Open Complex Systems Approach Utilizing ICT to Address Immune-Related Diseases in Aging Society

Tatsuya Kawaoka[1,2,3][a], Ryota Sakayama[3][b], Kousaku Ohta[1][c] and Masatoshi Funabashi[1,2,3][d]

[1]Sony Computer Science Laboratories, Inc. Takanawa Muse Building 3F, Higashigotanda 3-14-13, Shinagawa-Ku, Tokyo, Japan

[2]Kyoto University Research Division on Social Common Capital and the Future, Yoshidashimoadachicho 46 Inamori Center2F 228, Kyoto Sakyo-ku, Kyoto, Japan

[3]Synecoculture Association, Oiso 55, Oiso-Cho, Naka-gun, Kanagawa, Japan

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Abstract: Immune-related diseases, such as allergies, asthma, and dementia, are rising globally, driven by aging populations and declining ecosystem functions. Traditional elementary reductionist approaches struggle to address the complex pathologies underlying these diseases. This study explores a personalized, ecosystem-based approach to mitigating immune dysregulation using a supportive ICT platform. We developed a data-driven analytical system that identifies individual metabolic challenges through the measurement of multiple biomarkers and clinical interviews, categorizing them into metabolic traits such as inflammatory, stress-related, and glucotoxic factors. Based on these assessments, professional staff provided tailored lifestyle advice and rehabilitation interventions, including light exercises in high biodiversity environments. The results showed significant improvements in cognitive and immune functions: Participants exhibited a 3.5-point average increase in MoCA scores over three months, including functional recovery from Parkinson's disease and CVA. Furthermore, the study identified phytochemical-rich foods, such as coarse green tea, as significant factors enhancing rehabilitation outcomes. These findings emphasize the importance of synergy between ecological environments and public health initiatives, aligning with the Planetary Health framework. By integrating multivariate analysis, personalized interventions, and ecosystem considerations through an integrative ICT platform, this approach offers a scalable solution to addressing immune-related diseases and reducing social security costs, with implications for global healthcare and environmental policies.

1 INTRODUCTION

1.1 Increase in Immune-Related Diseases and Decline in Ecosystem Function

With international aging populations, the increase in various immune-related diseases has become serious issues in many countries, such as allergies, rheumatoid arthritis, asthma, and neurodegenerative diseases including dementia and Parkinson's disease (Furman et al., 2019; Hou et al., 2019; Kim and Lee, 2023). These diseases are difficult to address using traditional elementary reductionist methodologies (Funabashi, 2018; Ahn et al., 2006; Beresford, 2010; Rocca and Anjum, 2020): It is historically known that elementary reductionist approaches have saved many lives particularly in the case of infectious diseases and trauma, which are caused by external factors. On the other hand, the pathology of endogenous diseases results from complex interactions and complications in the body's internal mechanisms. The general cause is the breakdowns in immune systems, making it challenging to resolve them using elementary reductionist approaches.

[a] https://orcid.org/0000-0002-9606-5188
[b] https://orcid.org/0009-0000-4422-0716
[c] https://orcid.org/0000-0002-1360-8897
[d] https://orcid.org/0000-0002-7519-3084

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Furthermore, the large-scale intensification of food production has led to a decrease in the diversity of soil microorganisms in the environment (Gupta et al., 2022; Xue et al., 2022), which, in turn, affects the nutrients in the plants grown (Suman et al., 2022) and impacts the health status of animals, including livestock (Attwood et al., 2019). These changes negatively affect the immune system regulation of humans who consume these foods. Besides, numerous studies on gut microbiome have highlighted that its diversity plays a critical role in immune regulation (Zheng et al., 2020). The reduction in the diversity of gut microbiota, referred to as dysbiosis, has been reported as a common phenomenon in various neurological disorders, including dementia, Parkinson's disease, autism, and depression (Dutta et al., 2019; Ashique et al., 2024) A decline in ecosystem functions in the environment leads to a reduction in microbial diversity, which reduces the diversity of gut microbiota in the people living in that environment. The decreased diversity of gut microbiota weakens the immune system regulation, ultimately contributing to long-term disorders (Fig. 1). Since soil and gut microbiome are connected through food intake, it is important to consider the changes in ecological environments behind the recent rise of neurological diseases.

