A New Comprehensive Study on Aging - the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA)

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A new comprehensive longitudinal study of aging, the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA) started in November 1997. The participants of this study will be 2,400 residents aged 40 to 79 years who were age- and gender-stratified random samples selected from the NILS area. All participants provided written informed consent after a detailed explanation of the study. They will be examined at the NILS-LSA Examination Center every two years. Their first wave examinations will be finished by the end of March 2000. The examined variables number over 1,000, including clinical evaluations, medical examinations, anthropometry, body composition, physical functions, physical activities, psychological assessments, nutritional analysis and molecular epidemiology. By the end of September 1999, 1,643 men and women had completed their first wave examinations.


aging, epidemiology, longitudinal study, method

INTRODUCTION

The life expectancy of the Japanese population is the longest in the world. Both the absolute number and relative percentage of the elderly population in Japanese society is rapidly increasing 1). In 2020, the percentage of the elderly population in Japan will be the largest in the world. Along with these changes, various medical and care-giving problems for the elderly patient have arisen. Longevity science, with the goal that all of elderly people can live a long life with physical and mental health should be promoted in Japan.

Human aging is associated with many factors, including not only physical and physiological factors but also social and psychological factors. Thus, research into human aging requires many kinds of examinations and specialists in various areas. In addition, human aging research requires long-term study in which the same subjects are measured repeatedly to observe age-related changes 2-7). However, the number of researchers and budget for studies on gerontological and geriatric epidemiology are limited. It has been very difficult in Japan to start and to continue a large-scale and comprehensive longitudinal study of aging, despite a rapid increase in the elderly population.

In 1995, a new national research institute of aging in Japan, the National Institute for Longevity Sciences (NILS) was established and in 1997 the NILS-LSA (NILS-Longitudinal Study of Aging) started 8). The participants in the NILS-LSA are 2,400 randomly selected men and women aged 40 to 79 years from the NILS area. They will be examined every two years. Six to seven participants are now examined every day at the NILS-LSA examination center. The aging process is assessed by detailed questionnaires and examinations including clinical evaluation, body composition and anthropometry, physical functions, nutritional analysis, and psychological assessments. The data from the study will be useful to investigate the causes of geriatric diseases and health problems in the elderly such as depression, mental disturbance, restriction of ADL, low nutrition and physical activity. The data will also be useful to prevent these diseases and health problems in the elderly.

PROGRESS OF THE NILS-LSA

In 1990, projects of "Comprehensive Research on Aging and Health" were started by the Ministry of Health and Welfare to
promote longevity sciences in commemoration of the 60th year in the reign of Emperor Showa. A research group for a longitudinal study on aging was organized as one of these projects. Indices on aging were evaluated, the methodology for the longitudinal study was assessed, and many problems in actual longitudinal follow-ups using existing cohorts were analyzed by this research group in order to start a new comprehensive longitudinal study of aging in Japan. A pilot longitudinal study on aging started in 1992. A manual of the many procedures used in the study was published in 1996.

In July 1995, the National Institute for Longevity Sciences (NILS) was established as the leading national research center for aging and geriatric research in Obu city in the suburbs of Nagoya. In 1996, the Laboratory of Long-term Longitudinal Studies was established in the Department of Epidemiology to start a new longitudinal study of aging in Japan.

Various equipment necessary for geriatric research, such as magnetic resonance imaging (MRI) and peripheral quantitative computed tomography (pQCT) were set up in the NILS, and a special examination center for longitudinal study was established in the Chubu National Hospital. Physicians, psychologists, nutritionists, epidemiologists, and exercise physiologists were assigned to the Laboratory of Long-term Longitudinal Studies and the Department of Epidemiology.

In October 1997, a trial run of the examinations led by local volunteers started, and in November 1997, the NILS-LSA began as a large-scale and comprehensive longitudinal study of aging in Japan. Every day, six or seven participants were examined at the NILS-LSA Examination Center. By the end of September 1999, 1,643 men and women had completed their first examinations. By the end of March 2000, examinations of 2,400 participants will be completed. After that, all participants will be examined every two years. The total number of examined variables is over 1,000, including various areas of gerontology and geriatrics such as medical examinations, anthropometry, body composition, physical functions, physical activities, psychological assessments, nutritional analysis and molecular epidemiology.

