Aging genes and disease susceptibility genes

It is very rare for a human being to live 120 years; most people die from one of many diseases before reaching 120 years of age. Currently, the average human lifespan is thought to be about 40 years shorter than the maximum lifespan. Several lifestyle-related diseases, such as dyslipidemia, hypertension, diabetes, atherosclerosis, and cardiovascular disease, accelerate the aging process. The relationship between atherosclerosis and aging is particularly strong, as indicated by "a man is as old as his arteries". Susceptibility to lifestyle-related disease is influenced by genetic factors. Any gene that influences the development of disease is known as disease-susceptibility gene. The impact of disease-susceptibility genes on aging and average lifespan is thought to be much larger than the impact of aging genes on maximum lifespan.

Although disease-susceptibility genes determine the susceptibility of an individual to disease, including lifestyle-related diseases, a person with a specific disease-susceptibility gene does not always have the disease. Lifestyle or environmental factors might have much stronger effects on pathogenesis than any of the direct effects of the gene. For example, it should be possible to develop a new method for preventing a disease by investigating differences in lifestyle or environmental factors between individuals with and without disease in a group with a specific disease susceptibility allele. Moreover, investigation of longitudinal changes in modifiable risk factors such as lifestyle should be useful. A better understanding of changes in the incidence of a disease should be helpful for preventive genetic counseling; for example, a person with a specific disease-associated genotype may be able to reduce their personal risk of developing the respective disease if they double their physical activity.

Molecular epidemiology of aging

Genotypes related to aging or age-related disease are, in most cases, not single but multiple, and effects of genotypes are influenced by gene-to-gene interactions and gene-environment interactions. Thus, the analysis of genotypes is often difficult [6].

Case-control or association studies of genetic factors that affect aging or age-related diseases compare the frequency of genotypes in a group of cases with those in a control group. Usually, a relatively small number of cases and controls are examined in a case-control study. To date, many association studies have been conducted to identify genetic factors that affect or cause diseases and clinical condition. However, in most of these studies, gene-gene interactions and gene-environment interactions were not examined.

Affected sib-pair linkage analysis is a type of genome-wide analysis in which researchers study sib-pairs that are affected by a specific disease to identify disease-causing alleles [7]. Although significant linkage can be located in specific loci, identification of the actual disease-causing allele is usually difficult.

Calpain-10A, a member of the calpain-like cysteine protease family, was identified as a type 2 diabetes susceptibility gene in a genome-wide screen of affected sib-pairs of Mexican-American descent [8]. However, findings from other studies indicate that no association between the calpain-10 gene and diabetes exists in other population [9,10]. The results often differ based on the quality of the cohorts, especially for diseases such as diabetes, as numerous genes are related to glucose metabolism and obesity.

Findings based on affected sib-pair linkage analysis can be highly problematic. Collecting a large sample of sib-pair cases is often difficult, environmental factors are usually excluded, and the required genome-wide analyses are very costly. Association studies are better suited for the investigation of aging and age-related diseases because these involve many genotypes and many environmental factors. A large cohort is necessary for such analyses because each disease-related genotype may contribute a small amount to the onset of disease and because there are usually significant interactions with lifestyle and environmental factors. For example, in the analysis of dyslipidemia, contribution of genotype should be controlled for age, body size, diet, physical activity level, and among other factors. Multivariate and longitudinal analyses that account for changes in many examination results are essential in large cohort studies.

Epidemiologists and biostatisticians with experience in clinical medicine and human genome studies should develop methodologies for comprehensive and systematic assessments of many genotypes, lifestyles, and environmental factors in studies of molecular epidemiology. A large number subjects are necessary in epidemiological analyses of the associations between a disease and combinations of relevant genotypes. For example, in the case of combination of two genotypes with 10 percent mutation rate, the subject with both mutations is only 1 percent. To assess interactions between rare mutations at two different genes, a larger number of subjects are necessary than single mutation.

Based on whole-genome sequencing, the human genome encodes 30,000 genes, and in many cases, a single gene is highly pleiotropic because it has multiple roles and functions in multiple organs. For example, variants in the apolipoprotein ε4 gene are associated with lipid metabolism and atherosclerosis [11], and with Alzheimer's disease [12] and with osteoporosis [13]. A single allele of a gene may influence the aging process as well as the incidence of multiple age-related diseases, and the effect of the allele may be influenced by lifestyle, environmental factors, or both.