In recent years, in many countries, economic development has led to a decline in ecosystem functions, resulting in an increase in immune-related diseases (Acheampong and Opoku, 2023; Agache et al., 2024). With social changes and population aging, this trend is leading to challenges in the sustainability of social welfare systems and economic strain. To address these social-ecological issues and build a sustainable civilization, it is necessary to create human activities that do not lead to the breakdown of immune systems.

Cohort studies have shown that the incidence of immune-related diseases is lower in areas surrounded by greenery, underscoring the importance of urban and green space planning (Mueller et al., 2022; Rojas-Rueda, 2019). The functionality of ecosystems within people's living environments is closely connected to healthcare, welfare, and social security costs. Designing living environments that consider factors like microbial diversity and nutrient content in food, as well as planning human activities, is crucial for long-term public health risk management.

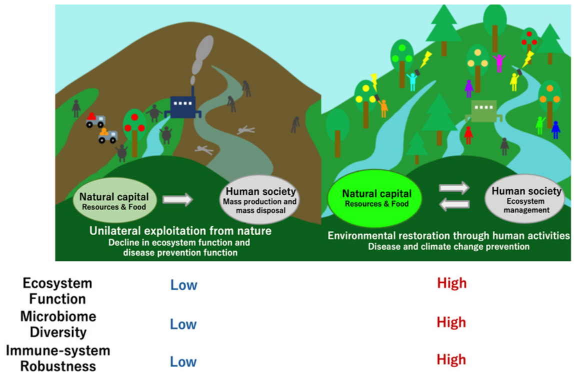

Figure 1: Ecosystem function and immune-system robustness.

1.2 The Increase in Dementia Patients and the Sustainability of Social Welfare Systems in Japan

Japan is one of the world's most rapidly aging nations, with nearly 30% of its population aged 65 and older. The sharp rise in dementia patients has become a pressing social issue, with approximately 20% of the elderly population estimated to be affected by dementia (Cabinet Office of Japan, 2017) . Social security costs have escalated, increasing nearly fourfold over the past two decades. A severe issue associated with dementia is the freezing of assets, with an estimated ¥215 trillion JPY (around $1.4 trillion USD) in assets held by dementia patients in 2020 (Kinoshita et al., 2024). These assets are estimated to increase by ¥6 trillion JPY (around $40 billion USD) annually, and the risk of these assets becoming inaccessible is high—equivalent to Japan's GDP growth. Dementia alone may thus result in economic losses comparable to Japan's GDP growth. Historically, Japan's prioritization of market efficiency has often come at the expense of biodiversity and ecosystem functions. Consequently, factors such as a decrease in gut microbiota diversity and reduced nutritional content in food may have led to immune dysregulation, contributing to an increase in immune-related diseases, including dementia. The economic impact of asset freezing due to dementia is becoming a growing threat to the economy. From a macroscopic perspective, a conflict between short-term profit pursuit and long-term gains of total well-being has emerged.

Globally, the rising prevalence of immune-related diseases such as allergies and asthma in children, suggests widespread immune dysregulation across generations (D'Auria et al., 2023). Combined with an increasing elderly population, this trend has created a substantial social burden—chronic diseases associated with aging have now become a global issue. According to WHO estimates, there are currently 50 million dementia patients worldwide (WHO, 2023), and this number is projected to grow. The economic losses attributed to dementia amount to $1.3 trillion (WHO, 2023). Japan's crisis with rising dementia cases and its strained social welfare system may serve as a warning for other countries facing a similar future.

This study aims to establish a scientific framework using ICT and multivariate analysis to synergistically enhance human immune system regulation and ecosystem functions, and clarify its underlying relationship through iterative amelioration of the system.

2 PERSONALIZED AND COMPREHENSIVE APPROACH TO IMMUNE-RELATED DISEASES

For immune-related diseases with complex pathologies such as dementia, multifaceted approaches focused on lifestyle factors—principally diet, exercise, and stress management—have shown effectiveness in previous studies (Galvan and Bredesen, 2007). A study on integrated care involving 100 participants reported cognitive improvements in 70% of those with mild cognitive impairment and 30% of patients diagnosed with Alzheimer's-type dementia (Bredesen et al., 2018). The research team further recommended supplementing nutrients involved in immune regulation, such as methylcobalamin, melatonin, vitamin B group, and other phytochemicals.