AIMS AND OBJECTIVES OF THE NILS-LSA

The main purpose of the study is the systematic observation and description of the process of aging in humans: (1) to quantify normal and successful aging as well as to clarify the occurrence and processes of geriatric diseases; (2) to determine reference values in the normal aging process by longitudinal observation. Normal aging is an ideal aging process that is not influenced by specific diseases.

There are many additional objectives as follows: (1) to find early markers for age-related diseases; (2) to clarify molecular genetic factors in aging and geriatric diseases; (3) to find factors associated with longevity; (4) to examine the effects of life-style, stress, life events and disease on the aging process; (5) to separate normal aging and age-related diseases; (6) to assess the effects of age on progressive changes in various diseases; (7) to determine predictors of age at death and disease risk factors as well as institutionalization and loss of independence; (8) to include various tests applied to the same subjects to determine whether aging is a physiologically and psychologically interactive and continuous processes or the end result of multiple independent processes; (9) to examine regional differences in factors of longevity and the relationship among life-style, aging and disease in Japan; (10) to examine race differences by international comparative study; (11) to assess social and economic changes with age in the elderly; (12) to develop indices of biological age; (13) to prepare the general population for research of clinical and social medicine.

TARGET POPULATION AND IMPLEMENTATION OF THE STUDY

Research area

For the detailed and comprehensive examinations at the NILS, the research area was determined to be in the neighborhood of the NILS, that is Obu city (population 70,000) and Higashiura town (population 40,000) (Figure 1). This area is located in the south of Nagoya city, and is a big city bedroom town and also industrial area of the Toyota group, but still has many orchards and farms, having both urban and rural characteristics.

This research area is geographically located at the center of Japan, and the climate is almost average for Japan. We examined the representativeness of the area via national postal questionnaire of prefecture-stratified random samples of 3,000 households from all prefectures in Japan, and showed that the life-style of this area was the most typical of all areas in Japan. It is expected that the results of examinations in this area will represent the average in Japan.

Subjects

The subjects of the NILS-LSA were men and women residents of 40 to 79 years old. They were stratified by both age and gender, and randomly selected from resident registrations in cooperation with the local governments (Obu city and Higashiura town). The number of men and women is to be the same to test gender difference. Age at the base line is to be 40 to 79 years and the number of participants in each decade (40s, 50s, 60s, 70s) is to be the same. The total number of participants will be 2400, that is 300 men and 300 women for each decade. They will be followed up every two years (Figure 2).

Recruitment and follow up of volunteers will be much easier than with random samples. However, volunteers generally tend to be rich, highly educated, and interested in health. Observation of these volunteers would produce results for economically and socially upper class people who are very healthy and live long. Examinations in random samples are necessary
to observe the aging process of ordinary Japanese who live ordinary lives.

**Implementation of the study**

Selected men and women who are assigned to the next month’s examination are invited by mail to an explanatory meeting that is held twice a month, once on Sunday and once on Monday (Figure 3). At the explanatory meeting, procedures for each examination and the importance of the continuation to follow up are fully explained. Participants are limited to those who understand all examination procedures and sign their names on a written form (informed consent).

The Department of Epidemiology of the NILS is taking the initiative for all examinations and investigations. All participants are examined from 9 am to 5 pm at a special examination center within a facility at the Chubu National Hospital located next door to the NILS (Figure 4). To examine 2,400 men and women in two years, that is 1,200 men and women per year, six or seven participants are to be examined each day, 4 days a
week from Tuesday to Friday, 200 days year. Taking advan-
tage of the fact that all participants can be examined at a center,
detailed examinations including not only medical evaluations,
but also examinations of exercise physiology, body composi-
tion, nutrition, and psychology can be tested. Each examina-
tion is to be extensive and most up-to-date, aiming at the

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<tr>
<th>Time</th>
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<tr>
<td>9:00</td>
<td>Reception, venipuncture</td>
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<td>9:05</td>
<td>Anthropometry, body composition</td>
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<td>9:10</td>
<td>Spirometer, sensory tests, etc</td>
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<td>9:15</td>
<td>Physical examination, venipuncture</td>
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<td>9:20</td>
<td>Rest</td>
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<td>Visual examination</td>
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<td>Lunch (Explanation of nutrition survey)</td>
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<td>Walking test</td>
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<td>Visual examination</td>
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**Figure 4.** Time table of examinations in the NILS-LSA.
internationally highest level. The follow up period is to be up to 30 years, but we hope to get significant longitudinal results within 5 to 10 years. By the end of September 1999, 1,643 men and women had completed their first wave examinations.

