Chapter 7
Cohort Profile: The Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience (The Nagahama Study)

Kazuya Setoh and Fumihiko Matsuda

Abstract The Nagahama Prospective Cohort for Comprehensive Human Bioscience is the first large-scale multipurpose genome cohort in Japan. The project started in 2007 with a new concept of "pre-primary prevention" aiming to realize personalized early disease prevention based on the genetic background of each individual, detailed measurement of biomolecules in the body and health-related clinical information over time together with the environment and lifestyle. The uniqueness of this human biology study is the multidisciplinary research infrastructure incorporating information science, mathematics, and social sciences. Cutting-edge technology in genomic medicine such as next-generation sequencing and multi-omics measurements is combined with an objective evaluation of environmental factors, records on sleep and other body activities, and the comprehensive social capital survey. Various research programmes have been launched on this information infrastructure, such as a skin aging study with industry and an association study between genetic factors and social and economic behaviour in collaboration with a governmental research institute. From 2020, a new socio-life science study for the COVID-19 pandemic consisting of SARS-CoV-2 antibody measurement and social capital surveys was initiated as a joint research effort of academia, government and industry.

Keywords Human biology · Pre-primary prevention · Genomic cohort · Multi-omics analysis · Socio-life science

1 Human Biology with Integrated Human Life Information

Epidemiological approaches using large-scale cohorts conducted in Japan and overseas have contributed significantly to elucidating risk factors and proposing preventive methods for diseases that are difficult to accomplish only by fundamental

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researches using cells and model animals or clinical investigations based on patient morbidity information. These studies often use macroscopic biomarkers such as physique and blood pressure with a limited number of typical biochemical measurements. However, the risk of developing the disease has not been fully explained only with these classical risk factors because of human genetic diversity.

On the other hand, genomic analysis technology, which has grown rapidly since the beginning of this century, has successfully applied to human disease genomics and enabled identifying susceptibility genes for a number of multifactorial disorders in a cross-sectional manner. Nonetheless, few cases directly contributed to disease mechanism elucidation, development of new treatments and drugs, and the prevention and therapy of such diseases. These facts strongly show the limitation of epidemiological approaches focusing only on classical risk factors and cross-sectional disease studies using genomic analysis.

Recent studies of human disease and aging focus more on intermediate phenotypes such as transcripts, proteins/peptides, and metabolites in addition to genomic information. Such biomolecule information is crucial to trace as biomarkers because these phenotypes directly reflect physiological conditions, including aging, and are associated with the onset and progression of various diseases. On the other hand, unlike genomic information, they change over time. Thus, to discover novel risk factors and disease-related biomarkers using intermediate phenotypes, it is crucial to comprehensively measure time-series biological samples obtained from a large number of healthy subjects using cutting-edge analytical technology and conduct an integrative analysis with health-related information such as environment and lifestyle, and disease morbidity.

The Nagahama Prospective Cohort for Comprehensive Human Bioscience (the *Nagahama Study*) is the first large-scale multipurpose genome cohort in Japan, recruiting 10,000 healthy individuals in Nagahama City of Shiga Prefecture. In this project, we have conducted an extensive health check once every five years, including physiological measurements, laboratory tests using blood and urine, and collected lifestyle, clinical, and environmental information. We also accumulated data on the onset, pathophysiology, and prognosis of diseases through periodical follow-up surveys of disease morbidity and death. In addition, time-series blood and urine samples have been collected and stored for analysis and measurement. A large-scale, high quality, and advanced research design enabling the discovery of novel biomolecules involved in diseases and aging considering human diversity has been highly evaluated worldwide. It plays an essential role as a research infrastructure for human biology and contributes to various genomic epidemiological studies.