Other studies revealed that many of the recommended nutrients are linked to the sane functioning of ecosystems (Tilman and Clark, 2014). Exposure to natural environments such as park visits and formal outdoor activities are expected to reduce risks of chronic diseases, known as nature prescription (Kondo et al., 2020). Furthermore, we reported improvements in immune markers and cognitive function through a rehabilitation approach that combines exposure to high biodiversity environments with the consumption of products derived from these ecosystems (Funabashi, 2022). Such an ecosystem-based approach can be considered in line with the current initiative of Planetary Health, where human and ecological health are mutually sustaining and enhancing each other (Funabashi, 2024a). While it provides promising scientific background to simultaneously address environmental restoration and immune system normalization, several barriers remain to be addressed for widespread social implementation.

One significant barrier is the shortage of personnel who are able to provide specialized advice on non-communicable diseases with comprehensive views on metabolism and lifestyle factors (Fig. 2). Each faucet in Fig. 2 represents lifestyle risk factors that influence immune system regulation, such as insufficient exercise, psychological stress, exposure to harmful substances, imbalance in dietary habits, and loss of gut/skin/oral microbiota. Improper lifestyle choices open these faucets, causing a rise in water levels that represents the accumulation of chronic inflammation. Chronic inflammation is counteracted by homeostatic maintenance functions, such as antioxidant activities and autophagy at the cellular level, depicted as water being drained from the bottom, which generally slows down as aging proceeds. As long as the drainage (homeostatic maintenance) exceeds the rate of water accumulation (chronic inflammation), the onset of disease can be prevented. However, health-degrading factors such as aging and improper lifestyle lead to the accumulation of chronic inflammation, ultimately resulting in the development of immune-related diseases. The onset process is analogically depicted as the water drowning the gut and brain functions: The accumulation of chronic inflammation initially causes dysregulation of the immune system in the gut, and by further impairing the function of the blood-brain barrier, leads to immune system dysregulation in the brain. The overall dysregulation can result in neuronal cell death and the onset of various neurodegenerative diseases. Based on the "hidden reef model" in ref (Funabashi, 2018). Additionally, individuals with the same disease may experience metabolic disruptions differently according to their genetic profiles and lifestyles, underscoring the need for personalized approaches.

To overcome these challenges, it is essential to establish a comprehensive assessment and management system that identifies lifestyle-related issues unique to each individual and provides guidance to encourage behavioural change. Leveraging such complex interactive processes with ICT through multivariate analysis and artificial intelligence could extend the capabilities of professionals in caregiving and welfare settings, facilitating the personalized identification of lifestyle issues and tailored advice for intervention.

For this purpose, we developed a system to estimate the metabolic profiles of the patients through multivariate analysis of biomarkers and clinical interviewing. The biomarkers obtained included approximately 60 types, such as Copper, Zinc, Sodium, Potassium, Calcium, CRP, etc., and clinical interviews included surveys on dietary and sleep habits. This system enables professional staff in caregiving settings to make specific lifestyle recommendations based on assessments of these biomarkers and related clinical records, as well as the integration of connectivity with ecological environments. A database of historical information is built by recording text-based descriptions of biomarker patterns, observed changes, and behavioral changes. This accumulation of records allows us to trace not only individual patients' history, but also guide interventions for other individuals with similar metabolic patterns. Through iterative recording and interactive evaluation, effective approaches can be documented and extracted according to the specificity of metabolic characteristics.

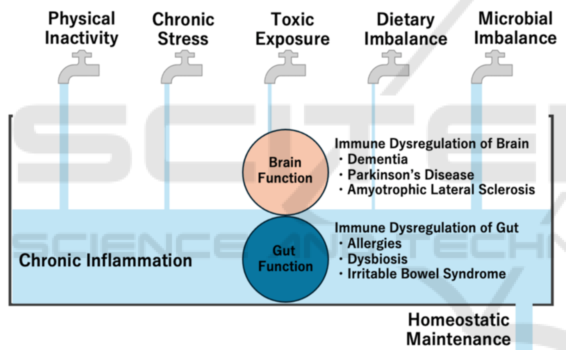

Figure 2: Immune-related diseases depicted as faucet model.