For the above-mentioned reasons, at least 2,000 middle-aged or elderly men and women should be selected, if possible, from a community-dwelling population as a basic cohort for a genetic epidemiological study of aging and age-related disease. Many alleles and candidate genes should be genotyped or, if possible, a genome-wide analysis of single nucleotide polymorphisms should be performed, and various life and environmental factors, medical findings, and disease markers should be assessed in a systematic way for each individual in the cohort. Moreover, for the assessment of time-dependent changes in lifestyle choices and environment factors, a comprehensive longitudinal study in which the subjects are observed repeatedly over time is desirable.

Research on the association of genotypes with common age-related diseases or disabilities that is controlled for many background factors can be accomplished with a nested case-control study design in which subjects with and without disease or disability are in the basic cohort. Research on genetic associations with differences in clinical parameters such as blood pressure, serum cholesterol level, and bone mineral density are also possible. For important geriatric diseases including Alzheimer's disease, Parkinson's disease, and femoral neck fracture, it is difficult to recruit enough affected patients from a single community-dwelling population to conduct a genetic association study. However, case-control study design is feasible if the patient group with the disease is recruited from collaborating hospitals and the control group without the disease is selected from the basic cohort.

Longitudinal epidemiological studies

Accumulation of basic data on aging is indispensable for the molecular epidemiological study of aging and age-related disease. The National Center for Geriatrics and Gerontology (NCGG) Research Institute (former National Institute for Longevity Sciences: NILS) is the leading national research center for aging and geriatrics; it is located in Obu City in the suburbs of Nagoya, Japan. In 1996, the Laboratory of Long-term Longitudinal Studies was established within the Department of Epidemiology, NILS; the initiative was focused on a new longitudinal study of aging in Japan. In October 1997, a trial run of the examinations was conducted, and in November 1997, we started the NILS-Longitudinal Study of Aging (NILS-LSA), a large-scale and comprehensive longitudinal study of aging in Japan [14]. Every day, six to seven participants were examined at the NILS-LSA Examination Center (***Fig. 2***). The first wave of the examinations finished in April 2000, and 2,267 participants (both male and female) had completed the examinations. The participants were examined every 2 years, and in July 2012, the seventh wave of examinations was completed.

The research area was defined as the neighborhood of NCGG, which included Obu City (population 79,000) and Higashiura Town (population 48,000). This area is located south of Nagoya, and is a bedroom town and also an industrial area of the Toyota group, and the area has many orchards and farms; therefore, the research area included both urban and rural characteristics. The research area is located at the center of Japan, and the climate is close to the average for all of Japan. We examined how representative this area is of Japan by conducting a national postal questionnaire of prefecture-stratified random samples of 3,000 households from all prefectures in Japan, and found that the lifestyle choices in the research were typical of all areas in Japan. Therefore, we expected that the results of the examinations in this area will be representative of Japan.

The participants in the baseline examinations of the NILS-LSA were males and females aged 40 to 79 years old. The population of Obu City and Higashiura Town was stratified by both age and gender, and participants were randomly selected from resident registrations in cooperation with the local governments. To test sex differences, the study cohort included equal numbers of males and of females; moreover, the numbers of participants within each decade (40s, 50s, 60s, 70s) were also to be equal. There are some dropout participants in each wave of the examination. These dropout participants were replaced newly recruited age- and sex-matched samples randomly selected from the resident registration except the participants over 79 years old. And, new participants, males and females aged just 40 years, were recruited every year. Recruitment and follow-up are expected to be much easier with volunteers than with randomly selected participants. However, because samples comprising volunteers generally tend to be interested in health, findings from samples comprising volunteers would produce biased results. Consequently, samples should comprise randomly selected participants in order observe the aging process of ordinary Japanese who live ordinary lives.

The participants were examined from 8:50 am to 4:00 pm at a special examination center within a facility at the NCGG. To examine 2,400 males and females in 2 years, that is, 1,200 males and females per year, six or seven participants were to be examined each day, 4 days a week, from Tuesday to Friday, 200 days (50 weeks) a year. We took advantage of the fact that all participants could be examined at the center; therefore, we could conduct detailed examinations that included medical evaluations as well as examinations of exercise physiology, body composition, nutrition, and psychology. Each examination was to be extensive and the most up-to-date, aiming at the internationally highest level in geriatrics and gerontology.