2 The Nagahama Study and Its Background

The *Nagahama Study* has been jointly implemented by Kyoto University Graduate School of Medicine and Nagahama City in Shiga Prefecture since 2007. This project aims to improve health awareness of oneself and the community and introduce new

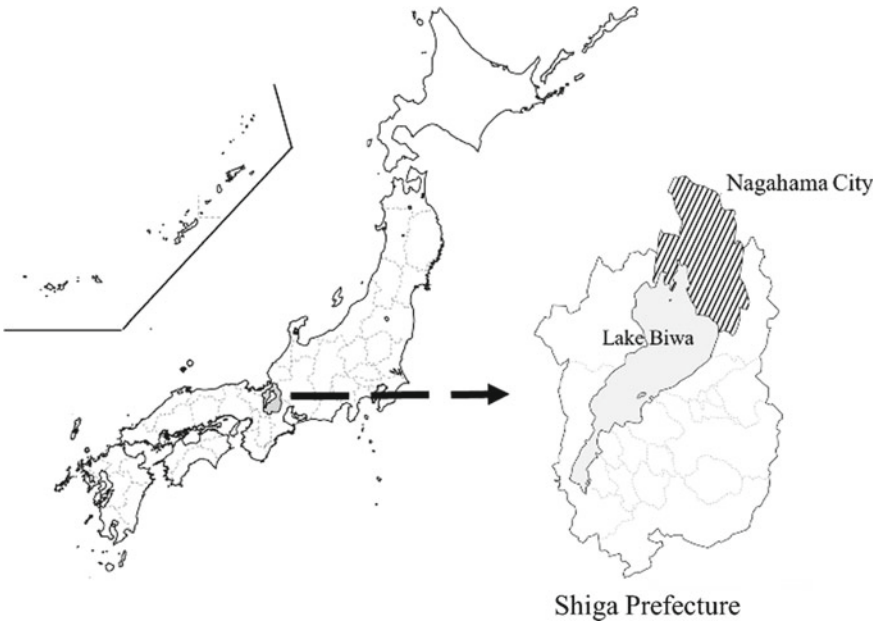

Fig. 1 Location of Nagahama city

health promotion passed on to the next generation. It consists of more than 10,000 healthy residents of Nagahama and is considered the largest cohort recruiting inhabitants of a single city (Fig. 1). Nagahama is a medium-sized local city with approximately 120,000 people and is located in the northeastern part of Lake Biwa, the largest lake in Japan. The proportion of the elderly aged 65 and over was around 20% at the beginning of the project in 2007. It has increased to approximately 28% in recent years, showing the same transition as the national level in Japan. Therefore, it is suitable for epidemiological studies that reflect the aging society in Japan. Nagahama City has a small population inflow and outflow. In addition, three core hospitals in the city form a medical service area of more than 200,000 people centered on Nagahama City. Therefore, it is possible to track the disease onset status of cohort study participants over a long period. This project contributes to the health promotion of Nagahama citizens through genomic epidemiology research and dissemination and enlightenment activities related to health. Nagahama citizens established the NPO "Health Promotion Zeroji Club". It supports this study from various aspects, such as recruiting participants for the project, managing medical checks, and organizing multiple health promotion activities.

3 The Concept of "pre-Primary Prevention"

In preventive medicine, which aims to prevent diseases that threaten health, the prevention stage is divided into three phases, namely, primary prevention (health promotion), secondary prevention (early detection and treatment), and tertiary prevention (rehabilitation). However, each individual is unique, and uniform prevention based on population averages may not be optimal for that individual. Therefore, we proposed the concept of "pre-primary prevention" ("Zero-Ji Yobou" in Japanese), which refers to a new concept of prevention that precedes primary prevention. It aims to realize optimal and early disease prevention for each individual based on their genetic background and detailed measurement of biomolecules in the body such as proteins, lipids, and metabolites. The importance of prevention prior to primary prevention has been advocated for a long time, and one example is the concept of primordial prevention proposed by Strasser (1978). Its idea was to prevent cardiovascular disorders by changing the sense of values in the population and the structure of the socio-economic environment to prevent the penetration of risk factors into the population. For example, activities to prevent the spread of undesirable eating habits in the population that increase disease risk by distributing reasonably-priced healthy foods and encouraging children to acquire desirable eating habits from school age were assumed. Primordial prevention precedes primary prevention but differs from pre-primary prevention in that it attempts to reduce risk through uniform guidance. Pre-primary prevention is a concept that leads to preemptive medicine, which aims to realize the lifelong increase of the quality of life by preventing or delaying the onset of disease through highly accurate pre-onset diagnosis and early intervention that is optimal for the individual.