3 METHODS

3.1 Data Analysis of Biomarkers

The values of 60 biomarkers were obtained from an ISO15189-certified analysis institution. The data were processed through multivariate analysis using a database and algorithm constructed based on literature and knowledge from experts in the medical and life sciences fields:

Each biomarker was analysed and categorized into five groups—inflammatory, stress-related, glucotoxic, toxic, and atrophic—based on metabolic characteristics. A comprehensive score for each metabolic trait was calculated according to the values of the corresponding biomarkers, and amelioration tasks were identified for each group. For example, recommendations for glucotoxicity include reducing the intake of simple sugars, such as those found in sweets, and increasing the intake of vitamin B1, which is involved in carbohydrate metabolism. By obtaining these analytical results and recommendations, care staff can provide personalized lifestyle guidance to individuals (see section 3.2). The advice also considered the effects of the natural environments, including the soil-gut microbiome connection and ecological origins of nutrients (see section 2). By accumulating databases about the correspondence between the metabolic conditions, the types of advice they receive, how their behaviour changes, and how their metabolic status evolves, we refine the database and evaluate the effectiveness of the advice for each subtype of challenge, leading to more sophisticated and tailored recommendations.

The system integrates multivariate analysis of objective biomarker data, including vitamins, minerals, and hormones, with subjective lifestyle data such as dietary habits, physical activity, and sleep quality (Fig. 3). Based on these analyses, we generate personalized lifestyle improvement plans. Care staff record details of lifestyle habits and physical activity as text data, which are then accumulated in the system. Based on the iterative analysis, care staff provide and revise personalized lifestyle advice. Changes in patients' health statuses were continuously recorded by care staff. The clinical and patient-reported outcomes were used to improve the model. The system incorporates multiple analytical models and is designed to be expandable, allowing for the addition of analytical modules as it evolves. Accumulation of real-world data is expected to enhance the accuracy of the system as a whole.

3.2 Personalized Advice by Care Staff

Professional care staff (including physical therapists and exercise therapists) identified individual metabolic challenges (see section 3.1) and provided personalized support regarding lifestyle habits such as diet and sleep. Additionally, comprehensive care was provided, including aerobic exercise, rehabilitation in high biodiversity environments (see section 3.3), and psychological stress relief through mutual advice among participants, all aimed at removing factors contributing to chronic inflammation. The frequency of care was generally at least once a week.

For example, lifestyle suggestions for inflammatory conditions include adopting glutenfree, glucose-free, and casein-free diets, consuming foods with antioxidant properties, and establishing regular exercise habits, including rehabilitation activities in high biodiversity environments. Instead of simply delivering scientifically correct information, a more personalized and interactive approach was taken by conducting interviews to understand each individual's personality and lifestyle. The guidance was then tailored to align with their preferences, gradually fostering changes in awareness and behaviour in a way that resonated with the patient's understanding.

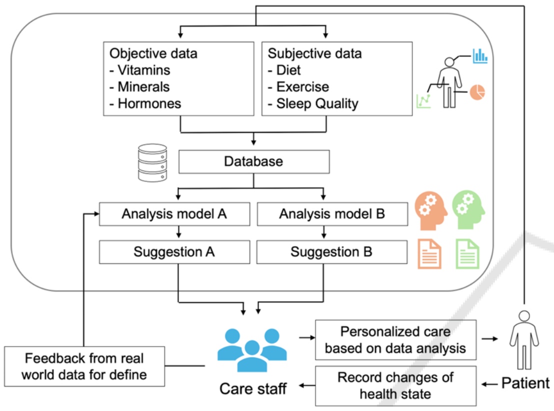

Figure 3: System overview.

3.3 Creation of High Biodiversity Environment

Based on the Planetary Health perspective (see section 2) and the concept of augmented ecosystems (Funabashi, 2018; Funabashi, 2024), we created a high biodiversity environment utilizing a 100m² abandoned farmland area. To enhance the ecosystem's self-organized development and avoid potential risk factors for health, only seeds and seedlings of edible plants were introduced in the field, without the use of fertilizers, pesticides, and continuous tilling. Before the introduction of edible plants, the area had around 10 species of naturally occurring vegetation, and after the seasonal introduction of edible plants throughout the year, the diversity resulted in approximately 100 plant species.

Rehabilitation activities were conducted for about one hour on the farm. These included walking training and strength exercises, such as squats. Participants engaged in seasonal activities like sowing seeds and harvesting vegetables, as well as eating the farm's products.

