on predictive diagnostics, targeted prevention, and treatments tailored to individualized patient profiles [8]. To maximize cost-efficacy, 3PM approach should be applied as early as possible in life. School children and students at Universities are certainly the target groups to reach the aims of 3PM in populations [18, 109–111].

In the context of the chapter, it is strongly recommended to implement below listed 3PM-related tools and relevant parameters to combat CVD epidemics in the population.

Suboptimal health status screening is instrumental to protect individuals against the transition from health to disease [6].

Endothelin-1 axes are involved in the regulation of vascular status and a myriad of processes highly relevant for physical and mental well-being. ET-1 blood plasma patterns are instrumental as a sensor of lifestyle quality and transition from suboptimal health conditions to diseases and as a predictor of aging and related pathologies [112].

Homocysteine metabolism presents the key pathways in post-genomic and epigenetic regulation mechanisms crucial for regulating methionine availability, protein homeostasis, and DNA-methylation. In particular, mild hyperhomocysteinemia remains frequently underdiagnosed although it is a strong indicator of an induced oxidative stress, systemic inflammation, impaired healing, compromised mitochondrial health, and increased risks of systemic disorders including coronary artery diseases, atherosclerosis, myocardial infarction, and ischemic stroke, among others [113].

Mitochondrial health risk assessment is instrumental for systemic effects including but not restricted to individualized cardiovascular health status. Mitophagy and mitochondrial "burnout" signals trigger SOS signals of developing downstream diseases such as chronic fatigue, accelerated aging, and associated pathologies. Contextually, a holistic predictive diagnostic test based on the mitochondrial health quality control is a powerful tool for advanced 3PM approach in primary and secondary care [114, 115].

Multi-parametric analysis and individualized phenotyping by artificial intelligence is instrumental for individualized health risk assessment in primary and secondary care for predictive approach and targeted prevention of potential risks [8].

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Personalized Management of Physiologic/ Ophthalmologic Particularities for Predictive Approach and Targeted Prevention of Primary Angle Closure Glaucoma Applied to Persons at Risk

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Abbreviations

ACA	Anterior chamber angle
ACD	Anterior chamber depth
ACV	Anterior chamber volume
AS-OCT	Anterior segment optical coherence tomography
AL	Axial length
AOD	Angle opening distance
AODA	Angle opening distance area
ARA	Angle recess area
I-Area	Iris area
ICurv	Iris curvature
IOL	Intraocular lens
IOP	Intraocular pressure
IT	Iris thickness
ITC	Iridotrabecular contact
IVol	Iris volume

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LE	Lens extraction
LPI	Laser peripheral iridotomy
LT	Lens thickness
LV	Lens vault
ML	Machine learning
GON	Glaucomatous optic neuropathy
PAC	Primary angle closure
PACD	Primary angle closure disease
PACG	Primary angle closure glaucoma
PACs	Primary angle closure suspect
PAS	Peripheral anterior goniosynechia
POAG	Primary open angle glaucoma
PD	Pupil diameter
SE	Spherical equivalent
SFCT	Subfoveal choroidal thickness
SLT	Selective laser trabeculoplasty
TIA	Trabecular iris angle
TISA	Trabecular-iris space area
TICV	Trabecular-iris circumference volume

1 Introduction

One of the features of modern medicine is the improvement of treatment from traditional (reactive) and to personalized one, based on individual predictors. This approach forms the new paradigm of treatment called the predictive, preventive, and personalized medicine (3PM/PPPM). The modern diagnostic technologies in ophthalmology provide a huge variety of clinical and anatomical parameters, which are sometimes difficult to assess in their totality. To this end, the search for individual biomarkers is of great relevance, which not only provide a personalized approach to the choice of treatment, but also make it as cost-effective as possible. At the same time, the development of quantitative predictors is recognized as the leading approach in modern paradigm of personalized medicine since they are the basis for the strategy of identifying different categories of the patients for whom standard treatment will not be successful. It is worth noting that the criteria for a personalized approach were initially of empirical nature, while the foundations of personalized medicine involve the use of evidence-based predictors of individualization. This review shows how the modern technologies with the use of machine learning methods allow using a differentiated approach to the treatment of primary anterior chamber angle closure.

Primary angle closure glaucoma (PACG) is still one of the leading causes of irreversible blindness. It is predicted that the number of glaucoma patients will have increased to 32 million by 2040 [1]. The risk of developing bilateral blindness is three times higher in PACG than in primary open angle glaucoma (POAG) [2].

Among many urgent problems associated with primary angle closure disease (PACD), the most important one is to determine the plan to treat primary angle closure suspect (PACs) and primary angle closure (PAC) to avoid the disease progression. Moreover, with the advancement of technologies for visualization of the anterior segment on optical coherence tomography (AS-OCT) and machine learning (ML) methods, the identification of both principle anatomical and topographic parameters, the determination of their threshold values [3, 4], as well as the development of classifications of ML-based AS-OCT images [5, 6], which allow to differentiate between the norm and pathology (PACs, PAC, PACG), are of great practical importance.

In early PACD, the choice of treatment tactics varies from complete refusal of treatment [7] to laser [8] and surgical interventions [9, 10]. Laser peripheral iridotomy (LPI) is a traditional method [11].

The ZAP study particularly clearly demonstrated the need for an individual approach to the choice of treatment for patients with early stage of PACD. In this study patients with bilateral PACs were observed, while one eye was randomly chosen for LPI, and the paired eye remained intact and served as a control [7]. After 6 years of follow-up, progression in the eyes with LPI was detected in 2% of cases (19 eyes out of 889), and in paired eyes in 4% of cases (36 eyes out of 889). Taking into account the data obtained, the authors recommended to abandon the widespread use of LPI for PACs. At the same time, the question of management of PACS remains open until now since its solution lies in the field of personalized medicine.

Some recent studies have reported on the higher efficiency of treatment of PACD with lens extraction (LE), including the removal of a transparent lens [12–14]. The EAGLE study (Effectiveness in Angle-closure Glaucoma of Lens Extraction Study Group) showed that LE has some advantages over LPI in PAC/PACG [12]. LE is associated with the higher risk of complications and the loss of physiological accommodation in relatively young patients, while LPI is a non-invasive, more accessible, and less expensive procedure. Therefore, the question rises how to choose LPI or LE should be the treatment of choice for PAC [15]. Obviously, the answer to this question lies in the field of personalized medicine. To solve this problem, it is necessary to search for the predictors of LPI and LE efficiency in each specific case [16].

It should be noted that the literature data on the predictors of LPI and LE efficiency in the treatment of PAC are ambiguous [17–21]. This fact is associated with the large number of estimated predictors correlating with each other, which makes it impossible to compare them in one study. It is possible to analyze clinical and anatomical parameters only with the use of machine learning methods, namely, the projection methods of multivariate statistical analysis that simultaneously take into account all available variables to assess treatment prognosis [22–27]. Moreover, the identification of predictors of treatment efficiency opens up the prospects for a personalized approach.

In cases of insufficient post-LPI IOP reduction and in the presence of contraindications to LE early PACD may be treated with the use of selective laser trabeculoplasty (SLT) [28–30].

Thus, the current studies are aimed at a personalized approach to the treatment of patients with early PACD, based on the predictive medicine data.

2 Differential Diagnosis of Early Stages of Primary Angle Closure Disease

According to the P. J. Foster classification, PACD includes PACs, PACs, and PACGs [31]. PACs are characterized by iridotrabecular contact (ITC) extending over two quadrants, normal intraocular pressure (IOP), the absence of increased IOP, peripheral anterior goniosynechia (PAS) and glaucomatous optic neuropathy (GON). PAC is diagnosed if there are more than two quadrants of ITC in combination with increased IOP and/or PAS, but without GON. In the presence of GON, PACG is diagnosed.

The assessment of the anterior chamber angle (ACA) by gonioscopy is essential to differentiate between appositional and goniosynechial closure of the ACA. Nevertheless, subjectivity, insufficient reproducibility of the method, unintentional compression during the examination can reduce the accuracy of the method [32]. Automatic gonioscopy is rather effective [33]; however, AS-OCT is currently an important method in detecting the early stages of PACD [34]. An example of ACA visualization of PAC on AS-OCT CASIA2, Tomey, Japan is shown in Fig. 1.

PACD differs from the norm in the values of the following anatomical parameters of an eye: axial length (AL), spherical equivalent (SE), anterior chamber depth (ACD), ACA, lens, iris, and choroid parameters.

2.1 Axial Length, Spherical Equivalent, Anterior Chamber Depth

According to the literature, short AL and shallow ACD are associated with occlusion angles [35]. The study by Y. Zhang demonstrated that PACs eyes significantly differ from the norm in short AL, shallow ACD, and high SE [6]. Moreover, S. Zhou et al. (2023) showed that the risk of PACD progression increases significantly in hypermetropia and minor ACD [36]. In addition, short AL in paired eyes with an acute PAC attack is associated with reduced angle opening distance (AOD750) [37].

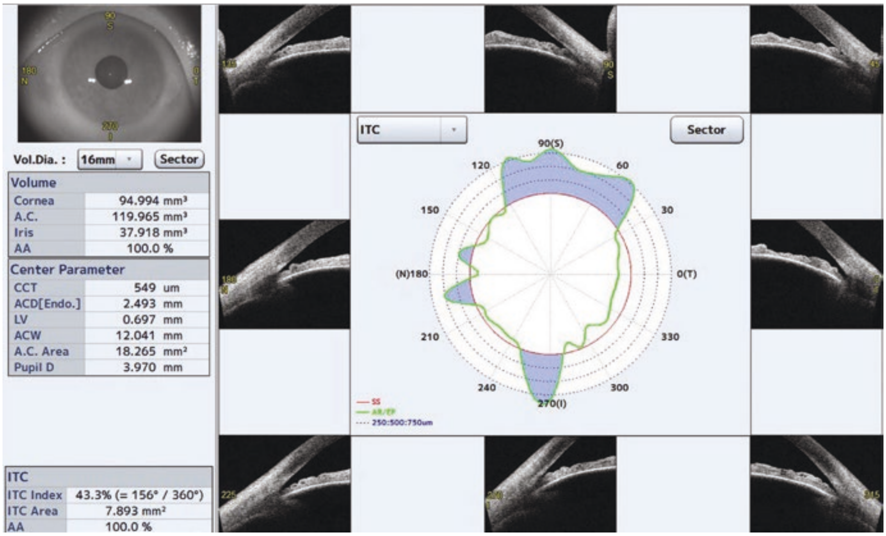


Fig. 1 Clinical example of anterior chamber angle imaging of a patient with primary angle closure on AS-OCT CASIA2, Tomey, Japan. Note: areas of goniosynechia, determined automatically during scanning, are highlighted in blue

2.2 Parameters of Anterior Chamber Angle

PACD is characterized by smaller ACA [4, 6, 38]. Thus, E. K. Melese et al. studied ACA parameters to determine the threshold values of occlusion angles in comparison with open angles, analyzing the data of the patients with POAG and PACG/PAC/PACs in a comparative aspect [4]. AOD750 in the lower sector, as well as trabecular-iris circumference volume (TICV) demonstrated high diagnostic value.

N.I. Kurysheva et al. revealed the threshold ACA values that allow distinguishing not only between the early PACD and the norm, but also between PACs and PAC [3]. TISA500 in the lower sector showed the highest accuracy in determining the early transition of PACs to PAC.

Y. Zhang et al. used three prediction algorithms for the detection of PACs (backward logistic regression, naïve Bayes' classification, and neural network) [6]. According to the study results, the ACA parameters in PACs were significantly less than normal (AOD500, trabecular-iris space area (TISA500), angle recess area, ARA750). It is worth noting that none of the algorithms met the requirements of population screening for PACD. The authors explained this fact by different mechanisms of ACA closure.

Nevertheless, in 2023 Y. Eslami et al. classified AS-OCT images into normal, PACs and PAC/PACG using deep learning [5].

2.3 Lens

The lens parameters (lens thickness (LT) and lens vault, (LV)) are associated with PACD. Moreover, LV is the most informative parameter in comparison with its thickness [39]. LV parameter characterizes the lens position relative to other structures of the anterior segment determining almost 70% of the variations in the width of the anterior chamber. An example of lens visualization in the PAC patient on AS-OCT CASIA2, Tomey, Japan is shown in Fig. 2.

It was shown that LV values determine the transition of PACs into PAC [3]. An increase in LV in PACD [38] leads to a decrease in ACD, ACA, and the disease progression. Maximal lens thickness and lens vault among PACD subtypes have been noted in acute PAC [40, 41].

2.4 Iris and Choroid

The parameters of the iris and foveal choroid are of particular interest to researchers as the markers of PACD.

It has been shown that an increase in iris curvature (ICurv), iris area (I-Area), iris thickness (IT750) on AS-OCT is associated with narrow angles even with the account of age, sex, ACD, AL, and pupil diameter [42]. Interestingly, W. Huang et al. reported on an IT750 increase in PACs/PAC, but not in PACG [43]. The authors explained this fact with a higher IOP in the PACG group leading to a decrease of the initially increased iris thickness.

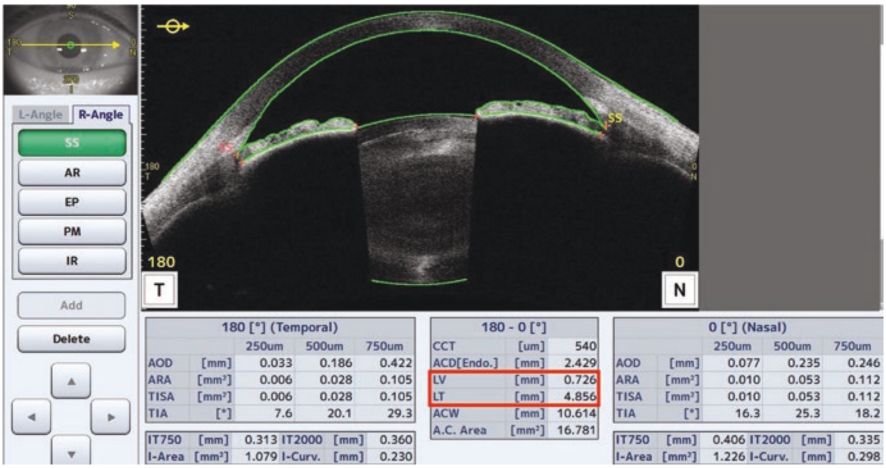


Fig. 2 Clinical example of visualization of the lens of a patient with primary angle closure on AS-OCT CASIA2, Tomey, Japan. Note: lens thickness (LV) and lens vault (LV) are highlighted in red

According to the literature, increased subfoveal choroidal thickness (SFCT) may be a predictor of early PACD [3, 44, 45]. Nevertheless, some authors described the choroidal thinning with prolonged AL in response to an IOP increase during dark room prone provocative testing in eyes with PAC [46]. W. Song suggested that if during the onset of an attack the choroidal thickness increases with an IOP increase, then it can become thinner again due to significant hypertension [47].

The correlation between the parameters of iris and choroid is of a particular interest. W. Huang et al. revealed an inverse correlation between the thickness of the iris and the foveal choroid in PACs/PAC/PACG, but not in the control group [43]. The authors explained this fact with the presence of a single blood supply system from the ophthalmic artery. With an increase in resistance to blood flow in the long posterior ciliary artery, blood flow increases in the short posterior ciliary artery, followed by the choroidal expansion. Subsequently, this mechanism was confirmed in another study on a group of patients with PACs and PAC [3].

Moreover, PAC treatment has been found to result in a change in the foveolar choroid thickness [14]. Thus, the post-LPI choroidal thickness significantly increased in all sectors, except for the upper and temporal ones, 3 mm from the center of the foveola, as well as in the foveola itself. The post-LE choroidal thickness increased in all sectors, except for the nasal one, 3 mm from the center of the foveola. There was no significant difference in SFCT between the groups after the treatment.

Therefore, the collected data demonstrate an increase in the choroidal thickness almost in all sectors after LPI, which is consistent with the results of other authors. It has been noticed that a 1 mmHg IOP decrease is associated with 3.4 μm SFCT increase [48]. Other studies comparing choroidal thickness before and after trabeculectomy [49, 50] have also demonstrated the involvement of the choroid in the PACD pathogenesis.

Thus, the biometric parameters of the patients with early PACD differ from the norm. AS-OCT image analysis is a key area in the development of predictive medicine in the field of PACD. Further research and the development of machine learning methods (neural network) are required to identify the threshold values of parameters in PACs and PAC for early detection of the disease.

3 Predictors of Treatment Efficiency in Early Stages of Primary Angle Closure Disease

3.1 Predictors of Laser Peripheral Iridotomy Efficiency

The current literature on the search for predictors of laser peripheral iridotomy success in PACD is rather ambiguous. This fact is explained by the choice of various postoperative clinical and topographic parameters taken by researchers for the success of treatment: hypotensive effect (ΔIOP), change in ACA, including according to AS-OCT, AOD500, AOD750, TISA500, TISA750, ARA500, ARA750, TICV500, TICV750, trabecular iris angle (TIA500), angle opening distance area (AODA750), ICurv, and ACD [8, 11, 17, 18, 22, 51–59]. The authors differently interpret the choice of one or another parameter as a criterion for assessing the success of treatment. It is known that AOD is a predictor of ACA closure, significantly correlated with gonioscopy data [60]; therefore, Δpost-LPI AOD750 is a criterion for the effectiveness of PACD treatment [17, 51–54]. The choice of a change in the trabecular-iris space area after LPI as a criterion for the treatment success is due to the fact that it is less affected by the variability of the iris relief in contrast to the AOD linear parameter [55]. Other researchers choose a change in post-LPI ΔAODA750 to avoid the influence of local changes in the iris relief [18].

The following predictors of LPI success in PACD were identified according to the literature:

- old age [22, 57, 59] and young age [54]
- high preoperative IOP [22, 51]
- increased lens thickness and lens vault [8, 18, 22, 51, 53, 54, 58] and the presence of cataracts [22]
- уменьшенная anterior chamber depth [22] и увеличенные ACD [17, 53] and anterior chamber volume (ACV) [59]
- smaller anterior chamber angle parameters (AOD750) [17, 52, 53] and Shaffer angle opening degree in superior sector [22]
- reduced axial length [53]
- increased iris curvature [11, 17, 22, 53, 57]
- smaller iris area [17, 57] and iris volume [18]
- increased iris thickness [51] and decreased IT [22, 55]
- reduced spherical equivalent [18]
- superior LPI location [17]
- reduced pupil diameter (PD) [17]

The discrepancy in age values as predictors of LPI success in PACD is associated with a different composition of patients in terms of age, ethnicity, and stage of PACD. The study by B. C. Ang et al., where young age was one of the predictors of treatment success, included the Japanese with PACs, PAC, and PACG with a mean age of 75 years [54], and the studies, where old age was a predictor, included the patients from India with PACs of 55 years old [59], mixed ethnicity group with PACs of 65 years old [57], and the Caucasians with PACs of 63 years old [22]. The inclusion of glaucoma patients in the study indicates a worse outcome in the elderly patients, possibly due to the trabecular meshwork pathological changes damaging the outflow of intraocular fluid [61]. Early intervention, at the stage of PACs and PAC, on the contrary, leads to a favorable result in elderly patients. The treatment outcome may also be influenced by ethnicity, suggesting different mechanisms of ACA closure [62].

A high initial IOP determining the success of LPI [22, 51] has been reported by all authors [56]. However, the lack of correlation between the LPI success and preoperative hypertension occurs due to a decrease in the number of topical hypotensive drugs [56].

The best result of LPI is associated with increased LV and LT [8, 18, 22, 51, 53, 54, 58] since lens enlargement with age [63] leads to narrowing and displacement of the iris-lens diaphragm, ACA narrowing, and pupillary block. S. Han et al. showed that the PACD patients with high LV and shallow ACD (Cluster 1 is a marker of pupillary block mechanism) had more pronounced post-LPI angle opening than the patients with relatively deeper ACD and lower LV (Cluster 2 is a marker of plateau iris configuration) [64]. Thus, the authors recommended personalizing the treatment of PACD depending on the pathogenetic mechanism of the anterior chamber angle closure.

The discrepancy in the values of ACD parameters as predictors of LPI success [17, 22, 53, 59] can be explained by the different composition of the participants. Therefore increased ACD was a predictor of success in the PACs groups, and shallow ACD—the PAC groups.

The researchers agree that initially low AOD750 values predetermine post-treatment ACA opening [17, 52, 53]. It is an interesting fact that the decreased ACA parameters measured by AS-OCT (TISA500) and by gonioscopy are predictors of PAC progression after LPI [65]. An example of visualization of the residual ACA closure of a PAC patient after LPI on AS-OCT CASIA2, Tomey, Japan is presented in Fig. 3.