From the beginning of the study, blood samples for gene analysis were collected from almost all participants. There would be no other accumulation of DNA specimens with very detailed back ground information in a community-dwelling population in Japan and other countries. To date, 230 genotypes have been examined, and the associations between genotypes with age-related diseases and parameters of aging controlling for various background factors including nutrition and physical activity have been investigated.

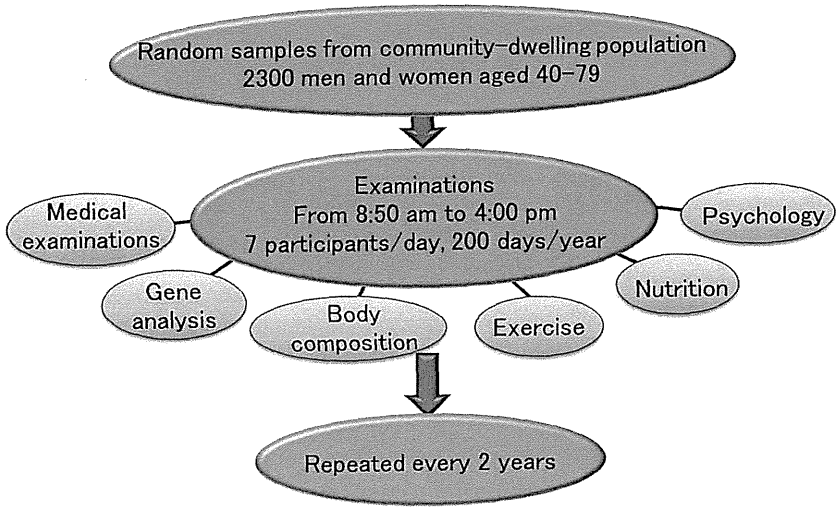

Fig. 2. **Implementation of the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA).**

Genotype and bone mineral loss with aging

Age-related changes in bone mineral density (BMD) were examined via dual-energy x-ray absorptiometry (DXA) and a peripheral quantitative CT (pQCT) in the NILS-LSA. We found 31 genotypes that were associated with BMD (***Table 2***). These are results from association studies between genotypes of candidate genes and BMD by DXA or pQCT.

Fig. 3 shows the effects of the estrogen receptor (ERα) XbaI genotype on the relationship between BMD and lean body mass in post-menopausal women [30]. BMD tends to be higher with more muscle mass estimated as lean body mass, and the effect of lean body mass is larger in AG/GG type than in AA type of ERα XbaI genotype. We suspect that, for the purpose of preventing osteoporosis, an increase in muscle mass is more effective in people with the AG/GG type than in those with the AA type.

BMD is higher in AA type in a cohort with low muscle mass, but BMD is lower in AA type in a cohort with large muscle mass. Findings from analyses of cohorts with different muscle mass reveal that there may be an inverse association between genotype and BMD. Lack in analysis of interaction between gene and life-style would be one of the causes of poor reproducibility in genome research. Thus, comprehensive analyses of the interaction with detailed data from nutrition surveys and lifestyle examinations including smoking, alcohol drinking, and physical activity are essential in the study of Anti-Aging and disease prevention.

Gene and age-related cognitive impairment

Many genes are likely to influence cognitive function, but the associations between genetic polymorphisms and age-related cognitive impairment are unclear. There are significant differences in age-related cognitive decline among individuals.

Klotho is a type I membrane protein that shares sequence similarity with members of the glycosidase family [31], and it

Table 2 ***Newly found or confirmed associations between genotypes and bone mineral density (BMD) based on NILS-LSA findings***