4 The Nagahama Rules

At the start of this project, the national ethical guidelines did not cover the various issues to be addressed in this project, such as acquiring global consent including the whole-genome analysis of apparently healthy individuals. Hence it was necessary to create our own rules on research ethics. Based on the current guidelines and local regulations, we conducted a pilot survey of a small number of people in 2007. Considering the issues that materialized through the survey, the "Nagahama Rules" were formulated after a lengthy discussion among medical biologists, experts in ethics and law, the Nagahama local government, and residents' representatives. In June 2008, these rules were made legally binding by being enacted as an ordinance of Nagahama City. Although it was a groundbreaking rule at the time of its enactment, social conditions and guidelines related to research ethics have changed. Therefore, careful discussions are ongoing among researchers, government officials, and experts to update it flexibly adapted to such changes and continue to be a fundamental principle of the project.

5 Survey Summary

5.1 Baseline Survey (FY 2007~2010)

The baseline survey recruited Nagahama citizens based on the following conditions: (1) between the ages of 30 and 74, (2) able to participate on their own, (3) no significant communication difficulties, (4) no severe diseases, symptoms, or health problems, and (5) autonomous decision to cooperate and participate in the project. The project started with a small number of participants (273) in 2007, and a total of 10,082 people have enrolled by November 2010. A written global informed consent was obtained from each participant, allowing researchers to use biological materials and information for future analysis and research in line with technological development.

5.2 First Follow-Up Survey (FY 2012–FY 2016)

Between the baseline and the first follow-up surveys, 370 individuals died or moved out of the city, and 16 withdrew the consent. As a result, 9698 were targets of the follow-up health check. Out of the 9698 individuals, 8559 returned to the follow-up, and the return rate was as high as 88.3% (8559/9698). In 2016, we conducted additional recruitment and obtained 1561 new participants, bringing the total number of participants at the end of the first follow-up to 10,120. In addition, we initiated an investigation of disease incidence during this period, which allowed the analysis of cerebrovascular and ischemic heart disease incidence using the medical record information of the three major hospitals in Nagahama City, namely, Nagahama Municipal Hospital, Kohoku Hospital, and Nagahama Red Cross Hospital.

5.3 Second Follow-Up Survey (FY 2017–)

In the second follow-up survey, 4754 people underwent medical check-ups in the three years up to FY2019. However, we needed to postpone health check-ups for FY 2020 due to the outbreak of COVID-19, expecting it takes place in FY 2021.

6 Survey Items

6.1 Questionnaire Survey

This survey aims to screen the participants' environment, lifestyle, and past and potential illnesses. To increase the accuracy of the dataset and avoid missing values, we asked participants to submit their answers before the health check-up and filled the unanswered parts with them at the venue. The main questions are shown in Table 1.

There are reports on the identification of factors related to poor sleep (Matsumoto et al. 2017a) and the risk for long-lasting cough (Matsumoto et al. 2017b), and the evaluation of diabetes risk based on the number of chewing (Yamazaki et al. 2013) using the questionnaire.

6.2 Biochemical Tests

A variety of measurements, including those not measured in the routine health check-up, were performed using blood and urine samples (Table 2). We returned measurement results with established clinical significance to the participants and contributed to the participants' health promotion plans. The specimens (plasma, serum, and urine) are collected and stored at the biorepository of the Center for Genomic Medicine, Kyoto University Graduate School of Medicine, and are used for research-based measurements.