The correlation between reduced axial length and a treatment success is discussed. Some authors have not revealed this correlation [18, 51, 52, 58], while others consider reduced AL to be a predictor of ACA expansion [53]. These discrepancies may be associated with different age composition of the groups and different stages of PACD in the patients included in the study, as well as the use of different devices for measuring the anterior segment parameters.

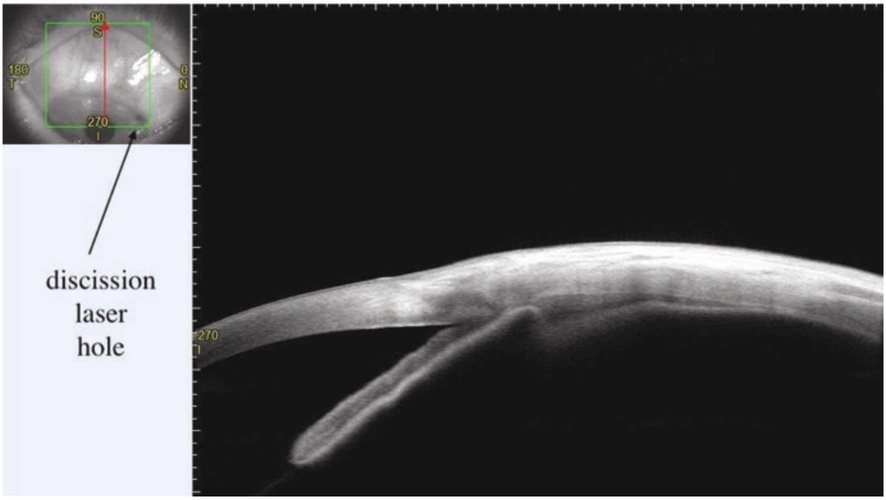


Fig. 3 Clinical example of residual closure of the anterior chamber angle of a patient with primary angle closure after laser peripheral iridotomy on AS-OCT CASIA2, Tomey, Japan

It is known that a steep iris is a marker of pupillary block [66]. Laser treatment results in iris flattening and ACA opening. So, increased iris curvature serves as a predictor of LPI success [11, 17, 22, 53, 57].

The issue concerning iris thickness as a predictor of LPI success in PACD is currently unresolved. It has been demonstrated that an ACA increase and a decrease in the iris curvature, regarded as the predictors of LPI success in PACs, are associated with thin irises [55]. Similar data were obtained by G. Huang et al., who showed that post-LPI AOD500 increase correlated with an initially smaller iris area [57]. It is known that the hypotensive effect of LPI is also determined by a thin iris [22]. T.A. Tun et al. reported that the LPI success was predetermined by a smaller initial iris volume [18]. R.Y. Lee et al. [55] explained the correlation between thin irises and wider ACA opening after LPI with the studies demonstrating the relationship between high elasticity of thin irises and low content of type I collagen in the iris stroma [67]. An increase in the iris stiffness may provoke a change in its mechanical properties, which negatively affects the results of LPI [68].

In contrast to the abovementioned studies, the study by A.C. How et al. associated an increase in AOD750 after LPI in PACs with initially thick irises (IT2000), which surprised the authors [51]. Therefore, they refer to the discrepancy between their obtained result and the mathematical model of J.S. Tiedeman describing the mechanism of pupillary block [69].

Superior LPI location, which provides the best topographic LPI result in PACs [17], is associated with the fact that the upper angle is the narrowest one [20] with the highest probability of goniosynechia [32]. According to the foregoing, it is clear that the predictors of LPI success are manifold.

It is worth noting that 11–25% of PACS eyes remain persistently closed after LPI [70]. According to other data, this figure is 19.4% [71]. Moreover, iridotrabecular contact ≥1 quadrant is detected in 59% of eyes [72]. Therefore, the maximum personalized approach to the choice of a PACD treatment method seems to be extremely relevant, taking into account the identification of the mechanisms of ACA closure [64] and the parameters determining the post-LPI risk of disease progression. In the 14-year longitudinal study of LPI efficiency in PACS patients, the risk of PACS-to-PAC conversion was reduced by 2/3 compared to a control fellow eye, which was not treated with LPI. Higher baseline IOP and lower anterior chamber dimensions were associated with the transition from PACS to PAC [73]. It should be emphasized that this study reported that the risk ratio for progression to PAC was only 0.31 (95% confidence interval, 0.21–0.46) in LPI-treated eyes compared to control eyes. Thus, the question of the feasibility of LPI in the early stages of PACD remains open.

3.2 Predictors of Lens Extraction Efficiency

Currently, lens extraction is used more often in the early stages of PACD [12–14, 20, 21], including PACs [9, 10], proving its effectiveness. There are relatively few studies aimed at the search for the predictors of LE efficacy in PACD [19–22, 74–76]. In most of the existing studies, the hypotensive effect of LE was considered as a criterion for assessing the treatment success [19, 21, 22, 74, 75]. The following parameters have been identified to determine the success of LE:

- elderly age [20, 22]
- male [20, 22, 76]
- high preoperative IOP [21, 22, 74–76]
- increased amount of preoperative glaucoma medications [75]
- increased lens thickness and lens vault [19, 22] and the presence of cataracts [22]
- smaller anterior chamber depth [22, 74] and higher ACD [19, 21, 76]
- reduced anterior chamber angle parameters [22, 75] and higher ACA values [76]
- low degrees of irido-trabecular contact [20]
- reduced axial length [22]
- increased iris curvature [22]
- reduced iris thickness [22]
- increased spherical equivalent [22]
- weak intraocular lens (IOL) power [20]
- lower preoperative visual acuity [22, 76]

In the study by T. Dada et al. based on multivariate analysis, baseline IOP in PAC was the most significant factor of the hypotensive effect of LE ($p < 0.0001$) [21]. At the same time, not all researchers report on this effect in the case of PAC treatment. According to C.E. Traverso et al. the hypotensive effect of LE is associated with high preoperative IOP only in the case of PACG treatment, but not the PAC treatment [19]. A possible cause may be pathological processes in the trabecular meshwork in PACG [61]. In addition, it may be associated with different study designs. In the mentioned study of C.E. Traverso et al. lensectomy in PAC was preceded by LPI in 47% of cases and by iridoplasty in 12%, and in PACG—38% LPI was performed without iridoplasty [19]. C.J. Liu et al. associated the hypotensive effect with high baseline IOP also only in the PACG group but not in the PAC group. The design of this study involved a joint group of PAC with PACs, and the eyes with pre-LPI were also analyzed [74].

The association of the LE success in PAC/PACs with male gender was found in the studies conducted by E. Melese et al. [20] and N.I. Kurysheva et al. [22]. Women are known to be at a higher risk of developing PACG, probably due to an anatomical predisposition [77]. According to H.A. Quigley et al., the prevalence of PACG is associated with female sex, while in POAG this relation has not been confirmed [78]. IOP increase has been shown to be associated with the onset of menopause [79]. In addition, a decreased level of female sex hormones negatively affects ocular hemodynamics [80]. Probably, hormonal factors also influence the post-LE ocular hemodynamics.

According to the literature, a small ACD [22, 74] and a narrow ACA profile [20, 22, 75] were the anatomical and topographic predictors of the hypotensive success of LE. LE-based ACA reconstruction eliminates several mechanisms of pupillary block (both lens and pupillary) by iris flattening after IOL implantation, occupying a smaller volume of the anterior chamber. It is known that the anterior-posterior size of IOL (1 mm) compared to the natural lens (4–5 mm) creates the conditions for an increased ACA profile due to the deepening of the anterior chamber with a subsequent decrease in ophthalmotonus. An example of the anterior chamber visualization of a PAC patient after LE at AS-OCT CASIA2, Tomey, Japan is shown in Fig. 4.

Figure 5 shows how a post-LE decreased lens volume leads to an increase in ACD, the size of ACA and the irido-trabecular space.

The correlation between the post-LE IOP decrease and the initially high lens vault and a steep iris is explained by more pronounced normalization of the ACA topography. Increased LV and a steep iris have been shown to be associated with pupillary block [64, 66].

The relation of thin irises with a pronounced hypotensive effect [22] is explained by the mathematical model of Tiedeman J.S [69]. Thick irises can exacerbate the treatment outcome by affecting ACA reconstruction due to the involvement of both pupillary and extrapupillary blocks simultaneously or sequentially [81]. Peripheral thick irises prevent the outflow of intraocular fluid through the trabecular meshwork.

The inverse correlation between the LE success and the IOL optical power is explained by Melese et al. with a small sample (28 eyes), including eyes with the same biometric parameters (AL, ACD, PD, and corneal curvature) taken into account when calculating IOL, although no significant correlations were obtained with any of the listed parameters [20].

Thus, the predictors of LE success in early PACD are currently ambiguous and further research is required. However, the positioning of LE in the early stages of PACD, including PACs, is becoming more common, proving its effectiveness over 10 years of follow-up [82].

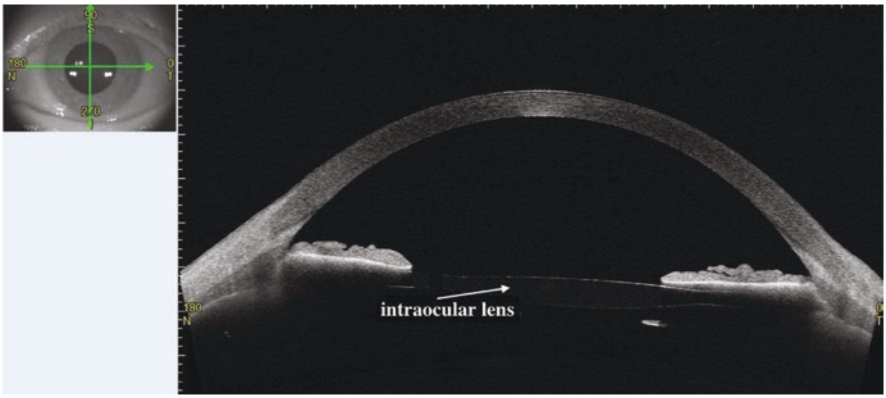
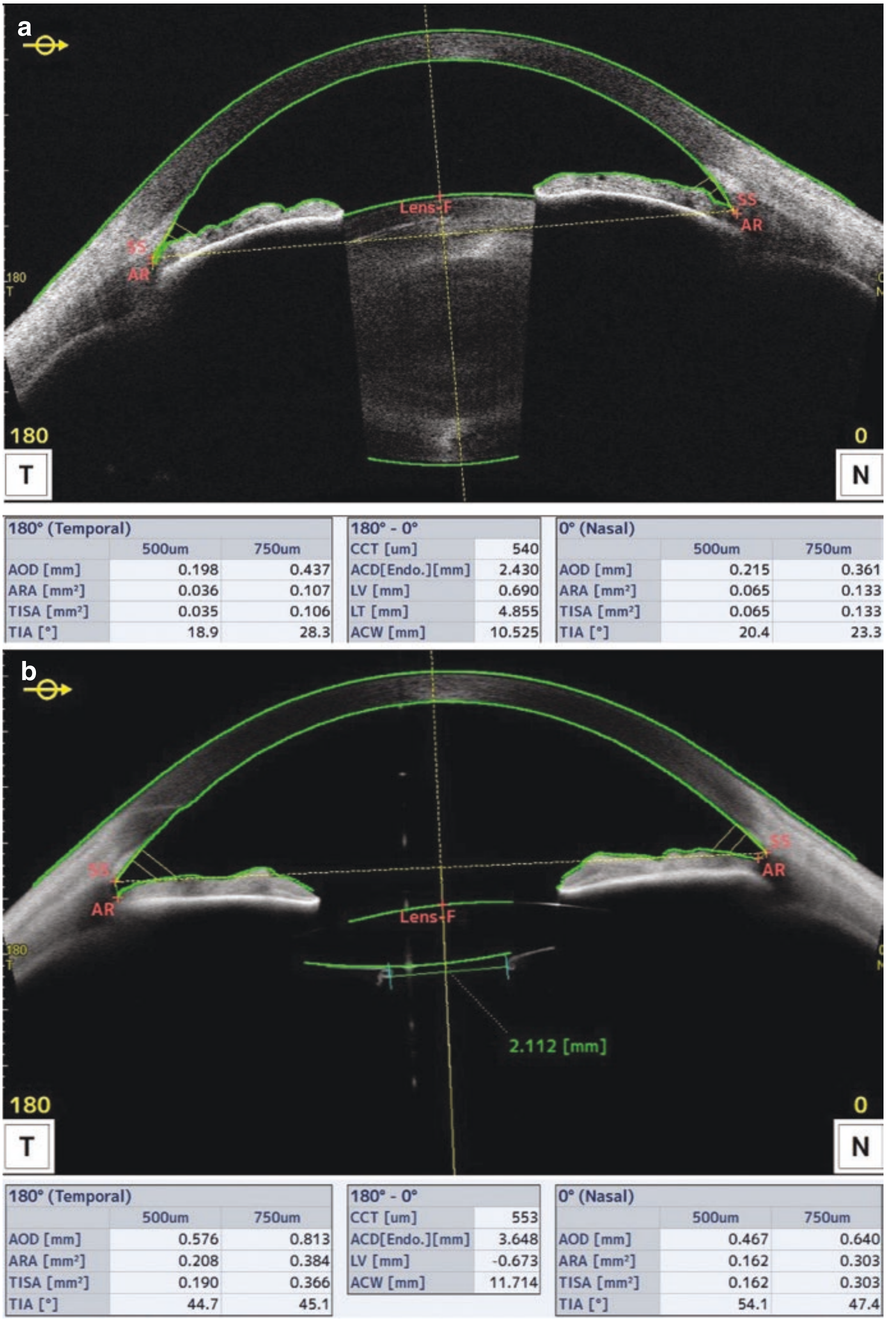


Fig. 4 Clinical example of visualization of the anterior chamber of the eye of a patient with primary angle closure after lens extraction on AS-OCT. CASIA2, Tomey, Japan



(a)

180° (Temporal)	500um	750um
AOD [mm]	0.198	0.437
ARA [mm²]	0.036	0.107
TISA [mm²]	0.035	0.106
TIA [°]	18.9	28.3

180° - 0°	
CCT [um]	540
ACD[Endo.][mm]	2.430
LV [mm]	0.690
LT [mm]	4.855
ACW [mm]	10.525

0° (Nasal)	500um	750um
AOD [mm]	0.215	0.361
ARA [mm²]	0.065	0.133
TISA [mm²]	0.065	0.133
TIA [°]	20.4	23.3

(b)

180° (Temporal)	500um	750um
AOD [mm]	0.576	0.813
ARA [mm²]	0.208	0.384
TISA [mm²]	0.190	0.366
TIA [°]	44.7	45.1

180° - 0°	
CCT [um]	553
ACD[Endo.][mm]	3.648
LV [mm]	-0.673
ACW [mm]	11.714

0° (Nasal)	500um	750um
AOD [mm]	0.467	0.640
ARA [mm²]	0.162	0.303
TISA [mm²]	0.162	0.303
TIA [°]	54.1	47.4

Fig. 5 Anterior chamber of a patient with PAC before (**a**) and after (**b**) LE on AS-OCT Casia2, Tomey, Japan. (**a**) Anterior chamber of a patient with primary angle closure before phacoemulsification. (**b**) Increase of the anterior chamber angle of the same patient after phacoemulsification and the implantation of the intraocular lens

4 Personalized Choice Between Laser Peripheral Iridotomy and Lens Extraction to Treat Early Primary Angle Closure Disease

Most of the studies aimed at the search for the predictors of treatment efficiency in the early stages of PACD are devoted to only one treatment method: either LPI [8, 11, 17, 18, 51–56], or LE, including eyes with prior LPI [21, 74, 75] and/or iridoplasty [19]. Only two studies compare the success predictors of both treatment methods [20, 22]. E. Melese et al. identified the factors that predict the effectiveness only of LE (elderly age, male gender, weak IOL power, low degree of the irido-trabecular contact, the Caucasians versus the African Americans) [20]. The common predictors of success for both treatment methods have been identified: elderly age, the presence of initial cataract, low corrected visual acuity, high preoperative IOP, narrow angles in the upper sector according to the Schaffer's scale, high LV, shallow ACD, steep and thin iris [22]. At the same time, the LE-specific parameters determining the hypotensive effect of the treatment were: high SE, short AL, male gender, narrow angles in the lower sector according to the Schaffer's scale, and the reduced parameters of the anterior angle. Such an analysis was achieved by applying a modeling method based on machine learning, taking into account 37 clinical and anatomical parameters. The authors concluded that LE should be the method of choice in short AL, a high spherical equivalent and a narrow ACA profile.

Using the machine learning methods [25–27], it is possible to predict the hypotensive effect of LE and LPI in each patient using regression models built for both treatment methods based on 37 clinical and anatomical parameters [83]. The authors assessed the result of the predictive calculation of the hypotensive effect of LPI or LE and suggested choosing a more effective method of treatment. By applying the significant variables selection method [26], a total of 4 parameters can be used, taking into account the availability of measurement in routine clinical practice (gender, IOP, AL, and ACD) to determine the treatment method (LE or LPI) [83].

Thus, one of the ways to solve the problem of choosing a treatment method for the initial stages of PACD is to use the machine learning methods that have proven their effectiveness in personalized medicine [23].

5 Selective Laser Trabeculoplasty to Treat Primary Angle Closure Disease

Selective laser trabeculoplasty is the most common treatment for POAG [84]. At the same time, SLT is known as an alternative treatment method of PACD in the eyes with previously performed LPI, provided that the trabecular meshwork is sufficiently visualized [29, 30, 85, 86], which is dictated by the risk of damage to the corneal endothelium [29]. The choice of SLT to treat PACD is associated with the forced use of topical hypotensive therapy after LPI with the risk of low compliance in the long term, including due to the economic component [87]. Furthermore, the role of SLT is undeniable in the case of allergies and systemic side effects to antiglaucoma drugs, as well as during pregnancy. In 2012, R. Sihota et al. used scanning electron biomicroscopy to study ACA structures in PACG and POAG [61]. They revealed similar histological changes in the trabecular meshwork of both groups, which made it possible to apply SLT in PACG as well.

It is known that the hypotensive effect of SLT is comparable with the use of prostaglandin analogues [85].

In PAC/PACG, a 20% IOP decrease from baseline without topical hypotensive drugs is observed in almost half of the cases 6 months after LPI [86]. L. Ali Aljasim et al. demonstrated that the LPI success at 1 year was 84.7% in the PAC/PACG group [88]. The long-term effect (6 years) of SLT in PACG is better than the effect of POAG and allows stabilizing glaucomatous optic neuropathy in the early stages of glaucoma [89].

S. Raj et al. reported that at 1 year after SLT 46.4% PAC/PACG patients achieved an IOP decrease of greater than 6 mmHg without the use of topical hypotensive drugs [28]. The mean IOP in both the PAC and PACG groups was comparable at all follow-up visits, except for the first week after SLT. IOP in PACG was significantly higher than in PAC ($p = 0.035$). The maximum hypotensive effect was noted on the first day, and the minimum—a week after laser intervention. High preoperative IOP was the only factor correlating with the hypotensive effect of SLT. The authors concluded that SLT is an effective post-LPI procedure.

In contrast to the abovementioned studies, N.I. Kurysheva et al. analyzed for the first time the effectiveness of SLT in PAC after LPI in the long-term period [30]. Already at the first year after the procedure, a significant difference in the IOP decrease in PAC in relation to PACG was revealed. This difference persisted throughout the entire follow-up period. Moreover, at 2 years after the treatment the need for topical hypotensive therapy was less in PAC than in PACG. The need for less use of antiglaucoma drugs is most likely associated with the deeper anterior chamber, the smaller lens thickness, fewer goniosynechia, and therefore the wider area of exposure in SLT.

Since the pathogenesis of primary angle closure disease is determined by the relative topographic features of the anterior segment, the treatment strategy is aimed at reconstructing ACA and reducing IOP, therefore, isolated SLT is not acceptable and SLT should be performed only after laser iridotomy. SLT is justified in the cases when LE is impossible, including due to the presence of contraindications, long surgery waiting period, refusal of intervention, and in some cases due to the refusal of lensectomy by the patients with high visual functions who are not always ready to replace the transparent lens. SLT after LPI as an alternative to LE may be considered as a replacement for continuous topical hypotensive therapy under dynamic follow-up.