4 RESULTS

4.1 Change in Biomarkers and Cognitive Function

This system has demonstrated an average improvement of 3.5 points on the MoCA, a cognitive function test scored out of 30 points, for seven patients in 3 months (Fig. 4, Funabashi, 2022).

The participants consisted of seven male and female elderly patients aged 65 and older, all with baseline MoCA scores of 25 or below. Fig. 4 A: Changes in homocysteine levels, an immune biomarker, comparing baseline values to those after three months. p-value=0.000491, n=7 (Student's t-test). Fig. 4 B: Changes in MoCA scores, a measure of cognitive function, comparing baseline values to those after three months. p-value=0.02734, n=7 (Student's t-test). Statistical significance: $p < 0.05$ (*), $p < 0.01$ (**).

Previous studies report that cognitive functions in early-stage Alzheimer's patients decline by approximately 3 points over 18 months without intervention. In contrast, conventional pharmacological approaches in the United States delay this decline by about 0.81 points, equivalent to 27% of the decline, at a cost of approximately $27 thousand USD per patient annually in the U.S., and the same prescription costs ¥3 million JPY ($20 thousand USD) in Japan. The annual progression delay effect of existing drugs is approximately 0.54 MoCA points. Thus, the 3.5-point improvement achieved by our system is roughly 6.5 times the progression delay effect of pharmacological approaches, equivalent to 6.5 years of progression delay. When compared to drug treatment, this improvement suggests an estimated contribution to social security systems of $130-150 thousand USD (in Japan and the U.S., respectively) per individual.

Additionally, applying the same scheme in our practice has demonstrated improvements in the UPDRS (Unified Parkinson's Disease Rating Scale) scores of two patients with Parkinson's disease. In the cases of CVA (cerebrovascular accident) post-rehabilitation, improvements in blood pressure and walking speed still occurred in patients who passed more than two years after the onset.

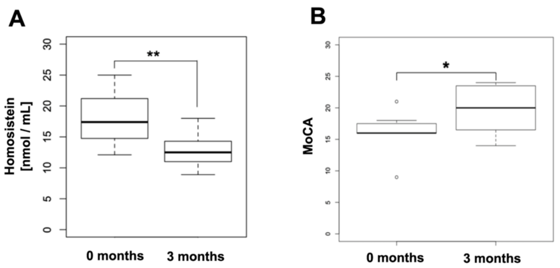

Figure 4: Changes in immune markers and cognitive function scores.

4.2 Extraction of Significant Associated Parameters

The system is capable of detecting parameters that are associated with the amelioration of rehabilitation performance. It includes not only the types of intervention and training in the rehabilitation program, but also correlated profiles of trainers and environmental factors such as geographical location and food intake. One of the significant associated factors we discovered is the intake of different kinds of drinks during the rehabilitation program, which comprised different antioxidant profiles.

Fig. 5 shows the statistically significant difference in the functional independence measures (FIM) and Philadelphia Geriatric Center Morale Scale (PGCMS) scores of 117 elderly patients with an average ± standard deviation of 77.7 ± 8.5 years old, during 4 months of rehabilitation among three groups who A: drank coarse green tea (bancha) with rich phytochemical content, B: coarse green tea with less variety and concentration of phytochemicals than A, and C: hot water, which was commonly used to extract tea in A and B.

The red solid line represents group A (phytochemical-rich bancha), the green solid line represents group B (conventional bancha), and the blue solid line represents group C (hot water). The dashed gray line indicates the statistical significance threshold of 5%, while the dotted gray line denotes the statistical significance threshold of 1%. The red, green, and blue dashed lines in the top right PGCMS panel correspond to the mean p-values of changes during the four-month rehabilitation period (1–4 months) compared to the initial condition (0 months) for groups A, B, and C, respectively. A complete set of FIM plots, including subcategories with significant improvements, is provided in Supplementary Material 3 (SM, 2024).

None of them suffered from acute illness, but they fell under the maintenance phase of returning to daily life after chronic illnesses such as dementia and Parkinson's disease, attacks of cerebral infarction or haemorrhage, and surgery such as excision of cancer and replacement with artificial joints. The four-month rehabilitation programs included training to improve physical fitness, such as muscle strength and aerobic exercise using light-load training machines (10 times for each exercise of trunk curl, back curl, chest press, shoulder press, leg adduction, leg press, and 5-20 min walking on a treadmill), and functional training to improve activities of daily living. See Supplementary Materials 1-3 (SM, 2024) for the details of the measurement, the p-values of changes for all items, and ref. (Ohta et al., 2022) for the phytochemical profiles of tea in groups A (Synecoculture tea grown under high ecological interactions and rich in secondary metabolites) and B (conventional tea grown under low ecological interactions and rich in primary metabolites).