6.3 Physiological Examination

We conducted measurements and examinations related to respiratory function, cardiovascular function, dentistry, and ophthalmology to evaluate physical functions (Table 3). Research results using the data include reports which revealed tooth loss in males and thinner retinal blood vessels measured by fundus photographs were associated with arteriosclerosis development (Asai et al. 2015; Kawashima-Kumagai et al. 2018). Furthermore, in 2007, the Japan Orthopedic Association proposed "locomotive syndrome" as a condition in which mobility function declines due to musculoskeletal disorders. Therefore, we conducted examinations to evaluate the locomotive syndrome in the first follow-up, including muscle strength and sense-of-balance measurements for 2127 participants aged 60 years or older (Table 4). These examinations revealed that hip muscle strength affects walking speed and stability only in women and that there are gender differences in the causes of walking difficulties (Inoue et al. 2017). We also discovered that a smaller lumbar kyphosis increases

Table 1 Measurements by questionnaire in the *Nagahama Study*

1. Questions for lifestyle and environmental factor related with health risk	
Basic information	Demographic/social information, weight change, occupation, educational background, cohabitation status, marital status
Life style information	Sleeping status, physical activity and fitness habits, undefined compliant
Alcohol intake	Drinking habits (kinds of alcohol, frequency, amount), age at abstinence
Cigarette smoking	Number of smoking year, number of smoking cigarettes, willingness to quit smoking, passive smoking history
Mental health	Partial SF36 (mental health: 5-item, social role: 7-item), depressive symptom
Anamnestic history	Disease history of participants and their family, mediation
Female health	Pregnant status, delivery history, menstrual status, female specific anamnestic history
Dietary lifestyle	Food habits (frequency, amount, time spent in a meal), dietary supplement, health food, food intake (kinds of food, frequency)
2. Questions for potential disease screening	
Gastroenterology	History of gastroenterological diseases (hepatitis, reflux esophagitis), interferon therapy
Respiratory medicine	Status of cough and wheeze, respiratory symptoms, history of respiratory disease (cold, hay fever, asthma, pulmonary diseases), pet breeding, activity in at-risk area for a respiratory diseases
Orthopedic surgery	Symptoms in knee and back, activity restriction because of back pain, complaint because of back pain
Urology	Complaints of urinary problems, frequency of urination, degree and frequency of urinal leakage, causal situation of urinal leakage
Rheumatology and immunology	Typical symptoms for collagen diseases and rheumatoid arthritis
Ophthalmology	History of eye diseases (myopia, hyperopia, astigma, glaucoma, cataract, age-related macular degeneration), history of operation for eye diseases
Oral and maxillofacial surgery	Dental treatment, complaint about oral state, history off oral diseases, masticatory ability (chewable food), tooth brushing habits (time spent in brushing, frequency, tools for brushing)

blood pressure during standing and a stooped posture is a determinant of orthostatic hypertension, which has been overlooked so far (Tabara et al. 2019).

In addition, we introduced cognitive function tests (Hasegawa scale and mild cognitive impairment (MCI) screening), head and neck MRI/MRA, and knee radiographs for participants aged 60 and over. 4923 people underwent cognitive function tests, of which 3191 took MRI/MRA tests. In 2013, we initiated a programme to monitor sleep and nocturnal blood pressure. This programme objectively assessed

Table 2 Measured biomarkers in the *Nagahama Study*

Sample	Measurements	Study		
		baseline (2007–2010)	1st follow-up (2012–2016)	2nd follow-up (2017–)
Blood	Complete blood count (13-item)	○	○	○
	Hemoglobin	○	○	○
	Hematocrit	○	○	○
	Glucose	○	○	○
	Hemoglobin A1c	○	○	○
	Insulin	○	○	○
	Total protein	○	○	○
	Albumin	○	○	○
	Globulin		○	○
	Total bilirubin	○	○	○
	Direct bilirubin		○	○
	Indirect bilirubin		○	○
	Alkali phosphatase (ALP)	○	○	○
	Aspartate aminotransferase (AST)	○	○	○
	Alanine aminotransferase (ALT)	○	○	○
	Gamma-glutamyl transferase (GGT)	○	○	○
	Choline esterase	○	○	○
	Total cholesterol (T-Ch)	○	○	○
	Low-density lipoprotein cholesterol (LDL-C)	○	○	○
	High-density lipoprotein cholesterol (HDL-C)	○	○	○
	Cholesterol subclass (5-item)	○		
	Rheumatoid factor (RF)	○		
	Anti-cyclic citrullinated peptide antibody	○		
	Antinuclear antibody (ANA) (8-item)	○		
	Nonspecific immunoglobulin E	○		
	Specific immunoglobulin E (8-item)	○		