Thus, SLT is an effective method for reducing IOP not only in PACG, but also in PAC, in cases of insufficient reduction in IOP after LPI. It can be assumed that in such eyes SLT is an alternative method in relation to LE, preventing the development of glaucomatous optic neuropathy.

6 Conclusions in the Framework of 3P Medicine

The present review follows the principles of 3P medicine in the research field of glaucoma. Recent international studies demonstrated great benefits of the paradigm change from reactive medical services to multi-level predictive diagnostics approach, phenotyping and patient stratification, targeted prevention and treatment algorithms tailored to individualized patient profiles which are pillars of predictive, preventive, and personalized medicine (3PM/PPPM) [90–98].

It is devoted to the problem of anterior chamber angle closure and highlights how the early detection of this condition, determination of its prognosis, and the formation of a personalized treatment algorithm allow preventing the development of one of the most severe forms of ophthalmopathology—primary angle closure glaucoma. Modern visualization technologies of the structures of the anterior and posterior segments, as well as the analysis of the data obtained on their basis by using machine learning methods provide the high level of **predictive** diagnostics. This makes it possible to select those patients who need an early start of treatment just in the early stage of PACD that corresponds to the concept of the **targeted prevention** of progression to the PACG development. The choice of a specific treatment method (in the context of PAC it is a peripheral laser iridotomy or lens extraction) is also based on an individual approach. This review shows how the determination of only four clinical parameters developed on the basis of machine learning methods contributes to making this choice and providing a **personalized** treatment of early stages of PACD.

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Multi-faceted Medical Care to Meet Individual Needs of Subjects with Excessive BMI: Professional Oral Hygiene and Periodontal Health Are in Focus of 3PM

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Abbreviations

API	Plaque index of proximal surfaces
BMI	Body mass index
BOP	Bleeding index of gingival papillae
KPU	Caries intensity index
PMA	Papillary-marginal-alveolar index
PPPM/3PM	Predictive, preventive, and personalized medicine
PSAF-ADA	Psycho-sensorial-anatomical-functional autodeadaptation

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1 Overall Management of Periodontal Health in Patients with Comorbidities Remains Challenging

It is customary to call comorbid states the coexistence of two and/or more diseases in one patient, pathogenetically and genetically interconnected, while the negative impact on the body does not add up arithmetically but multiplies geometrically. Today, there is no doubt that somatic pathology can provoke the appearance of many dental diseases or aggravate their course [1–3]. According to epidemiological studies, the prevalence of periodontal diseases tends to 100% and in the structure of dental morbidity is it second to the most prevalent caries. The modern etiopathogenetic concept of the development of periodontal diseases includes three mandatory components: the presence of periodontopathogenic microflora as part of a biofilm on the tooth surface, the necessary local conditions in periodontal tissues for the formation of a dysbiotic shift in the oral microbiota and the accumulation of inflammatory mediators, as well as general factors that regulate the metabolism of oral tissues, which determine the response to pathological effects and the rate of recovery of periodontal tissues damaged during inflammation [4–6]. In connection with the emergence of new data on the development of periodontal diseases, the emphasis on biofilm as the primary etiological factor was shifted towards the compensatory capabilities of the body associated with common factors. Microbial invasion, in turn, triggers processes that destroy periodontal tissues, the result of which depends on the state of the body's defense reactions that can both limit and provoke destructive processes in the periodontium [6].

2 Health Risk Assessment and Predictive Approach Are Crucial for Maintaining Periodontal Health

Health risk assessment is crucial for both—diagnosing and treatment algorithms of periodontal diseases and predicting the results. Obviously, in patients with concomitant systemic diseases, such as diabetes mellitus, the risk of developing and progressing periodontal pathology, as well as the severity and possibility of complications of this pathological condition, is much higher. However, the level of risk may be underestimated in patients who, in addition to severe somatic diseases, may have additional pathological conditions, such as chronic stress or distress, excessive weight, bruxism, and/or unhealthy life-style habits that can synergistically increase health risks. To this end, a comprehensive health risk assessment considering all modifiable and non-modifiable risk factors is instrumental for individualized patient profiling, robust predictive diagnostics and treatment algorithms tailored to the person. Contextually, per accumulated scientific evidence, an excessive BMI is a modifiable risk factor which creates strong predisposition to inflammatory and destructive lesions of the periodontium with cascading associated pathologies. Therefore, underestimation by patients and specialists of this risk factor leads to poor individual outcomes under the periodontal therapy and causes severe complication in implantology and orthopedic rehabilitation frequently observed in this patient cohort.

The relevance of investigating and mitigating health risks problem associated with excessive BMI in the formation of inflammatory-destructive lesions of the periodontium is primarily associated with its intensive growth, a high risk of developing concomitant diseases [7–10], a high frequency of severe complications and is directly related to insufficiently effective both non-drug and medicinal and surgical methods of treatment [2]. Contextually, the paradigm shifts from reactive medical services to predictive diagnostics, targeted prevention and treatment algorithms tailored to personalized patient profiles is in focus of multi-professional efforts to maintain periodontal health in primary (defined as suboptimal health conditions and protection against the transition from health-to-disease) and secondary (defined as protection against the disease progression and clinical manifestation of comorbidities) care [11, 12].

3 Study Design

A single-center, prospective, blind study was conducted at the Department of Therapeutic Dentistry and Periodontology of the St. Petersburg State Medical University. acad. I.P. Pavlov, Research Institute of ChLH and Dentistry and the City Periodontal Center PAKS. The study was approved by the institutional ethics committee**.**

The study involved 83 patients with type 1 diabetes mellitus (T1DM) aged 25 to 45 years, who made up two groups of comparison: group 1—patients with normal BMI (58 patients) and group 2—patients with excessive BMI (25 patients). The criterion for inclusion of patients in the first group was the value of the BMI ranging from 18.5 to 24.9 kg/m^2. The criterion for inclusion of patients in the second group was the excessive BMI ranging from 25 to 30 kg/m^2 (defined as pre-obesity). The dental criterion for inclusion in the study was the presence of chronic generalized periodontitis of mild to moderate severity (periodontitis I/II, class C) in accordance with clinical and radiological criteria. All patients were diagnosed with stable T1DM without complications. All patients were under dispensary observation at the St. Petersburg Regional Diabetes Center, their participation in the study was voluntary, in connection with which they filled out informed voluntary consent to participate in the study.

All patients included into the study underwent a comprehensive dental examination, namely a generalized survey, comprehensive clinical examination, determination of hygienic and periodontal indices (caries intensity index—KPU, simplified Green-Vermillion hygiene index—OHI-S, plaque index of proximal surfaces—API, papillary-marginal-alveolar index—PMA, bleeding index of gingival papillae—BOP), pH-metry of the oral fluid, microbiological examination of the contents of periodontal pockets.

All patients were offered a questionnaire containing tests for Korach's dental anxiety, Spielberger-Khanin's situational and personal anxiety, a compliance test (according to S.V. Davydov), a sheet of voluntary confidential information from the doctor to the patient (determining the level of PSAF-ADA).

After finalizing the clinical examination, patients in both groups of comparison underwent the first stage of active periodontal treatment—professional oral hygiene, including the removal of mineralized supra- and subgingival dental deposits using an ultrasonic scaler, air-abrasive treatment of the air-flow tooth surface using an air-abrasive mixture based on glycine, polishing of the crown and visualized root parts of the teeth with brushes and paste.

Further, a training conversation was performed with the patients on the rules and features of the implementation of individual hygienic dental measures, the tasks of which included the correction of individual theoretical and manual skills, as well as motivating the patient to comply with all treatment and preventive recommendations.

The re-examination of all parameters involved was performed after 1 month.

4 Data Analysis and Interpretation

According to the results of the examination in patients with T1DM with excessive versus normal BMI, the index of caries intensity of the KPU was similar: 11.12 ± 1.06 and 11.52 ± 1.17 units.

Green-Vermillion hygiene indices in both groups corresponded to satisfactory values (1.45 ± 0.12 points and 1.26 ± 0.08 points, respectively); however, the values of the plaque index on the approximate API surfaces corresponded to poor oral hygiene (72.68 ± 5.77% and 68.60 ± 3.94%).

The values of the papillary-marginal-alveolar index in both groups indicated the moderate severity of inflammation of the gingival margin (32.55 ± 3.23% and 35.48 ± 2.23%).

The bleeding index of the gingival papillae BOP indicated a high risk of progression of periodontitis (33.96 ± 6.56% and 30.80 ± 4.40%).

The pH of the oral fluid in the group of patients with T1DM and excessive BMI differed significantly from the pH level in the group of comparison with normal BMI (6.75 ± 0.12 units and 7.01 ± 0.09 units).

As summarized with Table 1, 1 month after the professional oral hygiene was performed, hygiene indicators improved.

The values of the Green-Vermillion indices and the plaque index on the approximal surfaces decreased in both groups of comparison. However, in the group of patients with normal BMI these changes were more pronounced.

The value of the papillary-marginal-alveolar index significantly decreased (by 24.28%) in the T1DM group with normal BMI indicating a decreased manifestation of an inflamed reaction in periodontal tissues after professional hygiene. In contrast, T1DM with excessive BMI these changes were insignificant (by 1%), apparently

Table 1 A comparative analysis of dental indices values among the groups of comparison (T1DM overweight versus normal BMI) before and after professional hygiene performance

	Overweight patients (n = 25)		Normal weight patients (n = 58)	
	Before	After	Before	After
OHI-S (points)	1.45 ± 0.12	1.28 ± 0.09	1.26 ± 0.08	0.97 ± 0.06
API (%)	72.68 ± 5.77	63.08 ± 4.55	68.6 ± 3.94	57.67 ± 3.41
PMA (%)	32.55 ± 3.23	31.64 ± 3.47	35.48 ± 2.23	24.28 ± 2.63
BOP (%)	33.96 ± 6.56	26.12 ± 6.49	30.80 ± 4.40	23.30 ± 3.94
pH (units)	6.75 ± 0.12	6.79 ± 0.07	7.01 ± 0.09	7.05 ± 0.09

due to the more severe course of periodontal diseases and the need to supplement the stage of professional oral hygiene with systemic antibacterial and anti-inflammatory drug therapy.

The degree of bleeding according to the results of the BOP test decreased in both groups of comparison, close to being equal.

The pH values of the oral fluid increased equally in both groups of comparison: in the group of patients with normal BMI, this indicator approached the normal values in contrast to the group with overweight T1DM patients.

The health status of the oral cavity improved in both groups. However, corresponding parameters (the hygienic status, the degree of inflammation of the periodontal tissues and the acid-base state of the oral cavity) demonstrated better lever of improvement in the group with normal BMI compared to the overweight patients that may be associated with a more severe initial impairments to the periodontium in the group of overweight T1DM, as well as with their evidently weaker response to treatments.

Overall microbiologic parameters were similar in both groups. However, in the overweight T1DM patients, microorganisms responsible for a more aggressive course of periodontitis were more prevalent such as Candida spp. and Prevotella intermedia; their prevalence remained higher in this group of comparison even after professional oral hygiene—see Table 2 and Fig. 1.

Fasting glucose levels remained the same in the T1DM group with normal BMI, namely 7.11 mmol/L and 7.10 mmol/L before and after professional hygiene performed, respectively. In contrast, in the T1DM group with excessive BMI, corresponding glucose level increased from 7.56 mmol/L (before) to 8.19 mmol/L (after)—see Fig. 2. The latter can be explained by inadequate stress reaction towards even a slight injury to the soft tissues of the oral mucosa in this group and a high level of anxiety in patients before dental treatment, which must be taken into account when performing invasive interventions to these patients.

The diabetes duration was similar in both groups (16.58 and 17.18 years, respectively). Diets were adhered to by 46.5% of patients of the first group and 40% of patients of the second group.

The level of glycated hemoglobin in the overweight T1DM group was slightly higher than in the normal BMI T1DM group, namely 7.97% and 7.59%, respectively.

Table 2 Qualitative and quantitative composition of periodontal microflora in the groups of comparison—T1DM with normal BMI versus T1DM with excessive BMI; comparative analysis was carried out before and after professional hygiene performed

Name of microorganism	Overweight patients ($n = 25$)		Normal weight patients ($n = 58$)	
	Microflora quantity upon initial examination	Microflora quantity upon initial re-examination	Microflora quantity upon initial examination	Microflora quantity upon initial re-examination
Staphylococcus aureus	$2000*10^3$	$400*10^3$	$1000*10^3$	$30*10^3$
Staphylococcus haemolyticis	$50*10^3$	$4*10^3$	$60*10^3$	$3*10^3$
Streptococcus sanguis	$2*10^3$	$0.4*10^2$	$3*10^3$	$0.5*10^3$
Streptococcus intermedius	$1*10^3$	$1*10^3$	$2*10^3$	$0.1*10^3$
Streptococcus mutans	$2*10^3$	$10*10^3$	$3*10^3$	$0.4*10^3$
Neisseria sicca	$20*10^3$	$1*10^3$	$2*10^3$	$2*10^3$
Neisseria lactamica	$0.2*10^3$	$0.1*10^3$	$0.1*10^3$	$0.1*10^3$
Rothia mucilaginosa	$3*10^3$	$0.4*10^3$	$5*10^3$	$0.1*10^3$
Moraxella catarrhalis	$0.4*10^3$	0	0	0
Corynebacterium xerosis	$0.4*10^3$	$0.3*10^3$	$0.05*10^3$	$0.02*10^3$
Veillonella parvula	$5*10^3$	$2*10^3$	$3*10^3$	$1*10^3$
Prevotella intermedia	$100*10^3$	$10*10^3$	$0.3*10^3$	0
Aggregatibacter actinomycetemcomitans	$1*10^3$	$0.3*10^3$	$0.2*10^3$	$0.1*10^3$
Candida albicans	$40*10^3$	$4*10^3$	$0.1*10^3$	0
Candida dubliniensis	$40*10^3$	$0.2*10^3$	$0.5*10^3$	0

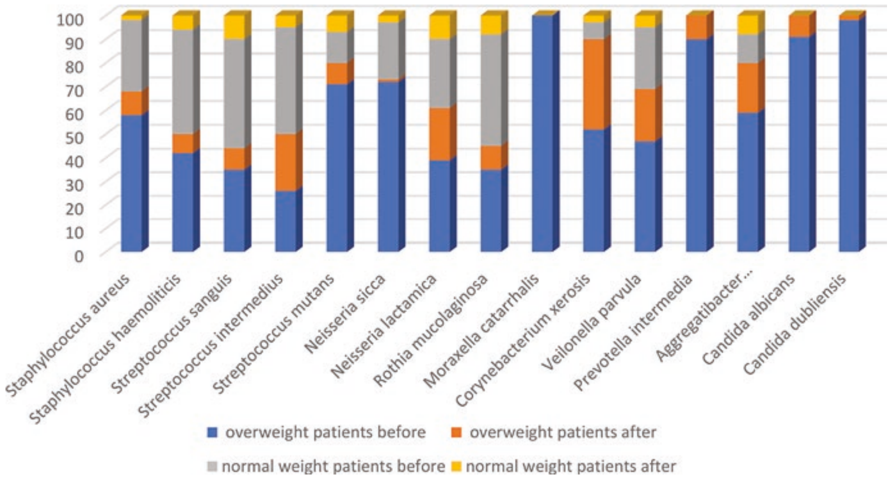

Fig. 1 Qualitative and quantitative composition of periodontal microflora in the groups of comparison before and after professional hygiene performed

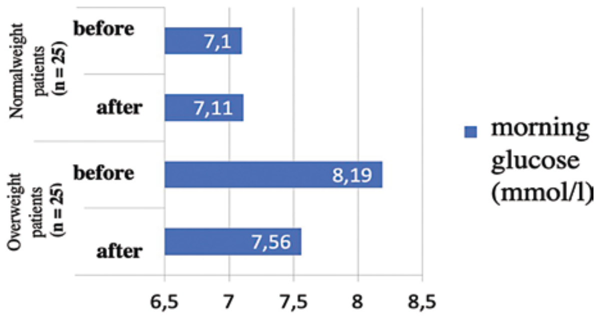

Fig. 2 Fasting glucose levels in both groups of comparison before and after professional hygiene performed

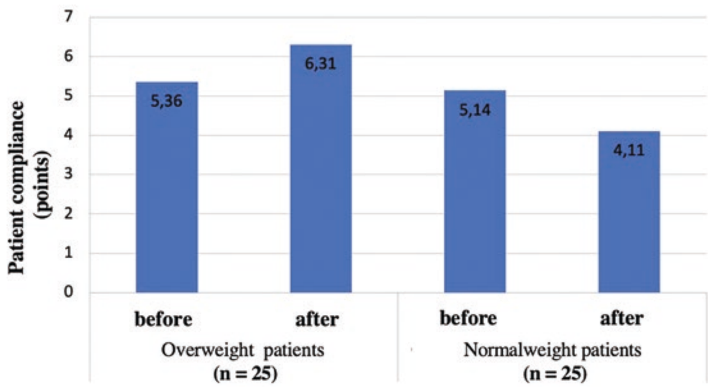

Fig. 3 Compliance evaluation in the groups of comparison before and after professional hygiene performed

Psychological survey revealed moderately positive initial levels of compliance in both groups of comparison, namely in group 1—5.14 points and in group 2—5.36 points. However, 1 month after conservative treatment of inflammatory periodontal diseases applied, in the second group, it worsened and became weakly positive—4.11 points, whereas in the first group it increased by 6.31 points as summarized in Fig. 3. To this end, no direct correlation between objective clinical improvement and subjective level of compliance was monitored demonstrating a discrepancy between the objective and subjective assessments.

Initially, the dental anxiety level in the T1DM group with normal and excessive BMI was 8.12 and 7.76 units (considered as a mild level of anxiety). After the therapy performed, corresponding levels slightly decreased in both groups, namely to 7.98 and 7.08 points, respectively.

Initially, situational anxiety in both groups was at low levels for both groups of comparison (first group—1.95 and second group—1.89), whereas personal anxiety was at an average level in both groups (first group—2.36, second group—2.2). After occupational hygiene performed, situational and personal anxiety in the first group decreased whereas in the second group of patients it increased as summarized in Fig. 4. This is considered as the group-specific phenomenon of T1DM overweight patients.

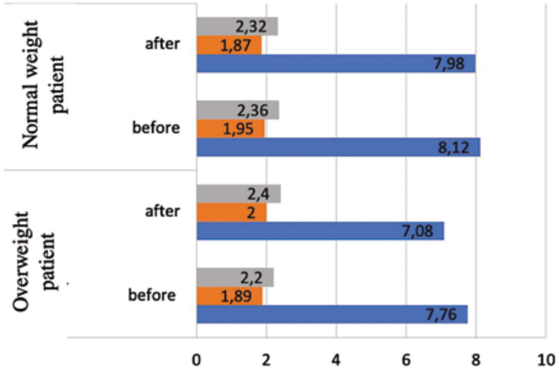

Fig. 4 Values of dental, situational, and personal anxiety recorded in groups of comparison before and after professional oral hygiene

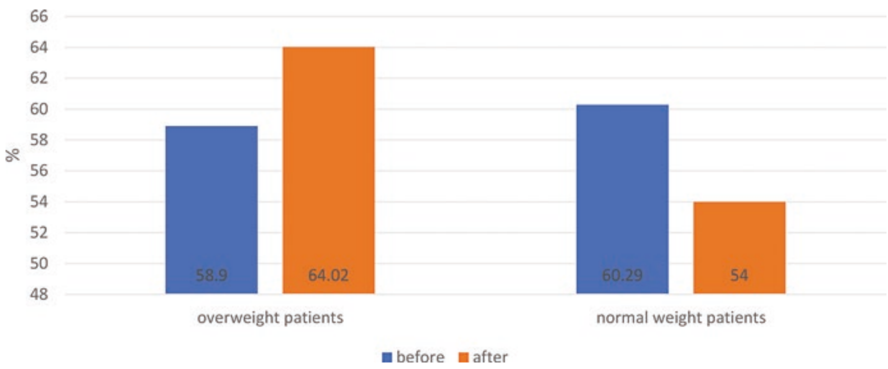

Fig. 5 Values of the level of PSAF-autodeadaptation recorded for the groups of comparison before and after a complex of professional oral hygiene

The level of PSAF-autodeadaptation in the first group was 60.29%, and in the second group—58.9%, which indicates minor maladaptation. Noteworthy, 1 month after the interventions, the level of autodeadaptation in the first group decreased, whereas it increased in the second group—see Fig. 5.

5 Conclusions and Expert Recommendations in the Framework of 3PM

Excessive BMI in patients with periodontal disease and diabetic history has been recorded as being indicative for more severe manifestations of pro/inflammatory reactions and for an increased risk of progressive periodontitis.