Information from the examinations that will be helpful to manage the health of participants is returned to individual participants as a report from the NILS-LSA.

**Informed consent**

All participants are fully informed of the following items. Only subjects who understand and accept examination procedures, and sign their names to a written form to participate in the study (informed consent) are included. This informed consent includes: (1) purpose of the study; (2) detailed procedures for each examination; (3) predictable danger; (4) participation in the examinations totally depends on free will, without any enforcement, and refusal to participate has no disadvantage; (5) to keep secret personal data from the examination.

We are paying particular attention to genetic analysis and preservation of blood and urine samples for future examinations. The Ethical Committee of the Chubu National Hospital has already approved all procedures of the NILS-LSA.

**EXAMINATIONS AND TESTS**

The normal aging process is assessed by detailed examinations including clinical evaluation, sensory aging, body composition and anthropometry, physical functions, nutritional analysis, and psychological tests (Table 1).

**Routine clinical evaluations**

First of all, physical examinations including history taking, auscultation and blood pressure measurement are taken by a physician, and during the medical examination the doctor reconfirms every participants willingness to participate in examinations. Venous blood and urine samples are collected early in the morning after at least 12 hours’ fasting.

Life-style, medical history and prescribed drugs are examined by questionnaires. These questionnaires are checked by a physician, and during the medical examination the doctor reconfirms every participants willingness to participate in examinations. Venous blood and urine samples are collected early in the morning after at least 12 hours’ fasting.

In addition to the usual blood and urine analysis, renal and liver functions, serum protein and lipids, and complete blood count, lipid peroxide, sex hormones and geriatric disease markers are also examined. Serum, DNA and urine samples are stored in deep freezers for future examinations. As for DNA analysis, genotypes which are related geriatric diseases such as Alzheimer’s disease, arteriosclerosis, osteoporosis, benign prostate hypertrophy and diabetes mellitus are examined with the agreement of the participants.

For physiological examinations, a head MRI is taken for all participants and stored in an image database. Intracranial tumors and vascular lesions are checked and brain volume is estimated via a computerized trace of the MRI. Pulmonary functions are examined with a spirometer. Blood oxygen saturation is also checked with an oxymeter. Blood pressure is measured by a physician as well as with an automatic blood pressure manometer. Electrocardiograms are assessed by computerized automatic diagnosis and Minnesota codes of the diagnosis are stored in a database. Cardiac functions and intima-media thickness of the carotid artery are assessed by ultrasonic tomography. Peripheral vascular function is assessed using a digital plethysmogram.

**Sensory aging**

Sensory functions are profoundly associated with QOL in the elderly. Visual and auditory disturbance causes various difficulties in the daily lives of the elderly. Sensory aging, including visual and auditory functions will be examined in detail. As for visual acuity, both distant vision (5 m) and near vision (33 cm) are assessed. Kinetic visual acuity, stereoscopic vision, color perception, contrast sensitivity, visual field, and intracocular pressure are also examined. An anterior eye segment analysis system is used for the assessment of cataracts. Fundus photographs are taken with a Topcon fundus camera (TRC-NW55). Autorefraction is done with the NIDEK-ARK700A. Refractive errors, in the spherical equivalent, are assessed.

Hearing acuity is assessed by pure-tone audiometry air conduction at 500Hz to 8000Hz in all participants and bone conduction in participants with hearing disturbance by air conduction. Middle ear function is also assessed by impedance audiometry. Peripheral skin sensory function is assessed using current perception thresholds at three different frequencies: 5, 250 and 2000 Hz. This is a non-invasive procedure to examine the function of three different sensory nerve fibers, that is Aα fiber, A ß fiber, and C fiber. Cognitive sensory function at the parietal lobe of the brain is assessed by a skin discrimination test.

**Body composition and anthropometry**

Osteoporosis is one of the major geriatric diseases. Osteoporosis causes chronic lumbago and bone fracture that disturbs activity in daily life in the elderly. Bone mineral density is measured by dual X-ray absorptiometry (DXA). Four scans, including whole body, lumbar spine L2 to L4, right and left femoral bone neck, are taken. Moreover, bone density is also measured by high quality peripheral quantitative computed tomography (pQCT).

For anthropometry measurements, height, weight, abdominal depth, circumferences of waist, hip, thigh and upper arm and other parameters are taken. Using ultrasonic tomography, intrabdominal and subcutaneous fat thickness and muscle thickness are evaluated. Intra- and extra-cellular fluid is mea-
Table 1. Examinations and tests in the NILS-LSA.