The results show that the associative parameter concerning the intake of drinks is correlated with the significant difference in performance: After four months of rehabilitation, only group A showed the improvement of total FIM at a significance level of 0.01 (p-value = 0.0088), as well as for the domain of motor functions (p-value=0.0021). The domain of cognitive functions did not reach the significance level of 0.05 (p-value=0.0515), but showed an exclusive increase in group A compared to the decreases in groups B and C. The group B and C did not show a significant change in the two domains. No other parameters could separate the rehabilitation effect more significantly than the drink groups A, B, and C.

In the six classifications of FIM, group A improved at a significance level of 0.05 for selfcare (p-value=0.0248), 0.01 for transfer (p-value=0.007), locomotion (p-value=0.002), and communication (p-value=0.0058). Among these, only transfer showed the improvement at a significance level of 0.01 in group B (p-value=0.0071) and 0.01 in group C (p-value=0.0267), but other combinations of classifications and groups did not show any significant change.

In the 18 items of FIM, group A improved at a significance level of 0.05 for bed/chair transfer (p-value=0.0277), walk (p-value=0.0236), expression (p-value=0.012), 0.01 for dressing upper body (p-value=0.0091), dressing lower body (p-value=0.0095), tub/shower transfer (p-value=0.0017), stairs (p-value=0.008). Among these, only tub/shower transfer showed an improvement at a significance level of 0.05 in group B (p-value=0.0215), and 0.01 in group C (p-value=0.0015), but other combinations of classifications and groups did not show any significant change.

The PGCMS showed maximum significant improvement after the third month at a level of 0.05 for groups A (p-value=0.036) and B (p-value=0.024). After the fourth month, group A showed the smallest p-value (p-value=0.05007). As the mean p-values of four-month rehabilitation, only group A showed a significant result (p-value=0.040). All p-values in this section are based on a two-sided paired t-test.

These results show an example of the detection of significant parameters correlated with the changes in rehabilitation performance that were not initially considered as clinical interventions.

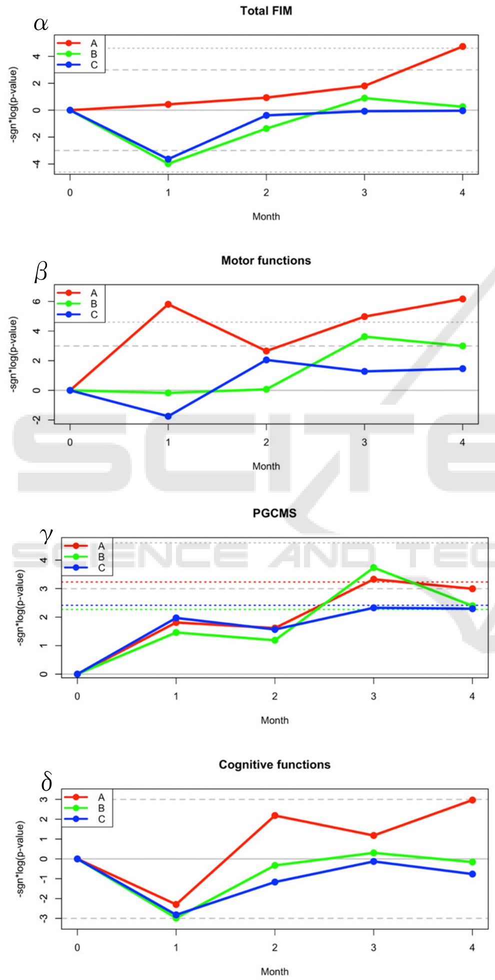

Figure 5: Dynamics of changes in major FIM categories and PGCMS during the rehabilitation of the elderly with bancha drinks. α : total FIM. β: PGCMS. γ: motor functions domain of FIM. δ: cognitive functions domain of FIM. X-axis: Time after the start of rehabilitation with bancha drinks. Y-axis: p-value of changes compared to the initial condition (0 months) in a logarithmic scale, with positive and negative signs that represent the improvement and alleviation of FIM scores, respectively.