Excessive BMI can be considered as an independent risk factor of a more aggressive course of periodontitis, due to more prevalent pathogenic microflora composition such as Candida spp., Aggregatibacter actinomycetemcomitans and Prevotella intermedia responsible for less positive dynamics after professional oral hygiene performed.

Due to the aggravation of the course of periodontitis, T1DM history and excessive BMI affected patients experience more pronounced psychological distress accompanied with higher levels of autodeadaptation. Noteworthy, application of reasonable elements of participatory medicine such as an explanatory and motivating conversation increased the adherence of patients to the treatments planned in the group with excessive BMI more significantly compared to the group with the normal BMI that again promotes the concept of individualized approach adapted to the needs of stratified patient cohorts.

Excessive BMI and T1DM history are risk factors to be considered providing periodontal services as likely to cause potential stress-related complications such as increased fasting glucose after occupational hygiene and manipulations such as the removal of dental deposits. Contextually, to inform relevant care-givers (dentist-therapists, periodontists, dental hygienists) is strongly recommended to adapt treatment measures to the individual risk profiles.

Finally, modifiable risk factors should be taken into consideration to apply mitigation measures prior to providing periodontal/dental care to individuals at increased risk. Patient phenotyping and stratification as well as predictive diagnostics are highly instrumental for these purposes [13–18].

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Systemic Inflammation as the Health-Related Communication Tool Between the Human Host and Gut Microbiota in the Framework of Predictive, Preventive, and Personalized Medicine

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Preamble

The level of synergies between the human host and gut microbiota is frequently underestimated. Previous research efforts were focused on correlations between the gut microbiota composition and severe medical conditions of the host. However, recent discoveries clearly demonstrated that there are much most aspects involved in this multi-faceted interplay including the health status stability of the host, their quality of life, disease-predisposition, health-to-disease transition, disease severity grad, therapy-resistance, and individual outcomes—all under direct influence of the gut microbiota quantity and quality setup. Moreover, a powerful instrument has been established in cross-talk between both partners, namely an inflammation which is systemically activated in the host (gastrointestinal tract, immune, neuro- and cardiovascular systems, etc.) as soon as the synergies between the partners

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becomes suboptimal. Therefore, a detailed understanding of mechanisms underlying systemic inflammation as the key-tool to regulate the quality and stability of cooperation between both partners is crucial for cost-effective screening programs and targeted disease prevention in primary and secondary care following the principles of 3P Medicine [1, 2].

The term “human gut microbiota” comprises all microorganisms inhabiting the human gastrointestinal tract. This dynamic population of microflora encompasses both—the microbiome and virome consisting mainly of the prokaryotic domain and to a lesser extent, also of fungi, parasites, archaea, and viruses. Taken together, in the human body there is an approximate parity between the overall number of own cells and bacterial ones [3] that gives a clue to the high level of reciprocity between both cellular populations at the local and organismal levels. There is a multi-factorial influence on the gut microbial ecosystem resulting in the inter-individual variation with great impacts on the individual health status.

The gut microbiota develops during infancy starting with the mode of the birth: via a vaginal delivery, the neonate is exposed to maternal vaginal bacterial environment with a strong predominance of Lactobacillus, Prevotella, and Sneathia genera in the microflora. A caesarean section predisposes a newborn to the maternal skin flora with the less diverse microbiotas and high prevalence of Staphylococcus, Corynebacterium, and Propionibacterium and concomitant risks of chronic infections and allergies and, therefore, a systemic inflammation developed later on in life [4–8].

Further, there is an evidence-based difference in gut microflora of breastfed babies compared to those fed with formula milk, due to a milk-composition which differs in bacterial, nutrients, and bioactive compounds profiles. Consequently, more diverse microbiota and predominant Bifidobacterium species are typical for breastfed-individuals, whereas mono-flora with predominant Enterobacteriaceae species are characteristic for the gut microbiota of the formula milk-fed infants with consequent impacts on their gut microbiota and associated effects such as systemic inflammation and related disorders developed later on in life [9]. Microorganisms perform a large spectrum of functions complementary to the host such as digesting specific components of dietary fiber exemplified with some carbohydrates indigestible for humans, which thanks certain micro-species undergo a fermentation into absorbable forms such as short-chain fatty acids (SCFAs). In turn, SCFAs demonstrate anti-inflammatory and immunomodulatory effects [10]. In a similar way, gut microbiota is capable of producing vitamins and other bio-compounds valuable for the host immune system to defend against pathogenic invasion and to protect the host against systemic inflammation and associated pathologies such as metabolic syndrome, cardiovascular disease, and malignant transformation.

1 Gut Microbiome and Systemic Inflammation

Results reported from previous investigations show, the human host gut microbiome constructs a huge microbial community within the stomach area (with a bacterial cell concentration between 10 and 10,000 per mL or g), the small intestine region (with a bacterial cell concentration between 10,000 and 100,000,000 per mL or g), and the large intestine area (with a bacterial cell concentration between 10,000,000,000 and 1000,000,000,000 per mL or g) [11, 12].

Before the innovation of advanced high-throughput sequencing methods (such as molecular diagnostic techniques based on the 16 small ribosomal subunit RNA (16S rRNA) gene (16S rDNA) for prokaryotes and 18S rRNA gene (18S rDNA) for eukaryotes), metagenomic approaches and progression of bio-informatics software tools (in silico studies), the most portion of our microbiome (~80%) were unidentifiable through the application of standard traditional wet lab techniques like culture media. In recent years with the help of new molecular and bioinformatic technologies and software tools in dry labs, we can find out about microbial populations associated with the human microbiome, particularly the gut microbiome [13–20]. It is estimated that the ratio of microbiome cells to human cells is 1.3, it means that the number of microbiome cells is 1.3 times more than the constitutive cells of the human body. Hence, >10^6 of human genes involving more than 99% of the human host genomic pool are recognized as microbial genes [21].

As previous studies show, *Firmicutes* (~65%) (e.g., *Bacillus*, *Clostridium, Enterococcus, Eubacterium*, *Lactobacillus*, and *Ruminococcus*), *Bacteroidetes* (23%) (e.g., *Prevotella* and *Bacteroides*), *Actinobacteria* (5%) (e.g., *Bifidobacterium*), and *Proteobacteria* (including lipopolysaccharide bearing Gram-negative bacteria, for example, *Escherichia* and *Helicobacter*) are identified as dominated bacterial phyla among gut microbiota and ~ 99% of the bacterial populations of the gut human host microbiome are detected as anaerobes [22–27]. *Escherichia coli* is an opportunistic pathogen that can be recognized as a bacterial causative agent of different infectious diseases, for example, urinary tract infections (UTIs) [28–35].

These bacterial phyla cover ~90% of the human host's normal flora. Indeed, an individual's microbiome is pretty stable for a long time; however, a collection of factors such as age, birth condition, diet, lifestyle, genetics, medication, and social contacts may alter the composition of the human host microbiome [22, 36–40].

2 An Interplay Between the Inflammation-Associated Gut Microbiota and Corresponding Host Phenotypes

The presence of a microbiome in the body of healthy people protects the human host body from pathogens. This feature is achieved by producing a wide range of metabolites and postbiotic products. The microbiome community acts as microbial consortia been built by a variety of microbial populations with their specific functions and activities. Some populations contribute to the fermentation of herbal carbohydrate complexes and convert these polysaccharides into short-chain fatty acids (SCFAs) [16]. The SCAFs act as molecular energies that support the gut epithelial cells, particularly the epithelial cells living within the colon. In parallel with this effective activity, the SCFAs can bind to G-protein coupled receptors (GPRs) to inactivate the histone deacetylase enzymes. This feature results in beneficial outcomes such as triggering regulatory T cells (T_{regs}) or may suppress the expression of pro-inflammatory cytokines which are secreted via antigen-presenting cells (APCs) [41–45]. In addition to SCFAs, microbial macromolecules of polysaccharides such as *Bifidobacterium longum* subsp. *longum* 35,624 superficial exopolysaccharide reduces gut inflammatory responses [46, 47]. In some cases, any decrease in the number of effective microbial populations, for example, the Gram-positive and anaerobe bacterial cells of *Faecalibacterium prausnitzii* leads to the appearance of inflammatory immune responses in the gut. This feature can be seen in inflammatory bowel disease (IBD) patients. The main reason is associated with the secretion of bacterial metabolites, including N-acyl homoserine lactones (the molecules involved in the bacterial quorum-sensing system), salicylic acid, and peptides [48–51].

Furthermore, the gut microbiome is involved in the biosynthesis of some vital amino acids and vitamins, and the secretion of some small molecules which interact with the human host body, for example, to mature, activate, and develop the immune system. The attachment of segmented filamentous bacteria or some microbial agents (sometimes pathogenic microorganisms) such as *E. coli* O157, *Citrobacter rodentium*, and *Candida albicans* upon the small intestinal epithelial cells induces T helper 17 ($T_{helper17}$) cells. In turn, activated $T_{helper17}$ cells trigger neutrophils which may lead to the activation of intestinal epithelial cells. This process results in the activation of group 3 innate lymphoid cells (ILC3s) and plasma cells (which express IgA) promoting the omission of extracellular pathogenic microbial agents [52–56].

According to the importance of microbiome, eubiosis resulting from the residence of good bacteria in the human host body may lead to an effective and suitable homeostatic balance in different parts of the human body like the gut. In contrast, dysbiosis, which is resulted from the uncontrolled condition of harmful bacteria via good bacteria in the human host body, may lead to dysregulation of the human host normal condition, imbalanced homoeostatic and physiological status, and diverse disorders and diseases, for example, immunoinflammatory responses [57, 58]. Hence, the occurrence of different types of inflammatory and autoimmune diseases is related to dysbiosis for the most.

2.1 Gender as the Non-modifiable Risk Factor

Some published reports show that specifically the post-puberty period in both males and females is associated with changes in the gut microbiome. In this regard, after this period, sex hormones are actively expressed and secreted in males and females; therefore, the sex hormones in both genders affect the gut microbiome structures.

According to reports, the ratio of bacterial cells to human host cells is higher in females (2.2) than in males (1.3). The term "micro-genderome" depicts the related interactions between the gut microbiome and sex hormones in different genders [59–62].

Several studies confirm the close association between sex/gender and the gut microbiome. Indeed, sex and gender are important factors that differentiate the human host gut microbiome [63]. Moreover, the terms "genderome" or "gut micro-sex" depict the sexual dimorphism feature associated with the microbiome [64–66].

Estrogen, as a sex hormone which can be produced via adipose tissue, adrenal glands, and ovaries (or through diet), affects steroid receptors, for example, estrogen receptor-ß. This functional activity of estrogen regulates microbial metabolism [67, 68]. Bacterial strains in the gut microbiome express and secrete the enzyme of β-glucuronidase activity, do contribute to the deconjugation of conjugated estrogen molecules. Deconjugated estrogens will be reabsorbed into the blood circulation. The circulating deconjugated estrogen molecules interact with estrogen receptors located within different systems, including the central nervous, musculoskeletal, reproductive, cardiovascular, etc. So, bacterial strains of gut microbiome with the ability to produce ß-glucuronidases, ß-glucosidases, and hydrolytic enzymes participate in the process of estrogens deconjugation. This implies that because of the gut microbiome β-glucuronidase activities, the conjugated estrogen molecules, which are absorbed by the liver and delivered to the gut through the bile, get deconjugated [59, 64, 69, 70].

Indeed, the endogenous estrogens in females are recognized in five forms: (1) estrone which is the major form of estrogens in menopausal females (E1); (2) 17β-estradiol, the major form of estrogen in non-pregnant and pre-menopausal women (E2); (3) estriol that is highly recognized in pregnant females (E3); (4) sterol (E4) and (5) 27-hydroxycholesterol (27HC). The circulating estrogen molecules in blood can be in detached or attached forms. The attached form of estrogen is usually linked to proteins. Estrogen molecules and the related metabolites are capable of being conjugated via the processes of glucuronidation or also through sulfonation [59, 69, 71, 72]. The conjugated forms of estrogens are discharged in feces, urine, and bile. Following previous reports, the human host diet and gut microbiome are determinative factors that regulate the functional activity of ß-glucuronidase enzyme. In this regard, those with the healthy condition who use fibers in their diet experience reduced fecal functional activity of ß-glucuronidase enzyme while, highly consumption of proteins and fatty nutrition in healthy individuals leads to the promotion of fecal available activity of ß-glucuronidase enzyme [59, 69].

Other studies regarding the relationship between the sex hormones of androgen and testosterone and gut microbiome have been achieved. As previous studies show, the gut microbiome can modulate the systematic levels of testosterone. This goal is performed by reducing 17β associated with androgen [73]. Moreover, secretion of a high amount of estradiol (the main sex hormone in females) and testosterone (the main sex hormone in males) results in higher bacterial diversity associated with gut microbiome [74]. Thus, sex hormones are effective modulators of microbiome diversity, and this process may lead to the induction of inflammatory immune responses [64, 73].

The Lactobacilli pertaining to *Firmicutes* phylum is one of the main bacterial genera and constitutes a portion of the vagina microbiome. Estrogens affect the spread and expansion of Lactobacilli populations in the vaginal environment in women and their presence in the vagina is known as a biomarker of the host's health [75].

Previous studies that considered the gut microbiome show, on the one hand, that female neonates encompass higher populations of *Clostridiales* relating to *Firmicutes* phylum rather than male neonates. On the other hand, male neonates contain higher populations of *Enterobacterales* belonging to *Proteobacteria* phylum rather than female neonates [75].

2.2 Age as the Non-modifiable Risk Factor

The microbiota composition depends on the means of delivery, environmental factors, and nutrition. In this regard, cesarean or vaginal delivery affects the individual's microbiota composition. During the first half year after birth, the facultative aerobic bacteria, for example, *Proteobacteria* begin to colonize within the neonates' gut to form the early gut microbiome. In parallel with this feature, oxygen consumption by the facultative aerobic bacteria results in the appearance of an anaerobic condition. Obligatory anaerobic bacteria such as *Actinobacteria* phylum (such as *Bifidobacterium*), *Bacteroidetes* phylum (like *Bacteroides*), and *Firmicutes* phylum (e.g., *Clostridium*) create the secondary microbial communities as a part of the gut microbiome [22, 75, 76]. It seems that the gut microbiome in early infants involves a limited species of those that are contributed to human milk oligosaccharide metabolism and about 25–30% of the microbiome population in infants originates from breastmilk including *Bifidobacterium longum* (belonging to *Actinobacteria* phylum) and *Streptococcus thermophilus* (belonging to *Firmicutes* phylum) [75, 77, 78]. After the breastfeeding period in infants, which normally takes up to 6 months, a new period begins. During this new period which usually continues up to 2 years (from days of 450–2000) old, "solid nutrients may lead to an accelerated progression in infants" gut microbiome both in structures and functions. This feature maturates the "gut microbiome, and its condition resembles the adults" gut microbiome. By the maturation of the gut microbiome, microbial metabolites, for example, SCFAs will be produced through the degradation of a wide range of components, including complex carbohydrates, glycans, mucin, etc. [78].

However, it should be mentioned that those infants who were fed by their own "mothers" breastmilk had higher levels of *Clostridiales* and *Lactobacillales* in their gut microbiome compared to those infants who were not fed by their own mothers' breastmilk [79].

In accordance with previous reports, the bacterial genera of *Bifidobacterium* and *Lactobacillus* can be transmitted via mother's breastmilk to neonates. This bacterial transmission from mother to neonate results in positive outcomes associated with cognitive development, neuro-behavior, and reduction in infectious diseases. In this regard, *Lactobacilli,* as a bacterial community of the infants' gut microbiome participate in carbohydrate metabolism in which a highly amount of acetic acid and lactic acid are produced. The carbohydrate metabolism recruits different metabolic pathways, including the phosphor-ketolase pathway, pentose-phosphate pathway, and Embden-Meyerhof pathway, which leads to the release of high levels of adenosine tri-phosphate (ATP) molecules to cover the infant's growth [75, 80]. On the other hand, the *Bifidobacteria*, as a bacterial community of the infants' gut microbiome, contributes to the fermentation of breast milk oligosaccharides, production of SCFAs, etc., which are necessary for the infants' growth. The SCFAs, as high caloric compounds, are metabolized by colonic- and hepatocytes to release ATP molecules [81–83]. In the age range of two to five, gut microbiome construction gets more stability than before by the presence of butyrate-producing species of *Bacteroidetes* and *Firmicutes* [84]. In the age range of 7–12, known as the pre-adolescent period, the gut microbiome is composed of microbial communities that contribute to development through the biosynthesis of effective compounds, for example, vitamin B_{12} and folate [85]. As previous investigations show, the gut microbiome in adolescent individuals aged 11 to 18, the dominant bacterial genera are *Bifidobacterium* and *Clostridium*. These bacterial genera are considerably higher compared to adults. The gut microbiome's function and structure differ in individuals older than 65. These changes are directly correlated to physiological changes, lifestyle changes, diet changes, promotion of inflammatory factors, etc.; all in all, the composition of the gut microbiome in old individuals gets significant changes such as a high level of *Enterobacteriaceae*, a reduced ratio of *Bacteroidetes* to *Firmicutes* compared to younger adults [86–88].

2.3 Imbalanced Stress Overload is Highly Relevant for Pro/Inflammatory Cross-Talk

There is a wide range of stresses which has different resources such as daily problems and arguments, life events, traumas, and adversities. Following previous studies, we now know that early life stresses, for example, sexual abuse, physical, emotional, and trauma in individual's childhood, set the related physiologic conditions in both body and brain to respond to the stressors in the future. This programming mechanism leads to negative feedback and dysregulation in the neuroendocrine-neuroimmune axis during adulthood [89–93]. On the other hand, the functional gut-microbiome-brain axis is active through an effective interaction between the gut microbiome and the central nervous system (CNS). Therefore, this process is bidirectional and several significant pathways participate in the communication between the brain and gut microbiome. According to currently accumulated knowledge, the hypothalamic pituitary adrenal [94] axis, neurotransmitters, vagus nerve, immune-inflammatory mechanisms, bacterial metabolites, and other unknown pathways contribute to this communication [89, 95–100].

In one investigation, a healthy pregnant female participated in the Trier Social Stress Test (TSST), in which her stool was evaluated. The results from evaluations associated with the individual's stool sample showed that diverse gut microbial taxa reacted to the acute stressor via the expression of cytokines and induction of cortisol secretion. In this regard, interleukin-6 (IL-6), C-reactive protein (CRP), serum cortisol, and tumor necrosis factor-α (TNF-α) response were recognized as positive overgrowth inductions for *Bacteroides*; *Megasphaera* and *Ruminococcaceae*; *Dialister* and *Rikenellaceae*; and *Bacteroides*, *Provotella*, and *Megasphaera*, respectively [89, 100]. In contrast, IL-6, C-reactive protein (CRP), serum cortisol, and TNF-α response were negatively correlated with Clostridiales, Lachnospiraceae, Dialister, and Enterobacteriaceae; and none; *Bacteroides*; and *Ruminococcaceae*, respectively [89, 100].

In other studies, the effects of chronic stresses on the gut microbiota were evaluated. In this regard, an investigation showed that a 1-month-length stress on 3-month-old infants in a childcare center had no considerable effect on the "infants" gut microbiota composition versus animal models with maternal separation [101]. The results obtained from another survey show that the preparing period for national examinations with a duration of about 6 months led to a reduction of *Bifidobacterium* spp. and promotion of *Streptococcus* spp. populations in the gut microbiome composition among 60 Japanese medical students [102]. Moreover, academic examinations as naturalistic stressors affecting the cortisol amount within the human body may reduce the lactic acid bacteria portion of the gut microbiome [102, 103]. Michels et al. [104] have shown that apart from nutrition intake, stressors both in children and adolescents cross-sectionally affect gut microbiome composition. The occurrence of high stress may lead to a reduction of *Firmicutes* phylum and the *Phascolarctobacterium* genus levels. It may simultaneously lead to promoting *Bacteroides*, *Methanobrevibacter*, *Parabacteroides*, *Rhodococcus*, and *Roseburia* [104]. Some effective surveys have been performed to detect the correlation between childhood adversities and the gut microbiome in humans. D'Agata et al. [105] performed their study in the neonatal intensive care unit (NICU) involving the infants' first 6 weeks as the earliest stages of their life time. In NICU, effective stresses may occur for the participating infants, such as medical procedures (e.g., pain) and infants' separation from their parents. The stress was measured via the Neonatal Infant Stressor Scale [45] as a related criterion. D'Agata et al. [105] have shown that considerable changes have occurred in bacterial communities at the genera level of the infants' gut microbiome composition. In this regard, the γ-Proteobacteria was recognized as the dominated bacterial taxon. The parameters of antibiotic consumption, birth weight, gender, stress exposure, and sampling time had particular effects on different bacterial genera. For example, stress exposure had an influent impact on the bacterial genera of *Proteus* and *Veillonella* [105]. Moreover, the consumption of antibiotics was another influential parameter that effectively affected *Clostridium perfringens* and *Proteus*. For those infants who consumed antibiotics and encompassed *Proteus* in their gut microbiome, the population of *Proteus* bacterial cells was considerably lower, while the populations of *C. perfringens* and *Citrobacter* bacterial cells were significantly higher. Furthermore, the population of *Proteus* bacterial cells was considerably lower in female infants. Interestingly, the week of sampling was important item for evaluation of the stress impact associated with *Bifidobacterium*, *C. butyricum*, *C. perfringens*, *Enterococcus*, *Escherichia*, *Proteus*, *Staphylococcus*, and *Streptococcus* [105].