Genes and genotypes		Effects on BMD	Ref.
Calcium metabolism related hormones and receptors			
VDR	Vitamin D receptor (A-3731G)	Femoral neck BMD is high in men with CC type	15
ESR1	Estrogen Receptor α (PP/pp)	BMD is low in elderly women with CC type	16
ESR1	Estrogen Receptor α (XX/xx)	BMD is low in elderly women with GG type	16
OST	Osteocalcin (C298T)	BMD is low in premenopausal women with TT type	15
ADR	Androgen receptor (CAG repeat)	BMD is low in premenopausal women with frequent CAG repeat	17
CYP17A1	Cytochrome P450,family 17, subfamily A, polypeptide 1 (T-34C)	BMD is low in postmenopausal women with CC type	18
Cytokines growth hormones and receptors			
IL6	Interleukin-6 (C-634G)	Radial BMD is low in postmenopausal women with GG type	15
TGFB	Transforming growth factor-β1 (T29C)	Radial BMD is high in elderly women with CC type	19
OPG	Osteoprotegerin (T950C)	Radial BMD is low in premenopausal women with CC type	20
OPG	Osteoprotegerin (T245G)	Femoral neck BMD is low in pastmenopausal women with GG type	20
CCR	Chemokine receptor 2 (G190A)	BMD is high in postmenopausal women and middle-aged men and with AA type	21
Bone matrix related protein			
MMP1	Matrix metalloproteinase-1 (1G/2G at-1607)	Radial BMD is low in postmenopausal women with 2G/2G type	22
MMP9	Matrix metalloproteinase-9 (C-1562T)	BMD is low in men with CT/TT type	23
COL	Collagen type1 (G-1997T)	BMD is low in postmenopausal women with GG type	24
ICAM1	Intercellular adhesion molecule-1 (Lys469Glu)	BMD is low in postmenopausal women with AA type	25
PLOD1	Procollagen-lysine 2-oxyglutarate 5-dioxygenase (Ala99Thr)	BMD is low in pre and postmenopausal women with GA/AA type	25
CX37	Connexin 37 (Pro319Ser)	BMD is low in men with TT type	25
Others			
KLOT	Klotho (G-395A)	BMD is low in pre and postmenopausal women with GG type	17
MTP	Microsomal triglyceride transfer protein (G-493T)	BMD is high in premenopausal women with TT type	18
VLDLR	VLDL receptor (triplet repeat)	BMD is high in men with more than 8 CGG repeat	18
ALAP	Adipocyte-derived leucine aminopeptidase (Lys528Arg)	BMD is high in premenopausal women with GG type	25
LIPC	Hepatic lipase (C-514T)	BMD is low in postmenopausal women with TT type	25
CNR2	Cannabinoid receptor 2 gene (A/G, rs2501431)	BMD is low in pre and postmenopausal women with AA/AG type	25
PON1	Paraoxonase-1 (Gln192Arg)	BMD is low in postmenopausal women with GG type	26
PON1	Paraoxonase-1 (Met55Leu)	BMD is low in postmenopausal women with TT type	26
PON2	Paraoxonase-2 (Cys311Ser)	BMD is low in postmenopausal women with CC type	26
DRD4	Dopamine D4 Receptor (C-521T)	BMD is low in men with CC type	27
FOXC2	Forkhead box C2 (C-512T)	BMD is low in men and women with T allele	28
PLN	Perilipin (C1243T)	BMD is low in men with C allele	28
MAOA	Monoamine oxidase A (uVNTR)	BMD is low in women with repeat less than 4	29
SH2B1	Src-homology-2-B (Ala484Thr)	BMD is low in women with A allele	29

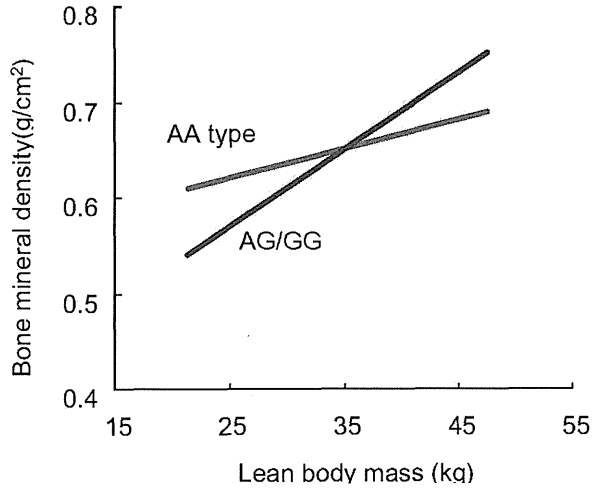

Fig. 3. **The effects of the estrogen receptor (ERα) XbaI genotype on the relationship between BMD and lean body mass in post-menopausal women. The BMD tends to be higher in women with more muscle mass as estimated as lean body mass, and the effect of lean body mass is larger in AG/GG type than in AA type of ERα XbaI genotype (modified from Kitamura *et al.*, 2007 [30]).**

is a fundamental regulator of aging in mice [32]. Mice lacking this protein exhibit multiple aging phenotypes and age-related disorders, including a shortened lifespan, reduced spontaneous activity, arteriosclerosis, infertility, skin atrophy, premature thymic involution, pulmonary emphysema, and osteopenia, although the function of klotho remains to be determined [31,33]. A human homolog of the mouse klotho gene was isolated and its structure was determined [34]. Cognitive impairment was previously shown in klotho gene mutant mice aged seven weeks or over [35]. The klotho gene may be mediate age-related changes in cognitive function in humans.