1) Health-related questionnaire
   Self-rated Health (SRH), Medical history, Clinical symptoms, Medical care,
   Lifestyle, Personal history (job, marriage, education, etc.), Menarche and
   menopause, Family history, Environment, Alcohol consumption, Smoking,
   Social and economic background

2) Routine clinical evaluations
   Physical examination
   Blood pressure
   Blood chemistry
      GOT, GPT, γ GTP, Total protein, Albumin, LDH, Alkaline phosphatase,
      Cholinesterase, Uric acid, Urea nitrogen, Creatinine, Calcium, Total cholesterol,
      Triglyceride, HDL-cholesterol, Lipid peroxide, Fasting glucose, HbA1c,
      Fasting insulin, Vitamin A, Serum sialic acid, Fe, Cu, Mg, Zn, free T3, free T4,
      TSH, Sex hormones (Total and free testosterone, Estradiol, DHEA-S and Sex
      hormone binding globulin)
   CBC: Red cell count, White cell count, Hb, Hematocrit, Platelet
   Urine analysis: Protein, Sugar, Urobinogen, Ketone, pH, Occult blood, Nitrite

3) Sensory aging
   Visual system
      Visual acuity: near vision (33 cm), distant vision (5 m), Kinetic visual Acuity,
      Refraction, Visual field, Retinal camera, Intraocular pressure, Color perception,
      Stereoscopic vision, Contrast sensitivity, Quantitative test of lens opacity,
      Corneal cell number
   Auditory system
      Audiometry (air and bone), Middle ear functions (Impedance audiometry)
   Skin sensory system
      Quantitative sensory test (Neurometer), Skin discrimination test

4) Medical examinations
   Automatic EKG analyzer
   Cardiac ultrasonic tomography
   Carotid artery sonography
   Pulse wave (digital plethysmography)
   Pulmonary functions (spirometer)
   Blood oxygen saturation (Pulse oximeter)
   DXA (Dual Energy X-ray Absorptiometry)
      Lumbar spine, Right and left femur neck, Total bone density, Body fat (total
      and segmental fat)
   High Quality Peripheral Quantitative CT (pQCT)
   Head MRI (Magnetic resonance imaging system)

5) DNA phenotype and disease markers
   Alzheimer's disease
      Apolipoprotein E phenotype, Protease phenotype, Peptidase activity and
      inhibitors, beta-amyloid peptide concentration accumulative beta-amyloid
      autoantibody, DLST phenotype, Mitochondria CCO
   Stroke and arteriosclerosis
      Angiotensin converting enzyme (ACE) phenotype, Platelet-activating factor
      acetylhydrazide activity (PAF-AH) and phenotype
   Osteoporosis
      Transforming growth factor beta 1 (TGF-b1) phenotype, Osteocalcin,
      Bone alkaline phosphatase, Aminoterminal cross-links of type I collagen
      (urine)
   Parkinson's disease
      N-methyl transferase activity and phenotype
   Obesity and diabetes
      CCK-A receptor phenotype, beta 3-adrenaline receptor phenotype, Leptin,
      Prostate hypertrophy
      alpha-1 adrenaline receptor phenotype
   Aging
      Mitochondria 5178 phenotype
Table 1 (continue). Examinations and tests in the NILS-LSA.

6) Body Composition
   Body fat measurement
   Air displacement (Bodpod), Impedance body fat measurement, DXA
   Body fluid measurement (Bioimpedance spectroscopy)
   Ultrasonic tomography
   Intrabdominal fat, Muscle thickness, Subcutaneous fat thickness
   Anthropometric measurements

7) Physical function
   Exercise test system
   Grip power, Sit-ups, Anteflexion, Static balance, Leg extension power,
   Static leg strength, Reaction time
   10 m Walking test (pitch, stride, speed),
   3D motion analyzer (four cameras and two force plates)
   Balance test (stabilometer)
   Physical activity (questionnaire)
   Electric pedometer (7 days average)

8) Psychological tests
   Interview
   Cognition (MMSE, WAIS-R), Life events, Stress, Basic ADL (Katz Index)
   Questionnaire
   Depression (CES-D), Personality (Self-esteem, EPSI, Locus of control),
   Social environment (Social support, Social network), Family Relations,
   QOL (LSI-K, SWLS), Stress coping, Instrumental ADL, Death Anxiety

9) Nutrition analysis
   Food and nutrition Intake
   Nutrition Diary (3 days) using scales and disposable cameras
   Food frequency questionnaire
   Dietary habit questionnaire

Examinations and tests

Assessments of body composition include air displacement (Bodpod), impedance body fat measurement, and DXA. Body fluid measurement is also conducted using bioimpedance spectroscopy. Anthropometric measurements include intrabdominal fat, muscle thickness, and subcutaneous fat thickness.