2.4 Behavioral Patterns Relevant for Inflammatory Risks

The hypothalamo-pituitary axis [94] is part of the limbic system, which is the most critical system that contributes to the coordination of adaptive responses in exposure to different stressors; therefore, it has a crucial role in the modulation of the main brain activities, for example, emotions and memory [106]. Stressors like environmental factors and any promotion of proinflammatory cytokines may lead to the activation of HPA. This process may lead to hypothalamus induction through corticotropin-releasing factor (CRF) production. The release of CRF results in the induction of pituitary gland which may lead to adrenocorticotrophic hormone (ACTH) expression. Production of ACTH triggers the adrenal cortex and leads to the secretion of cortisol. Cortisol, and an effective stress hormone, influences different body parts, for example, the human host brain. As a result, hormones and nerves determine the brain's coordinative role in gastrointestinal tract activities [106]. Therefore, different types of stresses and stressors, whether physical or psychological ones, may directly affect the HPA-gut (microbiome) axis as it can be seen in post-infectious irritable bowel syndrome [107]—known as a type of post-infectious gastrointestinal disorders—which may result in a wide range of gut-brain axis disorders, for example, anxiety and depression [108, 109].

On the other hand, the human host gut microbiome is composed of neurotransmitter-producing bacteria. The produced bacterial neurotransmitters are likewise those neurotransmitters that are detectable in the human host brain. Bacterial neurotransmitters' functions are limited to the gut and act as enteric nervous system regulators. In this regard, *Bacillus* spp. secrete dopamine and noradrenaline, *Escherichia* spp. produce noradrenaline and serotonin, while *Lactobacillus* spp. release acetylcholine and γ-aminobutyric acid (GABA). *Bifidobacterium* spp. are GABA producers, too. The yeasts of *Saccharomyces* spp. and *Candida* spp. biosynthesize noradrenaline and serotonin, respectively. In addition, the Gram-positive bacterial cells of *Enterococcus* spp. and *Streptococcus* spp. are serotonin producers [108, 110, 111]. This mechanism is one of the multiple microbial mechanisms that affect the CNS. The good bacteria of Bifidobacteria affects the CNS by promoting the level of tryptophan amino acid which is known as the precursor of serotonin. Simultaneously, a portion of Lactobacilli can change the metabolism, which can alter the metabolism GABA. This feature leads to alteration in the production of GABA receptors and their activities [112].

According to recorded reports, the vagus nerve, neurotransmitters, immune-, enteric nervous-, and autonomic nervous systems link the brain and gut microbiome showing effective communication pathways between them [21].

As previous investigations show, the frequency of the immune cells within the gastrointestinal tract is the highest compared with the other parts of the human host body. Furthermore, several types of immune cells are co-evolved with microbiome. These features explain the sensitive and complicated communications between the immune cells and the gut microbiome [113]. The Goblet cells, which are differentiated epithelial cells, can produce and secrete mucosal barriers within airways and intestines. This mucosal barrier separates the intestinal cells and the related microbial components. In addition, the secretion of the mucosal barrier by Goblet cells and the activity of this mucosal boundary is associated with the presence of the microbiome; the lack of this barrier is observed in germ-free mice and those mice which consumed antibiotics. A reported investigation shows that the microbiome in the small intestine triggers the secretion of meprin β, a zinc-dependent metalloprotease enzyme by the enterocytes. The meprin β acts as a mucin cleaver which may result in the mucin unfolding and entire expansion [114–116]. Indeed, mucus is constructed by different components, including MUC2 mucin, the main structural molecule in mucus. As previous investigations show, the spaces among villi and the top of villi situated in the small intestine are protected via the mucus. This protective mucosal layer is mobile and not joint to the villi; therefore, the movable layer of the mucus can easily be transferred by the intestinal peristaltic waves and other physical factors. The floating mucus appears to act as a bacterial trap which may move those bacteria away. This functional activity protects the intestinal epithelial cells against bacterial populations; the immobile mucosal layer is the influential environmental factor for bacterial overgrowth [116].

2.5 Nutrition is Pivotal for Pro- and Anti-Inflammatory Regulation Pathways

In parallel with the nutrient program and diet, which are recognized as the most influential factors that directly affect the construction of the human host gut microbiome and, in consequence, the immune system, the lifestyle items such as circadian clocks (circadian rhythmicity) and exercise (physical activity) are important items, too [23, 117–119]. Following recorded reports, the effect of diet on gut microbiome structure is fast and quick. In other words, the diet directly affects the microbial growth rate. Hence, a particular nutrient may lead to an increase in the growth of a category of bacterial populations. Normally, a diet involves both micronutrients including bioactive compounds, vitamins, and minerals (e.g., selenium and zinc)), and macro-nutrients such as lipids, carbohydrates, fibers, and proteins, which support human host body to have continuous development and growth through feeding [23, 120–122].

This process is achieved in parallel with some environmental factors comprising the pH and the permeability of the intestine. In this regard, some changes may occur in bacterial metabolites, leading to the occurrence or inhibition of the inflammation feature [23].

As known, the macro-nutrients are related to energy production and strengthening of the human host body structure. At the same time, the micro-nutrients contribute to the modulation of vital biochemical processes and keep the human host body healthy against various diseases. A wide range of micro-nutrient molecules is neutralizing free radicals, such as vitamins A, C, and E, and copper, zinc, and selenium minerals. Therefore, these types of micro-nutrients are known as antioxidants which can neutralize effectively free radicals such as reactive nitrogen species (RON) and reactive oxygen species (ROS) [120]. As previous studies show, insufficient consumption of antioxidants, for example, ascorbic acid, carotenoids, selenium, polyphenols, zinc, and tocopherols (vitamin E) through the diet leads to the occurrence of a wide range of chronic diseases. These diseases are associated with oxidative stress-related diseases including cancers and diabetes among others [120, 123–127].

Now it is well-established that the gut microbiome is pivotal to facilitate an effective absorption of a wide range of vital biomolecules such as macro- and micro-nutrients in human host body and simultaneously, protect the body from pathogens. As the results of previous studies indicate, the antioxidants are bi-functional molecules which on the one hand neutralize the free radicals and, on the other hand, support the human host's health through their positive effects on the gut microbiome composition [120, 128, 129]. Due to this evidence, the occurrence of any changes and functional dysbiosis in human host gut microbiome composition, which can be the result of environmental exposures, is directly correlated with a wide range of chronic disorders and diseases, for example, from enteric infectious diseases and respiratory diseases to IBD and colorectal cancer [130, 131]. It should be mentioned that the gut microbiome composition is known as a significant treasure for bacterial enzymes because the microbiome bacterial populations produce and secret a wide range of enzymes such as α-rhamnosidase, β-glucuronidase, β-glucosidase, sulfatase, and esterase(s) which target different types of molecules including glycosides, glucuronides, sulfates, amides, esters, lactones, etc. through the hydrolyzation mechanism. Moreover, further bacterial enzymatic reactions are achieved by bacterial populations pertaining to gut microbiome composition via the cleavage of biomolecule's aromatic rings. These enzymes involve decarboxylases, dehydroxylases, demethylases, isomerases, hydrogenases, reductases, etc. This vast treasure trove of enzymes enables gut bacterial populations to break down the eaten food by the human into its constituents for example, vitamins, amino acids, etc. These biomolecules participate in metabolic pathways (e.g., energy metabolism) and the immune system, known as human host physiological activities. So, the production and secretion of bacterial enzymes within the human host gut environment may lead to valuable and effective microbial metabolites including fatty acids such as linoleic acid and essential vitamins such as vitamins K and B group (like B_2, B_9, B_{12}) or hurtful and detrimental products [120, 132–134]. Simultaneously, the gut microbiome contributes to stimulation of the intestinal immune system, promoting the production of gut antimicrobial antibodies [113].

Although different factors, including clinical, environmental, feeding and maternal items, form the human host gut microbiota composition, the architecture of the individual's gut microbiome is established during the prepartum (pregnancy period) and postpartum (lactation period) periods. Because a mother shares her microbiome and the related metabolites with her fetus and infant during her pregnancy and after delivery [135, 136]. And the mother's gut microbiome composition is determined through her diet. Hence, maternal diet directly affects the future fetus's gut microbiome composition. Furthermore, any significant alternation in mother's diet during the pregnancy period leads to alternation in mother's gut microbiome composition and consequently, in the fetal gut microbiome composition. The mother's breastmilk composition is a determinative factor in infant gut microbiome composition. As we know, colostrum, which is the mother's postpartum first milk is quantitively low but high in quality. It contains effective components like antibodies and growth factors contributing to infant's immunity and growth, respectively. Although the composition of the maternal milk gets changes during the lactation period, vital nutrient components, and bioactive factors, for example, macro- and micronutrients, together with other compositions including pre- and probiotics and immunoglobulins still can be recognized during the alternation [137–140]. Cereals, fruits, legumes, and vegetables are essential sources for fibers with a high level of carbohydrates; olive oil and nuts have significant nourishing characteristics such as anti-inflammatory and antiatherogenic activities because of the presence of adequate nutrients containing unsaturated (poly) fatty acids; antioxidants such as polyphenols, phytosterols, terpenes, and flavonoids are known as bioactive nourish compounds. On the other hand, enriched food containing natural micro-nutrients such as minerals and vitamins protects the human host consumer against immunodeficiencies and malnutrition. Nutrient-rich foods support the human body's disorders, such as inflammations caused by poor diet or consumption of foods with high calories [141–144].

The gut microbiome composition is an effective biomarker for a healthy diet and human host health condition [145]. Due to this fact, consumption of the Mediterranean diet—which is introduced as a healthy diet—may lead to an increase in *Bacteroidetes* abundance and a reduction in *Firmicutes* abundance in the human host gut microbiome composition [145, 146]. Nutrients, food components, natural sources, and their effects on the gut microbiome composition are summarized in Table 1.

2.6 Abnormal Body Mass Index (BMI) as an Indicator of Potential Health Risks

BMI is calculated through the weight (kg)/height (m^2) formula. In this regard, the BMI can be categorized into five groups (1) underweight ($\leq$19.9 kg/m^2), (2) (normal (<25 kg/m^2), (3) overweight ($\geq$25 kg/m^2 to <30 kg/m^2), (4) obese ($\geq$30 kg/m^2), and morbid obese (> 35 kg/m^2) [174–176].

In parallel with changing microbiome composition by age variation, microbiome composition differs in individuals with different BMI. An abnormal weight in individuals either obesity/overweight or underweight shows the presence of a microbiome composition that does not belong to a healthy individual [147]. Furthermore, the microbiome composition is an effective biomarker for the recognition of balanced or imbalanced metabolisms.

As previous studies show, mothers with high BMI deliver infants who are predisposed to diabetes and obesity during their lives. Mothers with higher BMI and obesity have high levels of *Bacteroides*, *Staphylococcus*, and *Clostridium* and low levels of *Bifidobacterium* in their stool samples [135, 177–180].

Table 1 Nutrients, food components, natural sources, and their effects on the gut microbiome composition

Nutrient	Components	Food sources	Positive effects	Negative effects	Physiologic microflora	Pathologic microflora	References
Digestible carbohydrates	Mono-, di-, and polysaccharides, for example, fructose, galactose, glucose, lactose, maltodextrin, starch	Cereals, tuberous plants, etc.	Easily degrades into glucose	Non-communicable diseases, for example, asthma. Risk of metabolic disorders	–	Dysbiosis via an increase in *E.coli* and *C.albicans* abundances in mice; the increase of the gut inflammation through TLR4 signaling pathway; increase in systematic low-grade inflammation, colon inflammation in mice, mucus degradation via the increase in *Akkermansia muciniphila* abundance, increase in colitis through the decrease in the production of SCFAs and promotion of gut permeability	[147–150]

(continued)

Table 1 (continued)

Nutrient	Components	Food sources	Positive effects	Negative effects	Physiologic microflora	Pathologic microflora	References
Resistant carbohydrates (dietary fibers)	Lignin, non-digestible oligo- and non-starch polysaccharides, for example, cellulose, glucans, gums, hemicellulose, inulin, oligofructose, pectin, raffinose	Cereals, vegetables, some groups of fruits and human milk (in breast-feeding period)	Essential for gut eubiosis, they act as prebiotics and an effective source for the growth and proliferation of a wide range of microbial populations which may lead to the production and secretion of beneficial microbial metabolites, including carbon dioxide and methane gases, SCFAs, for example, acetate, butyrate, propionate, and monosaccharides. Insulin sensitivity increases and improves the activities of the gut barrier and the profile of the fats. The microbiota-accessible carbohydrates (MACs) in mice reduce the growth of pathogens like *Clostridium difficile,* which is known as an opportunistic pathogen that causes diarrhea	–	*Lactobacillus* spp. *Faecalibacterium prausnitzii*, and *Akkermansia muciniphila*, a mucin-degrading bacterium, have both been associated with beneficial health effects, including reduced inflammation and improved gut barrier function, respectively	–	[147, 151–156]

Nutrient	Components	Food sources	Positive effects	Negative effects	Physiologic microflora	Pathologic microflora	References
Proteins	Amino acids	Animals such as red meat and plants such as pulses, for example, beans, lentils, and peas	Bacterial proteolytic degradation in the distal colon and fermentation to produce SCFAs, for example, 2-methyl butyrate, isovalerate, and isobutyrate. Plant proteins, for example, glycated pea proteins, increase good bacteria and decrease harmful bacteria like *Bacteroides fragilis* and *Clostridium perfringens;* Increase in SCFAs such as acetate and butyrate led to a reduction of gut inflammation-associated proteins; the presence of resistant starches and bioactive compounds in plant proteins increases the gut microbial homeostasis	High risk of cardiovascular diseases (CVD), increase in amino acid L-carnitine and converting into γ-butyrobetaine and crotonobetaine and then into trimethyl amine Production of potentially toxic substrates such as nitrosamines, ammonia, and trimethylamine N-oxide Consumption of animal proteins has a high risk of CVD by increasing sulfate-reducing bacteria (SRB) increase in hydrogen sulfide and increase the risk of gut inflammation	*Plant protein consumption increases the amount of Bifidobacterium* and *Lactobacillus*, *Faecalibacterium*, *Clostridium*, *Eubacterium*, and *Roseburia*	*Consumption of* red meat and dairy products of animal origin, increase in *Alistipes*, *Bacteroides*, *Bilophila*, an increase of SRB bacteria, for example, *Desulfovibrio* spp., (high risk of CVD, and gut inflammation)	[39, 147, 157–165]

(continued)

Table 1 (continued)

Nutrient	Components	Food sources	Positive effects	Negative effects	Physiologic microflora	Pathologic microflora	References
Fats	Various types of fatty acids	Multi-saturated fatty acids. Mono-saturated fatty acids (MUFAs) such as eicosanoid palmitoleic and oleic in extra virgin olive oil, peanuts, and sesame. Medium chain fatty acids (MCFAs) in human milk and virgin coconut oil. Polyunsaturated fatty acids (PUFAs) in e.g., nuts, sunflower oil, fatty fish, etc.	Enriched foods with MUFAs positively affect gut microbiome composition in healthy and unhealthy human host bodies PUFAs are not biosynthesized by the human body and it should be taken from the diet	Correlation of saturated fatty acids (e.g., long-chain saturated fatty acids) and dysbiosis, increasing in *Firmicutes* and *Proteobacteria* and reduction in *Bacterioidetes*, rising inflammation in adipose tissue, promotion of insulin-resistance feature, and increase in gut permeability. Enriched diets by coconut oil enhance the bacterial abundances of *Clostridium*, *Staphylococcus*, *Lactobacillus*, *Allobacullum,* and the *Firmicutes*/*Bacteroidetes* ratio may lead to the occurrence of inflammation in adipose tissue and metabolic disorders. MUFAs may lead to enhance bacterial abundances of *Parabacteroides*, *Prevotella*, *Turicibacter* genera, and the *Enterobacteriaceae* family; the use of a diet with a high Ω-6/Ω-3 PUFA ratio may lead to enhancement of permeability in the gut barrier, dysbiosis, and appearance of metabolic disorders, for example, endotoxemiass	MAFs increase *Bifidobacterium* and *Lactobacillus*, improving cognitive and metabolic activities. The Ω-3 PUFAs re-establish *Firmicutes*/*bacteroidetes* ratio and enhance the beneficial bacterial producers of butyrate from *Lachnospiraceae*	High-fat nutrients, for example, milk fat with high content of sulfide, provide a suitable condition for SRB growth which may lead to a decrease in mucosal sulfide bonds and mucosal layer, leading to an increase in gut inflammation	[147, 166–173]

Recorded results depict high maternal BMI in pregnant mothers can be recognized as effective indicator for pregnancy complications; furthermore, this problem may affect their infants, too. For example, high BMI in pregnant women can be presumed as an alarm of risk for a wide range of chronic diseases, for example, diabetes, hypertension, and heart disease. These disorders include asthma, coronary heart disease, diabetes, hypertension, obesity, and stroke can also be seen in their infants during their lives [174, 181].

Although the underweight maternal BMI may lead to some limited complications, including low enhancement in premature birth and low decrease in birthweight in their infants, the occurrence of usual pregnancy complications such as gestational diabetes mellitus, pre-eclampsia, and obstetric interventions decreases.

2.7 Gut Microbiota-Associated Pregnancy Complications

Preterm birth is usually related to dysbiosis in vaginal microbiome composition [182–184]. The fetus is directly in contact with the mother's vagina during the birth. Hence the mother's vaginal health directly affects the infant's microbiome composition. The former studies show that the vaginal microbiome includes *Bacteroidales*, *Clostridiales*, and *Lactobacillales* [135, 177]. *Lactobacillus* is an influent bacterial member of the healthy vaginal microbiome composition because it keeps the pH of the vagina low and secretes bacteriocin, which may support the health of the vagina through the prevention of pathogens growth. However, the diversity of the microbiome composition decreases during pregnancy. In this regard, the prevalence of *Ureoplasma* and *Mycoplasma* abundances decreases in vaginal microbiome composition in pregnant women [185, 186]. Some investigations show that in healthy pregnant women, there is an abundance of four species of *Lactobacillus* comprising *L. jensenii*, *L. crispatus*, *L. vaginalis*, and *L. gasseri* in vaginal microbiome that increases while the abundance of bacterial causative agents of vaginosis involving *Parvimonas*, *Sneathia*, *Atopobium*, *Prevotella*, *Ruminococcaceae*, *Gardnerella*, and *Mobiluncus* decreases [187, 188].

Consumption of antibiotics in pregnant women considerably affects both mother and her infant's microbiome composition. Streptococci get domination in mother's gut microbiome composition and *Enterococcus faecalis* predominate the infants' microbiome composition. Moreover, administering antibiotics in normal vaginal delivery may promote Clostridium bacterial cells and decrease *Bifidobacterium* abundance [189–191].

Smoking in pregnant mothers has a direct effect on infants. In this regard, the infants exposed to environmental tobacco smoke compared to those not exposed to smoke encompass higher populations of *Ruminococcus* and *Akkermansia* in their gut microbiome composition. Moreover, tobacco-exposed infants between 3 and 6 months of age bear higher *Firmicutes*; and *Staphylococcus* and *Bacteroides* in their gut microbiome composition, respectively. The presence of Firmicutes may lead to obesity or overweight in children between the age of 1 and 3 months [192].