The effects of klotho gene genotype on cognition were examined in the NILS-LSA [36]. The subjects comprised 2,234 participants in the NILS-LSA aged 40 to 79 years. The klotho gene promoter polymorphism G-395A was identified, and cognitive function was assessed using the Japanese Wechsler Adult Intelligence Scales - Revised Short Forms (JWAIS-R SF) and Mini Mental State Examination (MMSE). The differences in cognitive function were compared between the GG type and GA/AA type of the klotho gene G-395A polymorphism. There was no significant difference in IQ between the GG type and GA/AA type in the subjects aged 40 to 59 years. However, the IQ level was significantly different in terms of the klotho genotype for subjects aged 60 to 79 years (p=0.004). The mean and SE of IQ levels of the subjects with the GG type and the GA/AA type at nucleotide –395 were 99.8 ± 0.5 and 102.6 ± 0.8, respectively. There were also significant differences in three subtests within the JWAIS-R SF: Information, Similarities, and Picture Completion for subjects aged 60 to 79 years. Also, the MMSE score was slightly lower for the GG type than for the GA/AA type (p=0.099).

There were statistically significant differences in cognitive function for klotho gene promoter polymorphism G-395A only in subjects aged 60 or over. This polymorphism may be associated with age-related cognitive impairment, and not associated with cognitive development during childhood to adolescence.

A new genetic strategy for Anti-Aging and prevention of age-related disease

The impact of genetic surveys could be enormously helpful for preventive treatments of geriatric disease as well as Anti-Aging. Previously, associations between disease and genotype were usually investigated by association studies of a specific genotype and a specific disease in molecular epidemiology research. However, we should clarify the following to apply results of epidemiological study to Anti-Aging medicine and preventive medicine: 1) the penetration rates of the genotypes in Japanese; 2) contribution rate to incidence of disease by each susceptibility genotype; 3) factors associated with development of disease in carriers of disease susceptibility genotype; 4) interactive effects with other genotypes; and 5) other physiological effects of the genotype.

These can be investigated in community-dwelling populations and patient cohorts that have detailed background data. Risk of disease can be estimated with the aid of accumulated data. The best-suited education and modification of lifestyles and the content and frequency of examinations for each individual can be determined based on the risk estimation can be applied for disease prevention and Anti-Aging.

Conflict of interest statement

The authors declare no financial or other conflicts of interest in the writing of this paper.

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Relationship between Physical Activity and Brain Atrophy Progression

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Running title: Daily physical activity and brain atrophy

Abstract

Introduction: Brain atrophy is associated with impairment in cognitive function and learning function. The aim of this study was to determine whether daily physical activity prevents age-related brain atrophy progression.

Methods: The participants were 381 males and 393 females who had participated in both the baseline and follow-up surveys (mean duration, 8.2 years). Magnetic resonance imaging of the frontal and temporal lobes was performed at the time of the baseline and follow-up surveys. The daily physical activities and total energy expenditures of the participants were recorded at baseline with uniaxial accelerometry sensors. Multiple logistic regression models were fit to determine the association between activity energy expenditure, number of steps, and total energy expenditure variables and frontal and temporal lobe atrophy progression while controlling for possible confounders.

Results: In male participants, the odds ratio of frontal lobe atrophy progression for the fifth quintile compared to the first quintile in activity energy expenditure was 3.408 (95% confidence interval [CI], 1.205-9.643) and for the number of steps was 3.651 (95% CI, 1.304-10.219). Males and females with low total energy expenditure were at risk for frontal lobe atrophy progression. There were no significant differences between temporal lobe atrophy progression and physical activity or total energy expenditure.

Conclusion: The results indicate that physical activity and total energy expenditure are significant predictors of frontal lobe atrophy progression over an 8-year period. Promoting participation in activities may be beneficial for attenuating age-related frontal lobe atrophy

and for preventing dementia.