(continued)

Table 2 (continued)

Sample	Measurements	Study		
		baseline (2007–2010)	1st follow-up (2012–2016)	2nd follow-up (2017–)
	Anti-chlamydia pneumonia antibody (IgG, IgA)	○		
	Anti-mycoplasma pneumonia IgA	○		
	Triglyceride	○	○	○
	Free fatty acid	○	○	
	Creatinine	○	○	○
	Uric acid	○	○	○
	Sodium		○	○
	Potassium		○	○
	Calcium	○	○	○
	Inorganic phosphate	○	○	○
	Chloride		○	○
	B-type natriuretic peptide (BNP)	○	○	○
	N-terminal pro-BNP (NT-pro BNP)		○	△
	Alpha-1 antitrypsin (AAT)	○		
	Angiotensin-converting enzyme (ACE)	○		
	High-sensitivity C reactive protein (hs-CRP)	○	○	○
	High-sensitivity prostate specific antigen (hs-PSA)	○	○	
Urine	Glucose	○	○	○
	Protein	○	○	○
	Blood	○	○	○
	Urobilinogen	○	○	○
	Bilirubin	○	○	○
	Sodium	○	○	○
	Potassium	○	○	○
	Ketone	○	○	○
	Microalbumin	○	○	○
	Creatinine	○	○	○

(continued)

Table 2 (continued)

Sample	Measurements	Study		
		baseline (2007–2010)	1st follow-up (2012–2016)	2nd follow-up (2017–)
	Cotinine	○		
	Beta C-terminal telopeptide	○		
	Type 1 collagen cross-linked N-terminal telopeptide	○		
	Power of hydrogen (pH)	○	○	○
	Specific gravity	○	○	○
	Urinary sediment (10-item)	○	○	○
	24 h urine collection(12-item)			○

○: Measured, △: Partially measured (limited period or limited subject)

the sleep length and cycle, and frequency of mid-wake, which subjective and low-quality questionnaires had been used for evaluation. We also investigated the presence of sleep apnea syndrome (SAS). Home blood pressure is considered more accurate than clinic blood pressure, and sleep blood pressure is a risk indicator for cardiovascular disease independent of daytime blood pressure. For this purpose, an oxygen saturation monitor, a wristwatch-type activity monitor, and a blood pressure monitor were loaned to the participants for approximately one week. The tests were conducted at home. 7647 participants joined the sleep test, which resulted in the accumulation of sleep data at the world's largest scale. We showed that SAS and hypertension/diabetes interact with each other and that their relationship is clinically noteworthy (Matsumoto et al. 2018a). We also revealed that blood pressure variability during sleep is not only diurnal but also seasonal (Tabara et al. 2018). Furthermore, poor quality sleep, especially nocturia, was shown to interfere with blood pressure reduction during sleep (Matsumoto et al. 2018b).

6.4 Genomic and Omics Analysis

We conducted a whole-genome SNP typing analysis using 9020 DNA samples obtained in the study. Out of these samples, 1695 were subjected to whole-genome sequencing using Next Generation Sequencing (NGS) technology. In addition to genomic analysis, we conduct intermediate trait analysis focusing on biomolecules in plasma such as metabolites, lipids, and proteins/peptides using mass-spectrometry and other technologies (Table 5). We finished the measurement of the metabolome