3 Conclusions and Expert Recommendations in the Framework of 3PM

The level of synergies the human host and gut microbiota have developed to satisfy needs of both cooperation partners to maintain their health is frequently underestimated. Research group with multi-professional expertise demonstrated an evidence-based interplay between the human host and gut microbiota including the health status stability of the host, their quality of life, disease-predisposition, health-to-disease transition, disease severity grad, therapy-resistance, and individual outcomes—all under direct influence of the gut microbiota quantity and quality setup. Thereby specifically pro- and anti-inflammatory mechanisms are the key-tool to regulate the quality and stability of cooperation between both partners. The multifaceted aspects of the pro- and anti-inflammation are crucial for implementing the principles of 3P Medicine in the area, the main pillars of which are the predictive approach, targeted prevention of the health-to-disease transition, patient stratification, and treatments tailored to individualized patient profiles [1, 2]. To this end, depending on the individual composition, the gut microflora profiles may be associated with both pro- and anti-inflammatory systemic processes relevant for primary and secondary care considering

– Individuals in suboptimal health conditions, for example, with family predisposition to severe pathologies, with abnormal BMI (both underweight and overweight), living in toxic environment, affected by non-compensated stress overload, carriers of relevant phenotypes, etc. [193–195].
– Individuals affected by chronic multisystem medical conditions such as metabolic syndromes and inflammation-related disorders [196, 197].

Pro- and anti-inflammatory pathways may be triggered by structural components of certain bacterial populations of the gut microflora: interleukins and other cytokines belong to the cascade of inflammatory pathways, whereas by-products of metabolic processes such as short-chain fatty acids possess a power to inhibit inflammation [2]**.** Pre- and probiotics application is a cost-effective treatment approach to be implemented based on the individualized patient profile and accompanying therapy monitoring at molecular and sub/cellular levels in a holistic manner [195]. In Table 2, probiotics application is exemplified for clinically relevant health and medical conditions.

Table 2 Probiotics exemplified for treatment of severe medical conditions associated with inflammation

Medical Condition	Known preventive effects and successful treatment	Strains	References
Oxidative stress overload	Yes	*Bifidobacterium animalis* subsp. infantis BLI-02, *Bifidobacterium breve* Bv889, *Bifidobacterium bifidum* VDD088, *B. animalis subsp. lactis* CP-9, and *Lactobacillus plantarum* PL-02	[198]
		*Lactococcus lacti*s MG5125, *Bifidobacterium bifidum* MG731, and *Bifidobacterium animalis* subsp. *lactis* MG74	[199]
		Lactococcus lactis CLFP 100, *Leuconostoc mesenteroides* CLFP 196, and *L. sakei* CLFP 202	[200]
		Bifidobacterium breve, *B. longum*, *B. infantis*, *Lactobacillus plantarum*, *L. acidophilus*, *L. casei*, *L. delbrueckii* subsp. *bulgaricus*, and *Streptococcus thermophilus*	[201]
		L. acidophilus, L .casei, L. rhamnosus, *L. bulgaricus, B. breve*, *B. longum*, *S. thermophilus*, Fructo-oligosaccharide	[202]
		Bifidobacterium animalis, *Lactobacillus rhamnosus*, and *Bacillus* LBP32	[203, 204]
		Bacillus SC06	[205]
		B. animalis subsp. *lactis* MG741; *B. breve* MG729; *L. reuteri* MG505; *L. rhamnosus* MG316	[206]
		Streptococcus thermophilus DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961	[207]

(continued)

Table 2 (continued)

Medical Condition	Known preventive effects and successful treatment	Strains	References
Impaired wound healing	Yes	Nanoparticle *Bifidobacterium bifidum*, *Lactobacillus acidophilus* and *Bacillus amyloliquefaciens*	[208]
		Lactobacillus fermentum and *Lactobacillus delbruekii*	[209, 210]
		Lactobacillus rhamnosus GG (ATCC 53103)	[211, 212]
		Lactobacillus acidophilus, *lactobacillus casei*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum*	[213]
		Lactobacillus acidophilus LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31, and *Lactobacillus delbrueckii ssp. bulgaricus* LBY-27	[209]
		L. plantarum; S. thermophiles	[214]
	Insufficient evidence	*Lactobacillus reuteri* (DSM 17938 and ATCC PTA 5289)	[215, 216]
		Saccharomyces boulardii	[217]
Diabetes mellitus type II	Yes	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium lactis,* and *Bifidobacterium longum*	[218, 219]
		Lactobacillus acidophilus La-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12	[219, 220]
		L. acidophilus, L.casei, L. rhamnosus, L. bulgaricus, B. breve, B. longum, S. thermophilus, Fructo-oligosaccharide	[202]
		Bacillus subtilis	[221]
		Lactobacillus plantarum	[222–224]
		Akkermansia muciniphila	[225–227]
		Akkermansia muciniphila, Clostridium beijerinckii, Clostridium butyricum, Bifidobacterium infantis and *Anaerobutyricum hallii,* inulin	[228]
		Lactobacillus acidophilus La5 and *Bifidobacterium lactis* Bb12	[229]
		B. bifidum, L. casei, L. acidophilus	[230, 231]
		Lactobacillus casei	[232]
	Subset of study participants	*Lactobacillus reuteri* DSM 17938	[219, 233]
	Insufficient evidence	*Lactobacillus casei Shirota*	[234]

Table 2 (continued)

Medical Condition	Known preventive effects and successful treatment	Strains	References
Hyperhomocys-teinemia	Yes	*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58	[235]
		B. Infantis DSM24737, *B. Longum* DSM24736, *B. Breve* DSM24732, *L. acidophilus* DSM24735, *L. delbrueckii ssp. bulgaricus* DSM24734, *L. paracasei* DSM24733, *L. plantarum* DSM24730, *S. Thermophilus* DSM24731	[236]
		L. plantarum	[219, 222]
Multiple sclerosis	Yes	*L. acidophilus, L. casei, B. bifidum* and *L. fermentum*	[237, 238]
		*B. infantis, B. lactis, L. reuteri, L. casei, L. plantarum,*and *L. fermentum*	[237, 239]
Colorectal carcinoma	Yes	*Bifidobacterium lactis* Bb12, *Lactobacillus rhamnosus* GG, oligofructose-enriched inulin	[240, 241]
		Bifidobacterium longum, Lactobacillus acidophilus, Enterococcus faecalis	[240, 242]
		Bacillus natto, Lactobacillus acidophilus	[240, 243]
		Lactobacillus plantarum CGMMCC No 1258, *Lactobacillus acidophilus* LA-11, *Bifidobacterium longum* BL-88	[240, 244, 245]
		Lactobacillus rhamnosus GG	[240, 246]
		Streptococcus thermophilus and *Lactobacillus delbruckii subsp. bulgaricus*	[240, 247, 248]
		Lactobacillus gasseri OLL2716 (LG21)	[240, 249]
		Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium lactis, Saccharomyces boulardii	[240, 250]
		Bifidobacterium longum	[240, 251]
Liver cancer	Yes	*Lactobacillus rhamnosus* LC705, *Propionibacterium freudenreichii subsp. shermanii*	[240, 252]
Gastric cancer	Yes	*Lactobacillus reuteri* PTCC 1655	[240, 253]
		Lactobacillus kefiri P-IF	[240, 254]
Cervical cancer	Yes	*Lactobacillus acidophilus, Bifidobacterium bifidum*	[240, 255]

(continued)

Table 2 (continued)

Medical Condition	Known preventive effects and successful treatment	Strains	References
Bladder cancer	Yes	*Lactobacillus casei* strain Shirota	[240, 256]
Breast cancer	Yes	Lactobacillus casei Shirota (LcS) and isoflavones from soy product	[240, 257]
	Ongoing clinical trial (NCT03358511)	*Laccharomyces boulardii, Lactobacillus plantarum, Bacillus subtilis, Bifidobacterium lactis, Bifidobacterium bifidum, Lactobacillus rhamnosus, Bifidobacterium breve, lactobacillus casei, Lactobacillus salivarius, Lactobacillus acidophilus, Lactobacillus brevis, Bifidobacterium longum*, and *Lactobacillus paracasei*	[248, 258]
Prostate cancer	Insufficient evidence	–	[259, 260]
Brain cancer	Glioblastoma cancer cell	Kefir drink supernatant (LAB)	[261]
Chronic fatigue	Insufficient evidence	–	[262, 263]
Rheumatoid arthritis	Yes	*Lactobacillus casei* (ATCC334)	[264, 265]
Musculoskeletal inflammation	Yes	*Lactobacillus casei* strain Shirota	[266]
		Lactobacillus rhamnosus PB01, DSM14870	[267]
Mitochondrial impairments	Yes	*Lactobacillus salivarius* subsp. *salicinius* AP-32	[268]
		Bifidobacterium infantis, *Bifidobacterium animalis*, and *Lactobacillus acidophilus*	[269]
CVD	***Yes***	***Bifidobacterium lactis HN019***	[270]
		B. bifidum, L. casei, L. acidophilus	[230, 231, 271]
		L. plantarum 299v (Lp299v)	[224, 271–274]
		L. rhamnosus GG (LGG)	[271, 275, 276]
		Lactobacilli. Biola, L. acidophilus LA-5, B. lactis Bb12, and L. rhamnosus GG, L. acidophilus LA-5 and B. lactis Bb12	[224, 277]
		Lactobacillus reuteri	[224, 278, 279]
		Lactobacillus Casei	[232]
	Insufficient evidence	*Lactobacillus casei* strain Shirota	[234]

Table 2 (continued)

Medical Condition	Known preventive effects and successful treatment	Strains	References
Allergies (dermatitis, eczema)	Yes	*Lactobacillus* GG	[280]
		Bifidobacterium lactis Bb-12 and *Lactobacillus rhamnosus* GG (LGG)	[280, 281]
		Lactobacillus rhamnosus 19,070–2 and *Lactobacillus reuteri* DSM 122460	[280, 282]
		LGG, *L. rhamnosus* LC705, B. breve Bb99 and *Propionibacterium freudenreichii* ssp. shermanii JS	[280, 283]
		Lactobacillus fermentum VRI-033 PCC	[280, 284]
		L. plantarum IS-10506	[280, 285]
		Mixture of *Lactobacillus casei, L. rhamnosus, L. plantarum, and Bifidobacterium lactis*	[280, 286]
	In children	*L. rhamnosus* and *Bifidobateria lactis*	[287]
	Insufficient evidence	*B. longum* BL999 and *L. rhamnosus* LPR	[288]
		Lactobacillus rhamnosus or *Lactobacillus GG*	[289]
		Lactobacillus acidophilus LAVRI-A1	[290]
Asthma	Yes	*Bifidobacterium bifidum, B. lactis, and Lc. lactis*	[291, 292]
	Insufficient evidence	*Lactobacillus reuteri, Lactobacillus rhamnosus* GG (LGG), *Lactobacillus paracasei* ssp *paracasei*	[284, 291, 293, 294]
Celiac disease/ gluten-sensitive patients	Yes (with gluten-free diet)	*Consortia I: Lactobacillus (Lp.) plantarum, (Lc.) paracasei, Bacillus subtilis, Bacillus pumilus, and consortia II: Lp. plantarum, Lc. Paracasei, Limosilactobacillusreuteri, Bacillus megaterium, B. pumilus*	[295]
		Lactobacillus helveticus R0052 and *Bifidobacterium longum* R0175	[296]
		Bifidobacterium longum	[297]
		Bifidobacterium breve	[298–300]
		Bifidobacterium breve, *B. longum*, *B. infantis*, *Lactobacillus plantarum*, *L. acidophilus*, *L. casei*, *L. delbrueckii* subsp. *bulgaricus*, and *Streptococcus thermophilus*	[301]

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Conventional and Traditional Medicine: A "Hand-in-Hand" Collaboration Benefiting the Patient and Healthcare at Large

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Abbreviations

NCDs	Non-communicable chronic diseases
PPPM/3PM	Predictive, preventive, and personalized medicine
SHS	Suboptimal health status
SHSQ-25	Suboptimal health status questionnaire-25
TCM	Traditional Chinese medicine

1 Modern Western Medicine

Modern western medicine, which can be stretched back to Greek medicine thousands of years ago and is the foundation of many of the modern health systems in the world [1]. Western medicine is defined as "A system in which medical doctors and other healthcare professionals (such as nurses, pharmacists, and therapists) treat symptoms and diseases using drugs, radiation, or surgery". The focus of modern Western medicine is symptomatic treatment. Related principles mainly included physical examinations based on the patient's symptoms and evidence-based diagnosis of a disease with clinically proven therapy [1]. With the rapid

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progress in industrialization, modern Western medicine has become the dominant stream in the medical field. It achieved a significant milestone in fighting infectious diseases with targeted therapies [2–4]. With this comes a longer life expectancy, and we realize that single-molecule medications cannot cope with more complicated diseases or disorders, such as age-related chronic diseases, immune diseases, and psychological illnesses. Moreover, most Western medicine is reactive medicine that diagnoses the disease after the onset, which is a late response from the perspective of preventative medicine [5]. Therefore, it is imperative to solve complicated health issues by applying comprehensive medical practices. Traditional Chinese medicine, which is a representative form of Eastern medicine, is a more personalized medicine that can provide more preventative care compared with Western medicine [5].

2 Eastern Medicine

Eastern medicine, occasionally referred to as "Traditional and Complementary Medicine", "Oriental medicine" or "alternative medicine", is the most ancient codified system of medicine that can be traced back more than 2000 years [6]. Traditional and complementary medicine has been playing an essential role in lifelong improvements in well-being and health [7]. According to the "Regional Framework for Harnessing Traditional and Complementary Medicine for Achieving Health and Well-being in the Western Pacific" reported by the World Health Organization, traditional and complementary medicine is suggested to have a supportive effect on the disease prevention and the management of long-term chronic conditions in primary healthcare settings [8]. The disease progress is generally complicated or accompanied by psychosomatic disturbances, and the prognosis of the disease is often affected by the environmental, social, and mental conditions of the patient. To improve public health interventions regarding health outcomes, a variety of efforts have been made. Related evidence-based interventions or therapies have been widely reported, and the summarized approaches are indicated in Fig. 1.

The basic philosophy of traditional and complementary medicine practitioners is to maximize the effectiveness and quality for the promotion of overall health status and well-being. Some traditional and complementary medicine, such as traditional Chinese medicine (TCM), Ayurveda [9], Bush medicine [6, 10], and Unani Tibb ("Greek Medicine" in Arabic) [11], are seeking, invoking, and restoring the balance of body elements. Taking the TCM as an example, the balance of "Yin" and "Yang" is a prerequisite for maintaining an overall health status for an individual [12]. Such framework usually relates to the whole person and applies complex patterns of disharmony or imbalance within the body for the disease diagnosis [12, 13]. Thus, TCM specifies the "disharmony pattern" and collects and compiles all the information about the physical and mental health conditions, i.e. the presented signs, functional and adaptive deficits, and other general characteristics of the patient [14]. The goal of TCM treatment is then to restore the individual's harmony by bringing

Fig. 1 Main categories and example of traditional and complementary medicine

the organism back into balance [6]. However, TCM lacks knowledge of molecular mechanisms in the aetiology of the disease, as well as scientific proof of the effectiveness of treatment for patients.

3 Integrative Medicine—Western Medicine Meets Eastern Medicine

Integrative medicine, the combination of both modern western and traditional eastern complementary medicine practices, has been proven scientifically to be both reliable and efficient [15]. Integrative medicine tends to emphasize the patient's preferences and attempts to address the physical, mental, and spiritual aspects of health status [16]. Main types or therapies of integrative medicine involves modern medicine practices such as advanced diagnostic approaches and surgical treatments, as well as traditional complementary medicine practices like herbs, acupuncture, and food treatment [17]. As a result, multimodal interventions—treatments that include at least two interventions, such as physical rehabilitation, psychotherapy, healthy lifestyles, and complementary health technologies—are prioritized in integrative medicine. This in turn explains why integrative medicine places more of an emphasis on treating the whole person rather than, say, a particular organ system (Fig. 2).

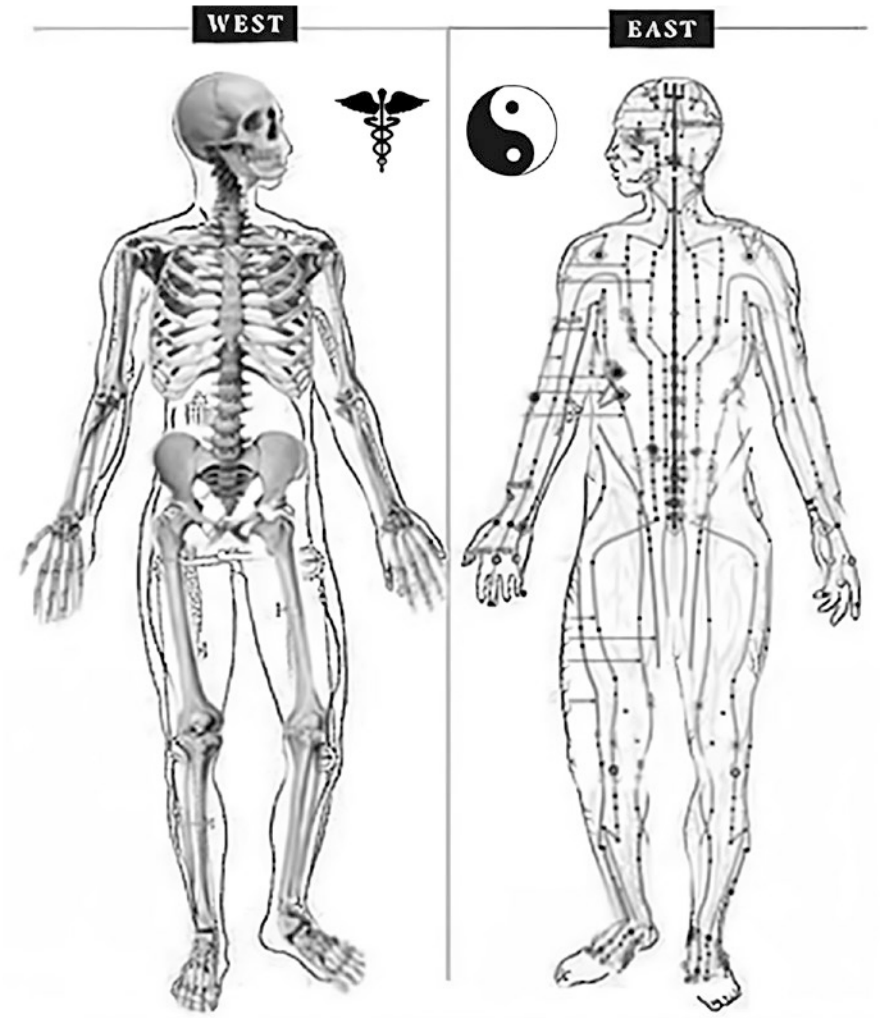

Fig. 2 The hand-in-hand, modern-traditional, Western-Eastern strategy within the framework of predictive, preventive, and personalized medicine (PPPM/3PM)

4 Suboptimal Health Status: A Bridge Between Western and Eastern Medicine

In order to assess the physical condition between health and disease from the perspective of predictive, preventive, and personalized medicine (PPPM/3PM), our team proposed the concept of “Suboptimal Health Status” (SHS) from the unique expertise aspect of TCM, allowing a strong bridge between modern medicine and traditional medicine [14, 18]. At the same time, by fusing the benefits of modern medicine and TCM principles, our team has established a solid, efficient, and trustworthy tool called the “SHSQ-25” for assessing SHS and promoting greater personalization of preventive care [19, 20]. In addition, we have implemented multilingual translations of SHSQ-25, including Chinese, English, Russian, Korean, Arabic, Japanese, Portuguese, Thai, and Slovakian. This can support us overcome language barriers and enhance the usefulness of the tool, which will be helpful for further expanding its application to a wider range of people. The novel hybrid strategy combines the benefits of both modern medicine and TCM. In addition, the fusion of the two fields benefits patients and improves the resources and collective knowledge of a committed professional community, ensuring the reproducibility of TCM methods and results [21].

Practical application of SHSQ-25 in the general population makes SHS a new dimension of health in translational medicine [18]. According to the prior research, SHS has been associated with a variety of diseases, disorders, and pathological alterations, including the changes of intestinal microbiota [22], telomere length [23], mRNA expression level of glucocorticoid receptor α (GRα) [24], cardiovascular health metrics [25], plasma cortisol [26], plasma catechol-amines [24], oxidative stress [27], blood transcriptome profiling [28], metabolites [5], plasma N-glycans profiling [29], and biological ageing [23], with an increased incidence of cardiovascular diseases [30], type 2 diabetes mellitus [31], metabolic syndrome [29], Parkinson’s disease [32], systemic lupus erythematosus [33], rheumatoid arthritis [34], dyslipidemia [35], stroke [36], and preeclampsia [37]. Therefore, SHS has an essential role in predicting the pathogenesis and progression of non-communicable diseases.