Key words:

Longitudinal study; Middle-aged and elderly; Accelerometry sensors; MRI

Introduction

1. Atrophy of brain structures is associated with impairment in cognitive function and learning function (the extreme case is Alzheimer's disease) (21). Brain atrophy progresses with aging (17). The gray matter volume decreases by approximately 15%, from the 20s through the 70s (38). A previous study reported that a decline in cognitive function is associated with the progression rate of brain atrophy over 6 years in normal elderly people (33). Thus, preventing brain atrophy may be a promising strategy for preventing cognitive impairment and decline.
2. Physical exercise appears to induce neurogenesis in the brain not only in animals but also in humans (11). The practice of juggling for three months increases the volume of gray matter in the bilateral mid-temporal area and in the left posterior intraparietal sulcus in young people (10). Similarly, the increase in brain volume in the anterior cingulate gyrus and frontal pole caused by juggling occurs in elderly people (3). In particular, aerobic exercise appears to suppress global and regional brain atrophy to effectively increase brain volume (14). Relatively little brain structural atrophy is seen in elderly people with high aerobic capacity (7). Six months of aerobic exercise increases the volume of the frontal lobe, temporal lobe, and hippocampus (8). Aerobic capacity is correlated with preservation of gray matter in the medial-temporal, parietal, and frontal areas in elderly people (18). Aerobic quick-step walking suppresses hippocampal atrophy and improves cognitive function in elderly people (15). These reports suggest the possibility that aerobic exercise prevents brain atrophy.

3. We hypothesized that brain atrophy progression can be prevented in middle-aged and elderly people with a high level of daily physical activity. Daily physical activities are correlated with aerobic capacity in middle-aged and elderly people (2, 6). In cross-sectional studies, high physical activity levels are related to larger superior frontal volumes (5). Increased physical activity is associated with greater average brain tissue volumes in the white matter of the corona radiata extending into the parietal-occipital junction (19). Although daily physical activities may prevent brain atrophy progression, there has been no specific longitudinal analysis showing that daily physical activity maintained at a high level prevents brain atrophy. Recent longitudinal studies have reported that elderly people with high levels of daily physical activity have a low risk of decline in cognitive function (26, 34). Demonstration of prevention of brain atrophy progression by high levels of physical activity in a longitudinal study may support the association between daily physical activity and cognitive function.

4. The aim of this study was to determine whether high levels of daily physical activity prevent brain atrophy progression with aging. We assessed the progression of frontal and temporal lobe atrophy with aging using 8-year follow-up surveys and magnetic resonance imaging (MRI) of middle-aged and elderly people. We also recorded the amount of physical activity (activity energy expenditure and number of steps) and total energy expenditure using a uniaxial accelerometry sensor. We evaluated the association between brain atrophy progression and daily physical activity and total energy expenditure in 774 community-living, middle-aged and elderly Japanese people using

longitudinal analysis.

Methods

Participants

5. The participants in this study were derived from the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA), which involves ongoing population-based biennial examinations of a cohort of approximately 2,300 persons. The participants in the NILS-LSA were randomly selected from resident registrations and stratified by both decade of age and sex. The NILS-LSA is a comprehensive and interdisciplinary study to observe age-related changes and consists of various gerontological and geriatric measurements, including medical examinations, blood chemical analysis, body composition, anthropometry, nutritional analysis, psychological tests, physical function, and physical activity. Details of the NILS-LSA have been described elsewhere (35).

6. The baseline participants of this study were 1,526 middle-aged and elderly people (773 males and 753 females) who completed the 2nd wave examinations of NILS-LSA between April 2000 and May 2002. Of these, 942 (61.6%; 481 males and 461 females) participated in the 8-year follow-up surveys (NILS-LSA 6th wave examination; from July 2008 to July 2010). The dropouts were 584 participants (292 males and 292 females). In male and female participants, the age at baseline of the dropouts was significantly higher than in the participants who completed both examinations (t-test, $p < 0.0001$). In males, the ratios of stroke and ischemic heart disease histories in dropouts were significantly higher than in the participants who completed both examinations (chi-

square test: stroke, $p = 0.0002$; ischemic heart disease, $p = 0.0019$). In females, there were no differences in the ratios of stroke and ischemic heart disease histories between the dropouts and the participants who completed both examinations. In males and females, the ratio of diabetes histories in dropouts was significantly higher than in the participants who completed both examinations (chi-square test: male, $p = 0.0077$; female, 0.0369). There were no differences in the ratios of hypertension and hyperlipidemia histories between the dropouts and the participants who completed both examinations in males or females. There were no differences in the ratios of severe atrophy in the frontal and temporal lobe between the dropouts and the participants who completed both examinations in males or females.