Table 3 Physiological measurements in the *Nagahama Study*

Category	Measurements	Study		
		baseline	1st follow-up	2nd follow-up
Anthropometric index	*Haight, weight, abdominal circumstance, body composition (fat, muscle, water)*	○	○	○
			○	○
Respiratory index	Spirometry	○	○	○
	Chest X-ray	○		
	Sleep apnea syndrome (SpO_2)		○	○
	Diaphragm echo			△
	Arteriosclerosis (CAVI, ABI, PWV)	○	○	○
Cardiovascular index	Blood pressure (SBP, DBP, cSBP)	○	○	○
	Orthostatic blood pressure		○	○
	Domestic and nocturnal blood pressure		○	○
	Echocardiography			△
	Carotid ultrasonography		○	○
	Advanced glycation end products		○	△
	Ear robe photograph		○	
Sensory system	Tactile recognition			○
	Double flash illusion test			○
Ophthalmic test	Fundus photograph	○	○	○
	Axial length	○	○	○
	Refractive index	○	○	○
	Intraocular pressure	○	○	○
	Optical coherence tomography		○	○
	Eye sight			△
	Visual field test			○
	Accommodation ability			○
	Ocular position			○
Dental check	Oral status (caries, periodontitis)	○	○	○
	Mastication ability	○	△	
Brain function	Cognitive function (dementia, MCI)		○	○
	Head/neck MRI, MRA		○	○

(continued)

Table 3 (continued)

Category	Measurements	Study		
		baseline	1st follow-up	2nd follow-up
Physical function	Measurements for locomotive syndrome		○	△
	Knee X-ray/MRI		○	○
	Bone density		○	

○: Measured, △: Partially measured (limited period)

Table 4 Measurements for locomotive syndrome in the *Nagahama Study*

Category	Measurement
Balance	Stabilometry, one-leg standing duration, stepping test
Muscular strength	Grip strength, knee extension force, toe grip strength, hip extensor force, hip abductor force, hip flexor fore, ankle plantar flexor force
Walking ability	10 m normal walk test, 10 m maximum walk test
Physical ability	Knee range of motion
Image inspection	Flat foot (echo imaging), pes valgus, (photograph), hallux valgus, (photograph)
Total motor function	Short physical performance battery (SPPB), Timed up and go test (TUGT), Locomo test
Questionnaire	The knee society score (Japanese)

Table 5 Omics analyses in the *Nagahama Study* (as of March 1, 2021)

Measurement	Method	Number of subjects
Genome analysis		
Exhaustive SNP typing	Genome scan (Illumina)	9020
Whole genome sequence	Next generation sequence (Illumina)	1695
Metabolome/lipidome analyses		
Hydrophilic metabolite (136-item)	Gas chromatography—mass spectrometry (GC–MS) (Shimadzu)	Baseline: 9775 1st follow-up: 9871 2nd follow-up: 3441
Hydrophilic metabolite (220-item)	Liquid chromatography mass spectrometry (LC–MS) (Shimadzu)	1st follow-up: 3648 2nd Follow-up: 358
Lipid metabolite (268-item)	Liquid chromatography mass spectrometry (LC–MS) (Shimadzu)	Baseline: 5707 1st follow-up: 8314 2nd follow-up: 358
Cell subsets analysis		
Markers for immune cell subsets (23-item)	Flow cytometry (SONY)	1st follow-up (October, 2014): 226
Proteome analysis		
Exhaustive protein assay (4808-item)	Aptamer assay (Soma Logic)	1st follow-up: 2000

in 9775 and 8316 plasma samples obtained at the baseline and the first follow-up surveys, respectively.

Many genome-wide association analyses have been conducted in this project to search for genetic determinants associated with traits and disease susceptibility. For example, reports have been made on the identification of biochemical markers (Setoh et al. 2015; Terao et al. 2014), amino acid profiles (Imaizumi et al. 2019), and novel gene regions associated with myopic maculopathy (Hosoda et al. 2018), a cause of blindness. Whole-genome SNP genotyping information is available to researchers through the National Bioscience Database Center (NBDC).