5 CONCLUSIONS

In this study, a multivariate analysis system was developed to identify metabolic challenges through lifestyle and biomarker data. The system was also applied to evaluate the combination of rehabilitation programs and intake of products connected with augmented ecosystem environments, under the scientific rationale of Planetary Health. Based on a systematic approach that considers immune dysregulation, ecosystem interactions (Fig. 1), and the complexity of non-communicable disease pathologies (Fig. 2), rehabilitation programs supported with our system showed substantial improvement in immune regulation and cognitive functions (Fig. 4). Based on the Japanese example, the estimated reduction in social security costs is $130,000–$173,550 USD per person.

The study also discovered significant factors associated with the rehabilitation program, such as the effects of tea rich in phytochemicals, grown in high biodiversity environments, on physical and cognitive functions: Significant improvements in motor function indicators and cognitive performance were detected in elderly participants (Fig. 5). These findings highlight the importance of inclusive and extensive analysis in the discovery of effective factors for systemic problem-solving, as well as multiple leveraging points that ICT could contribute to collectively harnessing the complexity of immune-related diseases.

The utilization of computational technologies in the healthcare domain has traditionally relied on elementary reductionist approaches. For example, high-throughput sequencing has enabled unprecedented speeds in pathogen analysis. This advancement has made it possible to e.g., rapidly decode viral genomes and develop a vaccination (Soon et al., 2013; Pérez-Losada et al., 2020). More comprehensive data analytics have contributed to revealing the various risk factors associated with long-term health, such as chronic disease prevention (Ng et al., 2020). Such elementary reductionist approaches have proven especially effective in addressing infectious diseases caused by single external factors, as well as detecting historically associated variables for health outcomes at the cohort level. However, it remained challenging to individually assess and treat non-communicable diseases in real time, influenced by multiple interacting factors, such as immune-related or metabolic disorders. To tackle these complex issues, the methodology of Open Systems Science has been proposed (Tokoro, 2017). This approach involves the following steps:

1. Hypothetically define a system where the problem is presumed to exist.
2. Model the problem within the defined system.
3. Investigate whether the model's behaviour over time remains consistent and aligns with the actual behaviour of the system.
4. If inconsistencies are identified, revise the model, redefine the system if necessary, and remodel the problem.
5. Repeat the process until satisfactory results are achieved.

The design of the present system (Fig. 3) incorporates the principles of Open Systems Science. It introduces a management-oriented perspective for practically solving complex problems, in contrast to the conventional science that primarily focuses on rigorous analysis and reconstruction of the phenomena. The pragmatic characteristic of Open Systems Science is particularly useful for the rapid proposal of integrative solutions to escalating social problems in real-world settings based on multidisciplinary frameworks, such as the ecological foundation of health (Funabashi, 2018). By continuously refining the model with novel data, the system is designed to balance both speed and effectiveness. The application of ICT and interactive system design based on Open Systems Science can be considered a novel structural methodology for addressing pervasive health issues, especially non-communicative chronic diseases.

In this study, we demonstrated that an integrated approach on lifestyle and rehabilitation improved both cognitive function and immune system regulation in dementia patients. The approach includes the utilization of ecosystem functions and the personalized advice on lifestyle habits. The outcome implies that this method can generate significant social impact at a much lower cost compared to conventional drug-based approaches. Additionally, we introduced findings that consuming tea grown in high biodiversity environments during rehabilitation contribute to the performance. Since the number of cases in this study is limited, it is necessary to further accumulate data through promoting social implementation in order to investigate its reproducibility. Due to the complexity and multifaceted nature of this approach, a societal framework must be built that could efficiently share knowledge on lifestyle guidance, how to create high biodiversity environment, and the access to nutritionally balanced food in an integrative manner.

Further development and validation could be achieved by accumulating case studies in wider contexts and refining the modules for data analysis, leading to more precise and effective applications of the established framework.

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iMARe, Inc. supported this study. “iMedit” is a trademark of iMARe, inc. “Synecoculture” is a trademark of Sony Group Corporation.

CONFLICTS OF INTEREST

Masatoshi Funabashi is the CEO of SynecO, Inc., a company involved in ecological augmentation. However, this did not influence the scientific analysis presented in this paper.

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