Exercise examinations

Grip power, leg extension power, sit-ups, and static balance, reaction time, and anteflexion are measured. Gait step length, pitch velocity, and 10m walking test (pitch, stride, speed) are assessed using a computerized automatic diagnosis system. A 3D motion analyzer with four cameras and two force plates is used. Physical activity is checked through detailed interviews using job-specific questionnaire sheets. Seven-day averages of physical activity are also measured using an electric pedometer.

Nutritional survey

Nutritional intakes are assessed through three-day dietary records using scales. Scales are distributed to all participants to record the weight of all foods consumed over three days. If it is impossible to weigh the food, size and approximate amount are noted. During lunchtime on the examination day, nutritionists provide instructions on food weighing and determining size and approximate amount. Disposable cameras are also provided to all participants. Before and after each meal, participants take pictures of all food eaten to record what kind of foods and how much food were eaten, and how much food is not eaten. Using these dietary records and photographs, nutritionists estimate actual food intake.

However, there are significant seasonal differences in daily food intake in Japan. Food intakes are also assessed by a food frequency and dietary habit questionnaire excluding seasonal differences. The average of amounts and frequencies of 166 representative foods eaten during the previous year are written. A dietitian interviews the subjects to confirm the amounts and frequencies.

Psychological testing

All participants are interviewed by psychology specialists. Cognition and intelligence are assessed using the Wechsler Adult Intelligence Scale-Revised Short Form (WAIS-R-SF) in all participants and the Mini-Mental State Examination (MMSE) in participants aged 60 years and over. Life events and stress coping are also assessed by interview. Basic ADL is checked via the Katz index.

Depressive state using CES-D, personality, self-esteem, social environment including social support, social network and family relations, life satisfaction scale (SWLS; Satisfaction with Life Scale) and QOL, stress coping, instrumental ADL and death anxiety are assessed using a questionnaire.

The examined variables number over 1,000, including vari-
ous areas of gerontology and geriatrics and these variables will be checked repeatedly every two years in the 2,400 participants. The staff of the NILS-LSA are full time researchers, researchers from hospitals and universities, research assistants such as administrators, clinical technicians, dieticians, psychologists, programmers and radiologists. The total number of staff is now 68.

**FUTURE OF THE NILS-LSA**

We will continue the NILS-LSA to investigate the natural course of aging and the changes that lead to disease. The first wave examination will be completed by March 2000. The participants will be examined every 2 years. The cohort of the NILS-LSA will be a dynamic cohort, that is, new subjects will participate in the study instead of those who will not attend their next examination. Participants who move out of the area are to be followed up by telephone interview or postal questionnaire. Medical records of the participants who die during follow-up will be checked to find out the cause of death.

The NILS-LSA includes collaborating studies with other research facilities in Japan and other countries as shown in Figure 5. Extensive tests and examinations should be repeated in longitudinal studies on aging. However, it is actually impossible to repeat many tests and examinations in multiple research facilities with the same protocols and methods. There are almost no comprehensive longitudinal studies on aging which have been followed up for a long period by multi-center collaboration in the U.S. or other countries.

However, cohort studies with common end points such as dementia and disturbance of ADL are also important for aging studies. A high number of subjects and cases during follow-up need to be obtained to get significant analysis results. We are going to start multi-center collaboration with common baseline examinations that relate to the end point of the follow-up.

Comparative studies of the aging process accounting for regional and cultural differences between northern and southern areas, or between urban and rural areas, are also important. In these comparative studies, the number of common examinations and tests should be limited and measuring errors of each test and examination should be small. The study design should be a cross-sectional or short-term longitudinal study, considering the difficulties involved continuing and repeating the examinations in all facilities with same protocols. An international comparative study collaborating with the Baltimore Longitudinal Study of Aging (BLSA) at the National Institute on Aging (NIA) in the U.S. is also planned.

We are going to make the data of this study public through the Internet. We hope that the results from this large longitudinal study of aging can serve the development of health science on aging.

**ACKNOWLEDGMENTS**

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**REFERENCES**