7 Related Research

7.1 Integrated Omics Research Aimed at Elucidating the Mechanism of Skin Aging

The skin is a vital tissue that serves as a barrier to protect the entire body from the surrounding environment. Skin-aging progresses due to ultraviolet light stimulation and aging, resulting in appearance changes with wrinkles and decreased water content in the skin. Visual skin aging affects communication in social life. In addition, it has been reported to be associated with systemic age-related diseases such as cardiovascular diseases and cognitive impairment (Christensen et al. 2009; Gunn et al. 2013). The study aiming to elucidate skin-aging mechanisms and identify associated factors was jointly conducted with CHANEL Research and Technology, Inc. 1252 participants joined the study in 2014. Skin elasticity and reflectance were measured, and high-resolution facial photo images were collected. We performed an integrated omics analysis of such skin condition-related markers with health-related questionnaires and genome/omics measurements. Analysis results successfully lead to the development of a new skin-care product. The first follow-up survey is scheduled for winter 2021.

7.2 Survey on Social and Economic Behaviour

It is known that social science factors such as social environment, economy, politics, and medical and biological factors affect people's health and diseases (Braveman and Gottlieb 2014). For example, preventive awareness of illnesses is related to risk judgment and decision-making (Tsutsui et al. 2010) and social relationships affect health and mortality (Holt-Lunstad et al. 2010; Kagamimori et al. 2009). In this project, the Institute of Economic Research of Kyoto University is taking the lead in conducting a questionnaire-based survey on social and economic behaviour. The survey has been conducted three times, in 2016, 2018, and 2020, with a response

rate of approximately 70% in each survey. The survey items include a wide range of socio-economic factors such as education and income, risk aversion, time discount rate, sense of fairness, sense of trust, attitude toward uncertainty, and items related to local networks. As an example of the results of this study, an analysis of social capital indexed in (1) social networks and support, (2) participation in social activities, and (3) trust in people, revealed that social capital has an impact on having "motivation for health" (improving lifestyle and receiving health guidance) (Sekine et al. 2020).

7.3 Socio-Life Science Study for COVID-19 Pandemic

The COVID-19 pandemic showed a nationwide spread of infection in Japan and significantly impacted ordinary lifestyles and the economy. Therefore, we are conducting a study by combining antibody tests and questionnaire surveys on 3000 residents participating in the *Nagahama Study*. This study aims to (1) accurately identify the actual status of SARS-CoV-2 infection, including subclinical infections, (2) identify populations at high risk of the infection, and (3) understand people's behavioural changes under the pandemic and started the survey in March 2021.

The statistics for COVID-19 in Japan are based on examining only those who have symptoms or have had contact with infected people. Therefore, subclinical populations (Liang et al. 2020) with no noticeable symptoms after infection are overlooked. In this study, we perform antibody tests to capture infection history, including subclinical cases accurately. We will use a highly accurate COVID-19 antibody test developed by the Pasteur Institute in France, which measures antibody titers against multiple epitopes of SARS-CoV-2. Therefore, it is a method with significantly improved sensitivity and specificity than conventional antibody tests that only detect antibodies to a limited number of epitopes (Rosado et al. 2021).

To assess factors that increase the risk of the spread of infection, it is essential to evaluate the correct knowledge and behaviour toward SARS-CoV-2 infection. In addition to medical and epidemiological factors such as age, presence of underlying diseases (Huang et al. 2020), awareness of prevention (for example, wearing masks, etc.) (Zhang et al. 2020), visiting epidemic areas and contact with infected people (Cohen et al. 2020), social scientific factors such as people's judgment of risk, mode of thinking and behaviour, and social status also affect the spread of infection. For example, the words and actions of the political party or politician one supports are said to influence individual risk management and are related to SARS-CoV-2 infection and COVID-19 incidence (Allcott et al. 2020). Therefore, the survey uses a questionnaire consisting of approximately 100 interactive questions from medicine and social science, which was developed in cooperation with the Research Institute of Economy, Trade and Industry (RIETI). For example, the questionnaire traces medical aspects such as underlying disease and observed symptoms, socio-economic factors such as risk preference, trust in the country or region, social ties, and economic status. Also, it contains changes in daily behaviour and preventive awareness that have occurred every three months since the emergence of COVID-19.

We expect that the findings obtained from this study give essential hints on dealing with COVID-19 in the future and as a basis for reasonable quarantine measures required in the event of a possible epidemic of emerging or reemerging infectious diseases in the future.

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