Investigations in the past years have indicated that SHS is primarily influenced by the lifestyle-related factors [38]. With the rapid development of industrialization in modern society, the current social living environment and lifestyles of individuals have changed dramatically, for example, the diversification of transportation has reduced the level of physical activity, which has led to the increased risk of SHS. Additionally, people are facing stress in numerous aspects, which involves personal, family, and social pressures, changes in life circumstances, overwork, complex interpersonal relationships, and psychological stress [39]. Given the multiple risk factors described above, the early intervention of SHS within the framework of PPPM/3PM are thus necessary before the onset of the diseases. Correspondingly, many early-stage interventions in the TCM are widely acknowledged, such as traditional physical exercise (e.g. Baduanjin, Chinese martial arts, Tai Chi, and Health Qigong Wu Qin Xi), moxibustion, cupping, massage, herbal medicine, and acupuncture [40, 41].

In more detail, for example, as one of the most common forms of qigong, Baduanjin exercise consists of eight separate and subtle movements [42]. While Wu Qin Xi is another type of traditional Chinese Qigong and also widely practiced, and it imitates the action and breathing movements of the five animals (deer, tiger, monkey, bear, and crane) and focuses on the unified regulation of body, mind, and breathing [43]. Other examples, such as moxibustion and cupping, are well-recognized complementary therapies. Moxibustion is one form of heat therapies involving burning plant materials named “moxa” on acupoints [44]. Cupping is one application of suction on the skin of the body to influence the fluid circulation and blood [45]. As a result, from the perspective of PPPM/3PM, it will be more crucial to prevent SHS using interventions from the TCM.

5 Conclusion, Expert Recommendations, and Future Perspective

In summary, both early detection and prevention of SHS can minimize the potential risk factors for SHS. This could potentially not only to improve individuals’ health outcomes and quality of life, but also could help to reduce the economic burden of NCDs on the global healthcare system. As the PPPM/3PM concept achieves, this successful hand-in-hand, modern-traditional, Western-Eastern strategy of healthcare will provide a holistic and comprehensive way that benefits both the individual and the global healthcare system.

Declaration of Interest Statement Declarations of interest: none.

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Tourism, Suboptimal Health Status, and Dementia

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Abbreviations

mRNA	Messenger RNA
NCDs	Non-communicable chronic diseases
PPPM/3PM	Predictive, preventive, and personalised medicine
SHS	Suboptimal health status
SHSC	Suboptimal Health Study Consortium
SHSQ-25	Suboptimal Health Status Suestionnaire-25

1 Introduction

With a faster pace of life and increased social pressure, a growing number of people are experiencing unhealthy lifestyles and the ensuing suboptimal health status (SHS) [1]. They often feel unwell but have no overtly diagnosable conditions [2]. According to the World Health Organization, only 5% of the world's population is truly healthy; that is, few are in "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity". The remaining 75% are in an intermediate state between health and disease, while 20% suffer from non-communicable chronic diseases (NCDs) such as diabetes, heart disease, cancer, and mental disorders [3, 4]. SHS tends to cause fatigue and can affect one's mental state, immune system, cardiovascular system, and digestive system. SHS often prompts hospital visits and poor quality of life [5]. NCDs kill 41 million people annually, accounting for 71% of the world's total deaths and representing a major threat—especially in an increasingly ageing society [6]. Despite remarkable medical investment, these diseases remain challenging to prevent [7]. Dementia, a neurological disorder, is a particular public health priority. It currently affects about 55 million people worldwide but is expected to afflict 78 million by 2030 and 139 million by 2050 [8, 9]. Unfortunately, as of now, dementia has no cure or powerful disease-modifying approaches. SHS and NCDs are caused by complex interactions among one's genes, age, environment, and lifestyle along with other factors. Their aetiologies are similarly complicated and have yet to be elucidated [10, 11]. In contrast to difficulties in modifying risk factors such as genes and age, one's environment and lifestyle can be altered to help prevent and relieve symptoms of SHS and NCDs [1, 12]. The philosophy of predictive, preventive, and personalised medicine (PPPM) involves forecasting individuals' predisposition to disease, providing targeted preventive measures, and creating personalised treatment algorithms. Bearing these principles in mind, SHS presents a window of opportunity to discover timely interventions for NCDs [13].

Travel is the most popular leisure and vacation activity of the twentieth century and offers many health benefits [14]. However, its positive impacts on SHS and NCDs (e.g. dementia) have gone overlooked thus far [15, 16]. As a promising non-pharmacological intervention, travel is part of a healthy lifestyle and involves environmental change [16]. It can contribute to health promotion, as well as disease prevention and treatment, in several ways (e.g. via cognitive, affective, conative, and sensorial dimensions), thanks to positive travel experiences [17]. Health issues generally fall within the medical science realm, while tourism is a social science. These domains seem disparate at first glance but are in fact related [18]. On the one hand, the high mobility of travel can exacerbate the spread of infectious diseases and lead to public health crises, such as SARS and COVID-19. On the other hand, it can improve individuals' physical and psychological health and partially alleviate public health concerns, such as population ageing and NCDs [16, 19]. Interdisciplinary collaboration between tourism and medical science is therefore warranted to address complex social issues [18]. This chapter summarises current knowledge about SHS and dementia and proposes that tourism can play a role in their management, creatively bridging the social and medical sciences. Potential research avenues are suggested accordingly.

2 Suboptimal Health Status

SHS refers to "an overall physical status between health and illness characterised by the perception of health complaints, chronic fatigue, and a constellation of physical symptoms such as the cardiovascular system, the digestive system, the immune system, and mental status; lasting for at least 3 months" [1]. Traditional Chinese medicine uncovered this intermediate state thousands of years ago and put forward preventive treatment theory in *The Emperor's Classic of Internal Medicine* [20]. SHS manifests in various ways, including reduced vitality, decreased function, and lower adaptive capacity of the organism [21]. Environmental pollution, social stress, and an unhealthy lifestyle are key risk factors for SHS [2]. This status usually causes dysfunction in multiple physiological systems along with other negative health outcomes; it can even deteriorate into chronic disease. A majority of NCDs progress from a reversible subclinical state to an irreversible disease state with obvious symptoms over a mere several years, placing a heavy burden on individuals, caregivers, and society [22]. Put simply, SHS is a critical risk factor for NCDs and typically precedes their onset. Early identification and intervention of SHS will provide new insight into NCD control and management, thus minimizing negative consequences [21]. Yet it is arduous to identify and assess SHS because its manifestations do not meet clinical diagnostic criteria in modern medicine. This condition can hence be easily ignored in the medical field [23]. Our team, the Suboptimal Health Study Consortium (SHSC), seeks to better understand SHS and encourage innovative clinical practices. We have explored validated SHS measures (Fig. 1), such as the Suboptimal Health Status Questionnaire-25 (SHSQ-25) and objective biological indicators [1, 5, 20]. These instruments are useful for recognizing high-risk groups to avoid under-diagnosis, enabling physicians to adopt targeted preventive responses

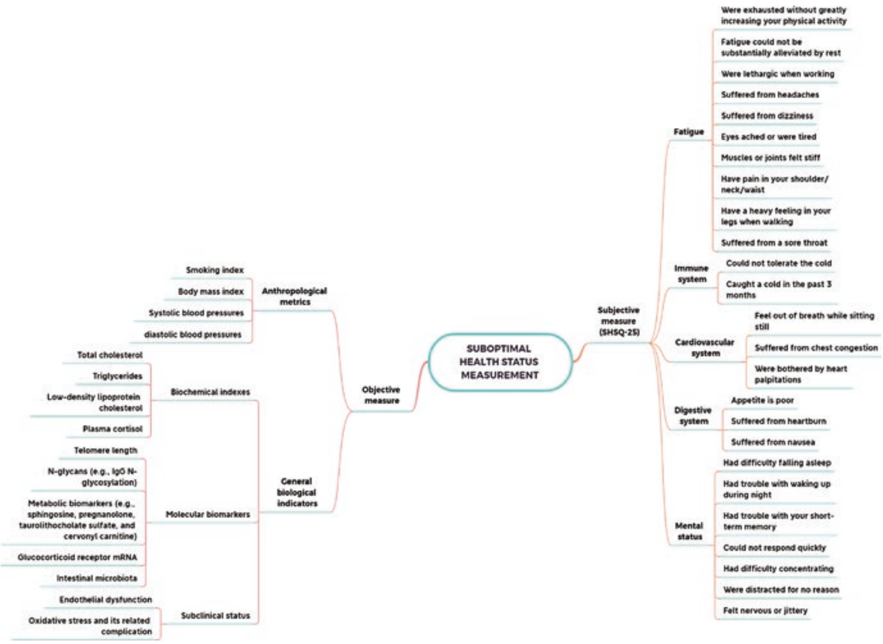

Fig. 1 Suboptimal health status measurement

before NCDs occur. Such measures are also helpful for excluding low-risk populations to obviate over-diagnosis and wasted medical resources [24].

The SHSQ-25, a self-report tool, was developed in 2009 to facilitate self-assessment [2]. It includes five domains—fatigue, the cardiovascular system, the digestive system, the immune system, and mental status—and 25 items. Respondents are required to score their discomfort experienced in the past 3 months. Each item is rated on a 5-point Likert-type scale with a total possible score of 100. Scores greater than 35 are considered SHS; the higher one's score, the more severe their SHS. As a simple, free, and convenient health measurement tool, this questionnaire is applicable to a wide range of surveys among the general population in clinical and community contexts. From a PPPM perspective, the SHSQ-25 provides an accessible way to evaluate health status and inform health judgements and public health operations [5, 23]. It has been translated into multiple languages (e.g. Chinese, English, Korean, and Russian) and has been used in multi-ethnic populations, including Asians, Africans, and Caucasians [1]. In addition, the instrument has been applied extensively to demonstrate the correlation between SHS and NCDs [3]. The China Suboptimal Health Cohort Study revealed that people with higher SHSQ-25 scores have a greater risk of cardiovascular and metabolic diseases [21, 23, 25]. Several studies in Ghana showed a high association of SHS with type 2 diabetes and preeclampsia [26, 27]. With the help of this measure, the concept of SHS should overcome the confines of traditional health evaluations to encourage proactive healthcare. Advances may include predictive diagnosis as well as targeted prevention and treatment [28].

To compensate for subjective deficiencies of the SHSQ-25, we have examined biometric signs of SHS—both anthropological metrics and general biological indicators [1, 29]. First, SHS is typically associated with changes in common anthropological metrics such as smoking index, body mass index, systolic blood pressure, and diastolic blood pressure [20, 22]. Second, because SHS affects several mental and physical systems, a number of biological indicators can guide assessment [30–32]. Three categories of interest are biochemical indices (e.g. total cholesterol, triglycerides, low-density lipoprotein cholesterol, plasma cortisol) [20], molecular biomarkers (e.g. telomere length, N-glycans, metabolic biomarkers, glucocorticoid receptor mRNA, intestinal microbiota) [22, 33–36], and subclinical status (e.g. endothelial dysfunction, oxidative stress, and associated complications) [26, 37]. These objective indicators are important for evaluating health and predicting disease progression. They can additionally contribute to a well-rounded view of the intricacies of SHS [38, 39].

3 Dementia

As a common NCD, dementia is "not a specific disease but is rather a general term for the impaired ability to remember, think, or make decisions that interferes with doing everyday activities" [40]. It consists of two primary symptom classes: cognitive degeneration (e.g. confusion, memory loss, reduced concentration, poor judgement) and psychological and behavioural symptoms (e.g. psychosis, aggression, agitation, sleep problems, depression) [41, 42]. There are many kinds of dementia, such as Alzheimer's disease, vascular dementia, and Lewy body dementia, each of which has varying symptoms. Of these, Alzheimer's disease is most prevalent, accounting for 60–80% of cases [8, 43]. The underlying causes of dementia are exceedingly complex: its aetiology is uncertain despite decades of research, and only a few risk factors have been identified. Prominent elements include age, genes, the environment, and lifestyle [44, 45]. The elderly population is most frequently diagnosed with dementia—roughly 80% of people with dementia are over age 75 [46]. The number of people with dementia will only continue to grow as ageing increases [47]. Worryingly, the onset of dementia is trending younger, and early-onset dementia cannot be ignored [48]. In addition to its constellation of effects, the depth of dementia's impact is staggering. It is the fifth largest contributor to worldwide disease burden. Its estimated yearly financial cost to the global economy exceeded $1 trillion in 2018 and is set to double by 2030 [49]. As such, dementia sits high on the medical agenda [50].

Dementia is also a twenty-first-century social health challenge [8]. Even though a multitude of medical resources have been devoted to its prevention and treatment, little encouraging progress has been made [51]. Theoretically, effective prevention can decrease the incidence of dementia. The medical community employs pharmacological and non-pharmacological interventions targeting a variety of risk factors (e.g. lifestyle-based aspects) to prevent dementia [47, 52, 53]. Yet pharmacological prevention strategies aimed at treating chronic diseases (e.g. diabetes, hypertension, hearing loss) in high-risk populations have significant side effects and limited effectiveness [54, 55]. Although benefits need to be observed in the long-term, non-pharmacological interventions including healthy lifestyle behaviours do not have adverse consequences and are widely recommended [56, 57]. Dementia treatment outcomes remain largely unsatisfactory: symptoms can be partly alleviated, but the disease cannot be cured [50]. More than 100 therapies have been eliminated in the past 10 years, and the failure rate of new drug development is 99.6%—far higher than the 81% failure rate of new drugs designed for cancer [58]. For decades, only five new drugs (i.e. donepezil, rivastigmine, galantamine, memantine, and namzaric) have been routinely used following approval from the U.S. Food and Drug Administration [50, 59]. However, their clinical efficacy and safety are controversial [51].

To make matters worse, academic misconduct has severely hampered dementia research. The journal *Science* recently claimed to have found strong evidence that images in a much-cited study underpinning a reigning theory of Alzheimer's disease, published 16 years ago in *Nature*, might have been fabricated. This alleged fraud is more than an academic scandal that has rocked the medical world; it may have misled 16 years of Alzheimer's studies, wasted billions of dollars in funding and made the dismal state of Alzheimer's research even sadder [60]. Numerous non-pharmacological approaches exist for dementia treatment, such as those targeting cognition, behaviour, emotions, and the senses [61, 62]. Such options are traditionally cost-effective and are strongly recommended as first-line interventions to relieve dementia symptoms [63, 64]. A range of non-pharmacological interventions have hence been suggested to prevent and treat dementia [65]. Travel is well worth trying as a recreational activity conducive to physical and psychological well-being [17].

4 Travel Therapy: An Emerging Health Intervention Embracing the Principles of PPPM

Tourism encompasses "the activities of persons traveling to and staying in places outside their usual environment for not more than one consecutive year for leisure, business, and other purposes not related to the exercise of an activity remunerated from within the place visited" [66]. It has brought substantial positive effects to the economy, culture, ecology, and social life [67]. The health benefits of travel have long been recognised [14]. For example, productive travel experiences improve the flexibility of bones and joints and lower the risk of cardiovascular disease, inflammation, headaches, and congestion, thereby enhancing physical health [68]. Travel can also contribute to psychological restoration and well-being by evoking positive emotions and memories that reduce stress, enhance cognition, and mitigate health issues [69]. Even with the proliferation of related studies, scholars have rarely pushed the boundaries of social science to investigate the more far-reaching health outcomes of tourism [16, 70]. The COVID-19 outbreak has highlighted a link between tourism and public health although these areas seem intuitively unrelated. Importantly, even as tourism can fuel public health crises by transmitting infectious diseases, it can contribute positively to public health by elevating people's physical and mental states [16].

Tourism involves food, accommodation, travel, visits, shopping, and entertainment [71]. It therefore has multiple functions to foster tourists' health and well-being [17]. Specifically, tourism allows people to escape from the everyday, embrace nature, and breathe fresh air to relieve stress [66]. Tourism can also enable people to better fit in socially, thus alleviating loneliness and social isolation [72]. Tourists who exercise can strengthen their bodies through physical exertion as well [73]. In an effort to creatively leverage these health benefits, we put forth travel therapy as "a therapeutic approach that enhances people's physical and psychological health and well-being through positive travel experiences and engagement" [70]. This form of therapy is an interdisciplinary concept integrating tourism and medical science. Through physical activity, socialisation, positive emotions, and healthy eating, travel therapy can serve as an effective non-pharmacological intervention for many health issues, similar to music therapy, art therapy, and other techniques [16, 17]. In addition to health enhancement and disease prevention among general tourists, travel therapy can aid tourists with SHS and NCDs (e.g. dementia, depression, cardiovascular problems). Travel can boost the physical and mental capacities of people with SHS to promote healthy states and prevent negative progression to NCDs. For tourists with NCDs, travel may ease symptoms and pain. This non-pharmacological intervention usually cannot cure disease [74]; however, it can act as a complementary intervention to slow disease progression and to maintain and improve patients' abilities to perform daily activities. These effects can promote one's quality of life and reduce societal health burdens [16]. Overall, travel should occupy a prominent position in disease management, especially for dementia where medications have limited success but noticeable side effects (Fig. 2) [17]. Travel therapy embraces the principles of PPPM by providing tailored experiences suited to people's characteristics. This approach promotes personalised prevention and treatment. For example, by gaining an in-depth understanding of tourists' needs and health status, travel experiences can be customised to include specialised physical activities, healthy eating choices, mind–body relaxation techniques, and wellness services [16, 70]. Such individualised measures can help maintain health, manage disease, and provide long-term wellness benefits.

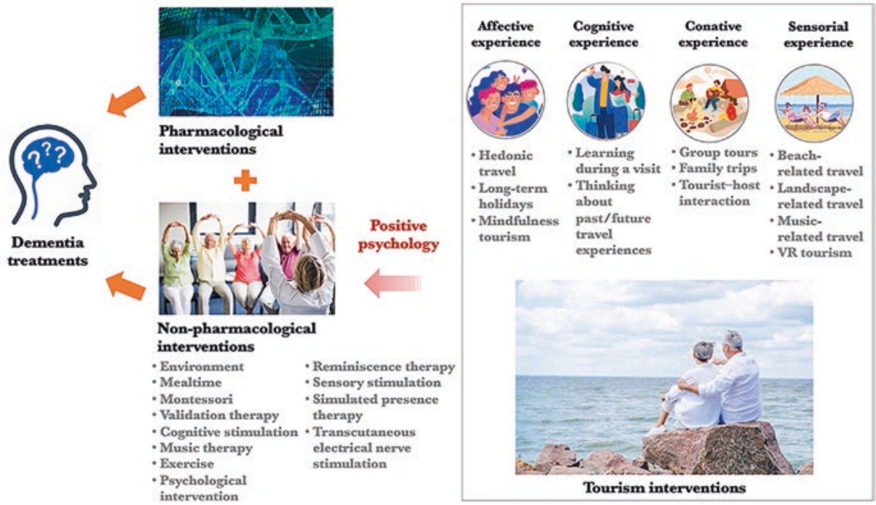

Fig. 2 Tourism as a dementia treatment based on positive psychology. (Source: Wen et al. (2022) [17])

5 Conclusions and Recommendations

In response to scientific and societal progress, interdisciplinary research—especially between the natural and social sciences—has emerged as a trend in academia to address social concerns. This chapter links apparently unrelated fields of tourism, SHS, and dementia through the interdisciplinary concept of travel therapy. Travel, as one component of a healthy and active lifestyle, represents a promising non-pharmacological intervention for SHS and NCDs (e.g. dementia). Travel therapy is an emerging intervention that embodies PPPM guidelines and can help resolve public health issues. Interdisciplinary studies linking tourism and medical science hold meaningful implications for stakeholders. Such work can help protect the rights (e.g. health equality, service equality) of people with health conditions by presenting a disease management option. Practitioners in medicine and tourism/hospitality can benefit from practical guidance to promote industry recovery and transformation, ultimately reducing burdens on society while fostering sustainable development. Relevant research may address diverse topics. First, because people with health conditions are an under-investigated tourist group, little is known about their travel behaviour (e.g. motivations, experiences, expectations, constraints). An in-depth understanding of their actions is essential. Second, more robust empirical research using multidisciplinary methods (e.g. interviews, randomised controlled trials, case–control designs) and biomarkers are strongly recommended. Such work can test the clinical efficacy of travel therapy, develop personalised tourism interventions in line with PPPM tenets, and maximise travel therapy's promise for public health [75].

Declaration of Interest Statement Declarations of interest: none.