7. Participants with severe atrophy in the 2nd wave examination were excluded, because severe atrophy was of a high-end grade that cannot be used to determine further atrophy progression. Participants in their 40s were also excluded because few participants of this age show brain atrophy progression. Participants with a current medical history of Parkinson's disease, dementia, or open head surgery were also excluded. Finally, the participants for this study were 381 males and 393 females.
8. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology, and written informed consent was obtained from all participants.

Brain MRI examination

9. Brain MRI was performed on participants at the 2nd and 6th wave examinations using a

1.5-tesla scanner (Toshiba Visart, Tokyo, Japan) at the National Center for Geriatrics and Gerontology. Each participant's head was oriented in the scanner and stabilized during the scanning procedure by a head support. To establish slice orientation, the first scanning sequence consisted of a T1-weighted sagittal series (repetition time [TR] 500 ms, echo time [TE] 15 ms, matrix 256 × 256) centered along the midline to define the orbitomeatal (OM) line. The second series of T1-weighted axial images (TR 500 ms, TE 15 ms, thickness 8 mm, gap 1.5 mm, matrix 256 × 256) and T2-weighted axial images (TR 4000 ms, TE 120 ms, thickness 8 mm, gap 1.5 mm, matrix 320 × 320) were oriented parallel to the OM line. Fourteen slices were taken during each examination.

10. The presence and degree of brain atrophy in the frontal and temporal lobes were assessed as no atrophy (I), mild atrophy (II), moderate atrophy (III), and severe atrophy (IV) (25, 36). The participants were divided into two groups based on results from the MRI in the 2nd wave examination and 6th wave examination: the brain atrophy progression group (Progress: degree of brain atrophy in the 2nd wave < 6th wave) and the brain atrophy non-progression group (Non-progression).

Daily physical activities and total energy expenditure assessments

11. We recorded daily physical activities and total energy expenditures of participants at the 2nd wave examinations using a uniaxial accelerometry sensor (Lifecorder; Suzuken, Aichi, Japan). Lifecorder can assess two types of activity energy expenditure by activity level: energy expenditure of activities (with body movements) and energy expenditure of

minor activities (working at a desk or reading a book). In this study, activity energy expenditure was estimated as the energy expenditure of both types of activities. Total energy expenditure was determined as the sum of basal metabolism, energy expenditure of activities, energy expenditure of minor activities, and thermic effects of food. Participants wore the Lifecorder constantly (except while sleeping or bathing) for a 7-day period. We calculated the mean activity energy expenditure, the number of steps, and the total energy expenditure from five days of records (the maximum and minimum records were excluded).

Other parameters

12. Body height and weight were measured using a digital scale. Body mass index was calculated as weight divided by height squared (BMI; kg/m^2). Body fat mass was assessed by dual X-ray absorptiometry (DXA; QDR-4500A; Hologic, MA, USA). Lifestyle factors (including alcohol intake, smoking habit, and education levels), medical history, and use of medications were assessed with questionnaires. These questionnaires were confirmed by a physician at the medical examinations. All prescribed and non-prescribed medications used during the previous two weeks were documented and brought by participants; the physicians confirmed and coded them. Users of antihypertensive, antilipemic, or hypoglycemic medications were considered participants with hypertension, hyperlipidemia, and diabetes histories, respectively.

Statistical analysis

13. The results are shown as the means ± standard deviation (SD) or standard error (SE).

Differences in continuous and class variables between the progression and non-progression groups were assessed with t-tests and chi-square tests, respectively. Cochran-Mantel-Haenszel statistics were used to examine the relationship between the age group and brain atrophy progression. Multiple logistic regression models were fit to determine the associations of activity energy expenditure, number of steps, and total energy expenditure variables with frontal and temporal lobe atrophy progression while controlling for the baseline decade of age group (38), BMI (19), education history (19), medical history (stroke, ischemic heart disease, hypertension, hyperlipidemia, diabetes) (4, 12, 24), and current smoking and alcohol intake as possible confounders (9, 37). Activity energy expenditure, number of steps, and total energy expenditure were modeled as sex-specific quintiles. Statistical testing was performed using the Statistical Analysis System release 9.1.3 (SAS Institute Inc. NC, USA). Significant probability levels were considered to be less than 0.05.