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Appendix

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Arabic Version of SHSQ-25

أسئلة اإلستبيان:

1	2	3	4	5
أبداً	من حين الى آخر	غالباً	غالباً جداً	دائماً

1	2	3	4	5	ما مدى تكرار شعورك/ي باألعراض التالية؟
□	□	□	□	□	1. إرهاق من غير زيادة ملحوضة في نشاطك البدني.
□	□	□	□	□	2. إعياء ال يمكن تخفيفه بشكل كبيرعن طريق الراحة.
□	□	□	□	□	3. الخمول أثناء العمل.
□	□	□	□	□	4. صداع الرأس.
□	□	□	□	□	5. دوار الرأس.
□	□	□	□	□	6. تعب أو إرهاق في العينين.
□	□	□	□	□	7. التهاب الحلق.
□	□	□	□	□	8. تصلب العضالت أو المفاصل.
□	□	□	□	□	9. ألم في الكتف, الرقبة أو منطقة الخصر.
□	□	□	□	□	10. شعورك بثقل في الساقين عند المشي.
□	□	□	□	□	11. شعورك بضيق في التنفس أثناء الجلوس.
□	□	□	□	□	12. إحتقان في الصدر.
□	□	□	□	□	13. خفقان في القلب.
□	□	□	□	□	14. فقدان الشهية لألكل.
□	□	□	□	□	15. حرقة في المعدة.
□	□	□	□	□	16. الغثيان.
□	□	□	□	□	17. عدم القدرة على تحمل البرد.
□	□	□	□	□	18- صعوبة في النوم.
□	□	□	□	□	19. عدم القدرة على النوم المتواصل أثناء اليل.
□	□	□	□	□	20. صعوبة في تذكر األشياء على المدى القصير.
□	□	□	□	□	21. عدم اإلستجابة للمؤثرات بسرعة.
□	□	□	□	□	22. الصعوبة في التركيز.
□	□	□	□	□	23. تشتت ذهني من دون سبب.
□	□	□	□	□	24. شعور بالتوتر.
□	□	□	□	□	25. إصابة بنزلة برد في الثالث أشهر الماضية.

Chinese Version of SHSQ-25

	对于下表中所列的问题，在过去的三个月内，这些症状在您身上发生的频率是怎样的?	1 完全没有	2 很少有	3 有	4 多数有	5 几乎总是
1	您觉得疲劳吗(在运动量没有明显增加的情况下)?					
2	您的疲劳在休息后能缓解吗?					
3	在工作时您有困倦或倦怠的现象吗?					
4	感觉头痛					
5	感觉头晕					
6	眼睛酸胀					
7	咽喉疼痛					
8	肌肉和关节经常感到发僵或僵硬					
9	肩、颈或腰部酸痛					
10	走路时感到双腿沉重					
11	静息时感到气短					
12	胸闷					
13	心悸					
14	食欲减退					
15	胃部不适					
16	消化不良					
17	低热或怕冷					
18	入睡有困难					
19	多梦或易惊醒的情形					
20	记忆力减退					
21	反应能力下降					
22	注意力不集中					
23	没有原因的心烦意乱					
24	紧张、焦虑现象					
25	您是否患过感冒					

Dutch Version of SHSQ-25

Dotazník SHSQ-25

	Hoe vaak was het in de afgelopen 3 maand dat u (uw)	1 Nooit of bijna nooit	2 Soms	3 Vaak	4 Heel vaak	5 Altijd
1	uitgeput was zonder uw fysieke activiteit aanzienlijk te verhogen?					
2	vermoeidheid ervaarde die niet substantieel kon worden verlicht door rust?					
3	lusteloos was tijdens het werk?					
4	leed aan hoofdpijn?					
5	last had van duizeligheid?					
6	ogen vermoeid waren of pijn deden?					
7	last had van keelpijn?					
8	spieren of gewrichten stijf aanvoelden?					
9	pijn had in uw schouder / nek / taille?					
10	u een zwaar gevoel in uw benen had tijdens het lopen?					
11	zich buiten adem voelde terwijl u stil zat?					
12	last had van een verstopte borstkas?					
13	last had van hartkloppingen?					
14	een verminderde eetlust had?					
15	last had van brandend maagzuur?					
16	last had van misselijkheid?					
17	koude omgevingen niet kon verdragen?					
18	moeite had om in slaap te vallen?					
19	's nachts meerdere keren wakker werd?					
20	problemen had met uw kortetermijngeheugen?					
21	niet snel kon reageren?					
22	moeite had te concentreren?					
23	zonder reden werd afgeleid?					
24	zich nerveus of zenuwachtig gevoeld?					
25	een verkoudheid had in de afgelopen 3 maanden?					

English Version of SHSQ-25

	How often is it, that you (your)	1 Never or almost never	2 Occasionally	3 Often	4 Very often	5 Always
1	were exhausted without greatly increasing your physical activity					
2	fatigue could not be substantially alleviated by rest					
3	were lethargic when working					
4	were lethargic when working					
5	suffered from dizziness					
6	eyes ached or were tired					
7	suffered from a sore throat					
8	muscles or joints felt stiff					
9	have pain in your shoulder/neck/waist					
10	have a heavy feeling in your legs when walking					
11	feel out of breath while sitting still					
12	suffered from chest congestion					
13	were bothered by heart palpitations					
14	appetite is poor					
15	suffered from heartburn					
16	suffered from nausea					
17	could not tolerate the cold					
18	had difficulty falling asleep					
19	had trouble with waking up during night					
20	had trouble with your short-term memory					
21	could not respond quickly					
22	had difficulty concentrating					
23	were distracted for no reason					
24	felt nervous or jittery					
25	caught a cold in the past 3 months					

Japanese Version of SHSQ-25

	3か月以内でのあなたの頻度で:	1 全くないまたはほとんどない	2 時々ある	3 よくある	4 頻繁によくある	5 毎回ある
1	運動をあまりしてなくても疲れを感じましたか?					

	3か月以内でのあなたの頻度で:	1 全くないまたはほとんどない	2 時々ある	3 よくある	4 頻繁によくある	5 毎回ある
2	休んでも疲れが取れなかった経験はありますか?					
3	仕事中、疲れや眠気を感じましたか?					
4	頭痛はありましたか?					
5	めまいはありましたか?					
6	目の疲れや痛みはありましたか?					
7	のどの痛みはありましたか?					
8	筋肉や関節が固くなりましたか?					
9	腰、肩、首に痛みを感じましたか?					
10	歩いている途中、足に重みを感じましたか?					
11	座っているとき、息苦しく感じましたか?					
12	肺が圧迫されてる感じはしますか?					
13	動悸を感じましたか?					
14	食欲がないと感じましたか?					
15	胸やけを感じましたか?					
16	吐き気を感じましたか?					
17	寒い場所にたえられないときがありましたか?					
18	眠りにつくのが難しいときはありましたか?					
19	夜中に起きることがありましたか?					
20	短期記憶に問題はありましたか?					
21	質問に対し、早く答えれないときがありましたか?					
22	集中力に問題がありましたか?					
23	理由もなく集中力が途切れたことはありましたか?					
24	興奮や緊張を感じたことはありましたか?					
25	3か月以内に風邪をひきましたか?					

Korean Version of SHSQ-25

증상	전혀 없었다	거의 없었다	그렇다	자주 그렇다	거의 항상 그렇다
B1. 귀하는 피곤하십니까(운동량이 현저히 증가되지 않는 경우)	1	2	3	4	5
B2. 귀하는 휴식 후 피로가 풀릴 수 있습니까	1	2	3	4	5
B3. 귀하는 일할 때 졸리거나 권태로운 현상이 있습니까	1	2	3	4	5
B4. 두통	1	2	3	4	5
B5. 머리가 어지럽다	1	2	3	4	5
B6. 눈이 쓰리고 탱탱하다	1	2	3	4	5
B7. 인후통	1	2	3	4	5
B8. 근육과 관절은 항상 경직되거나 뻣뻣함을 느낀다	1	2	3	4	5
B9. 어깨, 목 또는 허리가 시큰거리다	1	2	3	4	5
B10. 걸을 때 다리가 무겁다	1	2	3	4	5
B11. 숨을 죽일 때 숨이 가쁘다	1	2	3	4	5
B12. 가슴이 답답하다.	1	2	3	4	5
B13. 속이 떨리다	1	2	3	4	5
B14. 식욕 감퇴	1	2	3	4	5
B15. 속이 안 좋다	1	2	3	4	5
B16. 소화 불량	1	2	3	4	5
B17. 저열 혹은 추위를 탄다	1	2	3	4	5
B18. 잠들기 힘들다	1	2	3	4	5
B19. 꿈이 많거나 놀라 깨기 쉽다	1	2	3	4	5
B20. 기억력이 감퇴하다	1	2	3	4	5
B21. 순발력이 떨어지다	1	2	3	4	5
B22. 집중력이 떨어지다	1	2	3	4	5
B23. 이유 없이 정신이 사납다	1	2	3	4	5
B24. 긴장, 불안	1	2	3	4	5
B25. 귀하는 최근 1년 동안 감기에 걸린 적이 있습니까	1	2	3	4	5

Portuguese Version of SHSQ-25

		1	2	3	4	5
	Nos últimos 3 meses, o quão frequentemente você	Nunca ou quase nunca	Às vezes	Frequentemente	Muito frequentemente	Sempre
1	Esteve exausto mesmo sem ter aumentado muito a sua atividade física?					

	Nos últimos 3 meses, o quão frequentemente você	1 Nunca ou quase nunca	2 Às vezes	3 Frequentemente	4 Muito frequentemente	5 Sempre
2	Experienciou fadiga que não pode ser substancialmente aliviada com descanso?					
3	Esteve sonolento e apático (letárgico) no trabalho?					
4	Sentiu dores de cabeça?					
5	Sentiu tonturas?					
6	Ficou com os olhos doendo ou cansados?					
7	Sentiu dor de garganta?					
8	Sentiu rigidez nas articulações ou músculos?					
9	Esteve com dores no pescoço/cintura/ombro?					
10	Sentiu suas pernas pesadas enquanto caminhava?					
11	Se sentiu com falta de ar enquanto estava sentado?					
12	Sentiu os seus pulmões congestionados?					
13	Se incomodou com palpitações no coração?					
14	Teve falta de apetite?					
15	Sentiu queimação no peito/estômago (azia)?					
16	Sentiu náuseas?					
17	Não conseguiu tolerar ambientes frios?					
18	Teve dificuldades para dormir?					
19	Ficou acordando durante a noite?					
20	Teve problemas com a sua memoria de curta duração?					
21	Não conseguia responder rápido a perguntas?					
22	Teve dificuldade de concentração?					
23	Ficou distraído por nenhuma razão aparente?					
24	Se sentiu nervosa(a) ou ansioso(a)?					

	Nos últimos 3 meses, o quão frequentemente você	1 Nunca ou quase nunca	2 Às vezes	3 Frequentemente	4 Muito frequentemente	5 Sempre
25	Teve uma gripe nos últimos 3 meses?					

Russian Version of SHSQ-25

	Как часто это происходит с Вами?	1 никогда или почти никогда	2 редко	3 часто	4 очень часто	5 всегда
1	Испытываете ли Вы усталость, не связанную с увеличением физической активности					
2	Испытываете усталость, сохраняющуюся после отдыха					
3	Испытываете ли Вы сонливость во время работы					
4	Беспокоит ли Вас головная боль					
5	Бывает ли у Вас головокружение					
6	Чувствуете ли Вы боль или усталость в глазах					
7	Болит ли у Вас горло					
8	Беспокоит ли Вас скованность, дискомфорт в мышцах или суставах					
9	Беспокоят ли Вас боли в шее, плечах, пояснице					
10	Ощущаете ли Вы чувство тяжести в ногах при ходьбе					
11	Испытываете ли Вы одышку в покое					
12	Чувствуете ли Вы стеснение в груди					
13	Бывает ли у Вас учащенное сердцебиение					
14	Бывает ли у Вас сниженные аппетит					
15	Беспокоит ли Вас изжога					
16	Испытываете ли Вы тошноту					
17	Болеете ли Вы простудными заболеваниями					
18	Беспокоит ли Вас бессонница					
19	Просыпаетесь ли Вы среди ночи					
20	Испытываете ли Вы затруднения с кратковременной памятью					

		1	2	3	4	5
	Как часто это происходит с Вами?	никогда или почти никогда	редко	часто	очень часто	всегда
21	Чувствуете ли Вы снижение скорости реакции					
22	Испытываете ли Вы трудности с концентрацией внимания					
23	Отвлекаетесь ли Вы без причины					
24	Нервничаете ли Вы или впадаете в панику					
25	Страдали ли Вы простудой за последние 3 месяца					

Sinahla Version of SHSQ-25

පූර්ව මාස 03 තුල ඔබ කොපමණ වාරයක්	1	2	3	4	5	ලකුණු
	කවදාවත් නැහැ හෝ කවදාවත් නැති තරම්	ඉදහිට	බොහෝ විට	නිතරම	සෑම විටම	සෞඛ්‍ය සේවකයන් විසින් සම්පූර්ණ කිරීමට
1. ඔබේ ශාරීරික ක්‍රියාකාරකම් වඩාමනත් ලෙස ඉහල දැමීමකින් තොරව වෙහෙසට පත් වී ඇත්ද?						
2.විවේකය මඟින් සලකිය යුතු ලෙස අඩු කළ නොහැකි තෙහෙට්ටුව අත් විඳ ඇත්ද?						
3.වැඩ කරන විට උදාසීන වී ඇත්ද?						
4.හිසරදයෙන් පීඩා විඳ ඇත්ද?						
5.කරකැවිල්ලෙන් පීඩා විඳ ඇත්ද?						
6.ඇස් රිදීම හෝ ඇස් වෙහෙසට පත් වී ඇත්ද?						
7.උගුරේ අමාරුවෙන් පීඩා වින්දා ද?						
8.මාංශ පේශී හෝ සන්ධි දැඩි බවක් දැනුනාද?						
9.ඔබේ උරහිසේ/බෙල්ලේ/ඉඟටියෙහි වේදනාවක් තිබේද?						
10.ඇවිදින විට ඔබේ කකුල් වල තද ගතියක් තියනවද?						
11නිශ්චලව හිඳින විට හුස්ම හිර වීමක් දැනුනාද?						
12.පපුවේ තද වීමෙන් පීඩා වින්දා ද?						
13.හෘද ස්පන්දනය/ගැස්සීම නිසා පීඩාවට පත් උනාද?						
14.ආහාර රුචිය දුර්වලද?						
15.පපුව දැවිල්ලෙන් පීඩා වින්දාද?						
16.ඔක්කාරයෙන් පීඩා වින්දාද?						
17.සීතල පරිසරය ඉවසිය නොහැකිද?						
18.නිදාගැනීමට අපහසු වූවාද ?						
19.රාත්‍රී කාලය තුල අවදි වීමේ ගැටළුවක් තිබුණාද? උදාරෑට නින්දෙන් අවදි වීම.						
20.ඔබේ කෙටි කාලීන මතකය සමඟ ගැටළු ඇතිව තිබුණාද?						
21.යමකට ඉක්මනින් ප්‍රතිචාර දැක්වීට නොහැකි වුනාද?						
22.අවධානය යොමු කිරීමේ අපහසුවක් ඇති වුනාද?						
23. හේතුවක් නොමැතිව අවධානය වෙනතකට යොමු වුණාද?						
24.කේන්තියක් හෝ ව්‍යාකූල බවක් දැනුනාද?						
25.පසුගිය මාස තුන තුල සෙම්ප්‍රතිශ්‍යාව වැළඳී තිබේද?						

Slovak Version of SHSQ-25

Dotazník SHSQ-25

	Odpovedzte, prosím, na všetky otázky tak, že zapíšete X pod frekvenciu (1-5), ktorá, podľa Vás, najviac zodpovedá skutočnosti vo Vašom prípade.	1	2	3	4	5
	Ako často ste:/Ako často sa stáva, že:	Nikdy alebo skoro nikdy	Zriedka	Často	Veľmi často	Stále
1	unavený, aj keď nevykonávate výrazne zvýšenú fyzickú aktivitu?					
2	neviete zmierniť únavú tým, že si oddýchnete?					
3	malátny pri vykonávaní práce?					
4	trpíte bolesťami hlavy?					
5	trpíte závratmi alebo nevoľnosťou?					
6	trpíte bolesťou očí alebo únavou?					
7	trpíte zápalom hrdla?					
8	máte stuhnuté svaly alebo kĺby?					
9	máte bolesti v ramenách, krku, drieku?					
10	cítite, že vaše nohy sú akoby ťažké pri chôdzi?					
11	lapáte po dychu napriek tomu, že kľudne sedíte?					
12	trpíte sťaženým dýchaním?					
13	Vás rozruší tzv. „búšenie srdca“?					
14	máte slabú chuť do jedla?					
15	trpíte pálením záhy?					
16	trpíte nevoľnosťou s nutkaním na zvaracaie?					
17	nedokážete tolerovať chlad?					
18	máte ťažkosti so zaspávaním?					
19	trpíte zobúdzaním sa počas noci?					
20	máte problém s krátkodobou pamäťou?.					
21	nedokážete rýchlo reagovať?					
22	máte problém sústrediť sa?					
23	ste bezdôvodne roztržitý alebo zmätený/á?					
24	cítite nervozitu alebo paniku?					
25	ste mali nádchu v posledných troch mesiacoch?					

Spanish Version of SHSQ-25

	¿Con qué frecuencia es que usted (su/sus)	1 Nunca o casi nunca	2 Ocasionalmente	3 A menudo	4 Muy a menudo	5 Siempre
1	estuvo exhausto sin aumentar significativament su actividad física?					
2	fatiga no pudo ser aliviada sustancialmente por el descanso?					
3	estuvo letárgico cuando trabajaba?					
4	sufrió de dolores de cabeza?					
5	sufrió de mareos?					
6	ojos dolían o estaban cansados?					
7	sufrió de dolor de garganta?					
8	músculos o articulaciones se sentían rígidos/as?					
9	tiene dolor en su hombro/cuello/cintura?					
10	tiene una sensación de pesadez en sus piernas cuando camina?					
11	siente falta de aire mientras está sentado/a?					
12	sufrió de congestion en el pecho?					
13	fue molestado por palpitaciones en el corazón?					
14	tiene poco apetito?					
15	sufrió de acidez estomacal?					
16	sufrió de nauseas?					
17	no pudo tolerar el frío?					
18	tuvo dificultad para conciliar el sueño?					
19	tuvo problemas para despertarse en la noche?					
20	tuvo problemas con su memoria a corto plazo?					
21	no pudo responder rápidamente?					
22	tuvo dificultad para concentrarse?					
23	se distrajo sin razón aparente?					

	¿Con qué frecuencia es que usted (su/sus)	1 Nunca o casi nunca	2 Ocasionalmente	3 A menudo	4 Muy a menudo	5 Siempre
24	sintió nervioso/a o tembloroso/a?					
25	se resfrió en los últimos 3 meses?					

Thai Version of SHSQ-25

	สำหรับคำถามทีแสดงในตารางด้านล่างอาการเหล่านีเกิดขึน กับคุณบ่อยเพียงใดในช่วงสามเดือนทีผ่านมา? (ตัวเลือกเดียว ต่อบรรทัด)	1 ไม่เคย	2 มีบ้าง	3 มี	4 บ่อยครัง	5 เป็นประจำ
1	คุณรู้สึกเหนือยไหม (ในกรณีทีไม่มีการออกกำลังกายเพิมขึน อย่างมีนัยสำคัญ)					
2	ความเหนือยล้าของคุณดีขึนหลังจากพักผ่อนได้หรือไม					
3	คุณรู้สึกง่วงนอนหรือเหนือยจากการทำงานหรือไม					
4	รู้สึกปวดหัว					
5	รู้สึกวิงเวียน					
6	เจ็บตา					
7	เจ็บคอ					
8	กล้ามเนือและข้อต่อมักรู้สึกตึงหรือแข็ง					
9	เจ็บไหล่คอหรือเอว					
10	รู้สึกหนักขาเมือเดิน					
11	หายใจถีขณะพัก					
12	แน่นหน้าอก					
13	ใจสัน					
14	ไม่อยากอาหาร					
15	ไม่สบายท้อง					
16	อาหารไม่ย่อย					
17	ร้อนๆหนาวๆ					
18	นอนหลับยาก					
19	ฝันหรือตืนได้ง่าย					
20	ลืมง่าย					
21	การตอบสนองลดลง					
22	ไม่มีสมาธิ					
23	หงุดหงิดโดยไม่มีสาเหตุ					
24	วิตกกังวล					
25	ในปีทีผ่านมาคุณเคยเป็นหวัดหรือไม่					