Results

Characteristics of the participants

14. Table 1 shows elementary statistics of the study variables in male and female participants. The mean follow-up durations of all participants were 8.2 ± 0.3 years. There were no significant differences in baseline age, BMI, or number of steps between male and female participants. Body height and weight, alcohol intake, and education history were significantly higher in males than in female participants (each, $p < 0.0001$). The

percent of body fat in females was significantly higher than in male participants ($p = 0.0126$). The activity and total energy expenditures in males were significantly higher than in females (each, $p < 0.0001$). There were no sex differences in the ratios of stroke, ischemic heart disease, and hypertension histories. The ratio of hyperlipidemia history in females was significantly higher than in male participants ($p = 0.0060$). The ratios of diabetes history and smoking habits in males were significantly higher than in female participants (diabetes history, $p = 0.0126$; smoking habits, $p < 0.0001$).

Progress of frontal and temporal lobe atrophy

15. Table 2 shows comparisons of the incidence of frontal and temporal lobe atrophy progression in each age group. Frontal lobe atrophy progression from the 2nd wave examination to the 6th wave examination was present in 55 of 381 (14.4%) males and 35 of 393 (8.9%) female participants. The ratio of participants with frontal lobe atrophy progression in males was significantly higher than in female participants ($p = 0.0213$). Aging raised the percentage of participants with frontal lobe atrophy progression in males and females (p trend < 0.0001).

16. Temporal lobe atrophy progression from the 2nd wave examination to the 6th wave examination was present in 100 of 381 (26.3%) males and 78 of 393 (19.8%) female participants. The ratio of participants with temporal lobe atrophy progression in males was significantly higher than in female participants ($p = 0.0344$). Aging raised the percentage of participants with temporal lobe atrophy progression in males and females (p trend <0.0001).

Brain atrophy progression and physical activity level

17. Table 3 shows the activity energy expenditure, number of steps, and total energy expenditure in the frontal and temporal lobe atrophy progression and non-progression groups. In the frontal lobe, activity energy expenditure ($p = 0.0095$), number of steps ($p = 0.0131$), and total energy expenditure ($p < 0.0001$) were significantly higher in the male non-progression group than the progression group. In female participants, total energy expenditure was significantly higher in the non-progression group than in the progression group ($p = 0.0097$). There were no differences in the activity energy expenditure or number of steps between the female non-progression and progression groups.
18. In the temporal lobe, there were no differences in activity energy expenditure or number of steps between the non-progression and progression groups in male or female participants. The total energy expenditure was significantly higher in the non-progression group than in the progression group in male and female participants (males, $p = 0.0028$; females, $p = 0.0096$).

Risk of brain atrophy progression according to physical activity level differences

19. The results of multiple logistic regression analyses for risk of brain atrophy progression according to differences in the physical activity level in males and females are shown in Tables 4 and 5, respectively. In male participants, the odds ratio of frontal lobe atrophy progression for the comparison between the fifth quintile in activity energy expenditure and the first quintile was 3.408 (95% confidence interval [CI], 1.205-9.643). The odds ratio of frontal lobe atrophy progression for the comparison between the fifth quintile in number of steps and the first quintile was 3.651 (95% CI, 1.304-10.219). The odds ratios

of frontal lobe atrophy progression for the comparison between the fifth quintile in total energy expenditure and the first and third quintiles were 4.816 (95% CI, 1.037-22.376) and 4.639 (95% CI, 1.191-18.067), respectively.

20. In female participants, there were no significant differences between frontal lobe atrophy progression and physical activity parameters. The odds ratios of frontal lobe atrophy progression for the comparison between the fifth quintile in total energy expenditure and the first to third quintiles were 12.363 (95% CI, 1.029-148.594), 12.743 (95% CI, 1.292-125.792), and 21.539 (95% CI, 2.381-194.839), respectively.

21. We also evaluated temporal lobe atrophy progression using the adjustment model, similar to the frontal lobe atrophy progression analysis. There were no significant differences between temporal lobe atrophy progression and physical activities or total energy expenditure (Tables 4 and 5) in any groups of participants.

Discussion

22. Using longitudinal analyses, we showed that a high level of physical activity and total energy expenditure suppressed the frontal lobe atrophy progression that is induced by aging.

23. An inactive daily life appears to be a risk factor for frontal lobe atrophy progression. In male participants, those with the lowest activity energy expenditure (1st quintile; <143.2 kcal) had a 3.408-fold risk of frontal lobe atrophy progression compared to those with the highest activity energy expenditure (5th quintile; ≥284.4 kcal) (Table 4). Similarly, males with the fewest number of steps (1st quintile; <5736.0 steps) had a 3.651-fold risk of