of Aging (NILS-LSA). Details of the NILS-LSA are presented elsewhere [18]. It is a biannual examination checking the physical and mental condition of ordinary Japanese people, so as to clarify the effect of aging. It is conducted by the National Center for Geriatrics and Gerontology (NCGG), in Japan. The National Institute for Longevity Sciences (NILS) is a research section of NCGG. The participants were chosen randomly from the residents of Obu city and Higashiura-cho, in Aichi prefecture, Japan. For this study, data from 1167 persons were analyzed (59.2 ± 10.9, mean ± SD). Participants were 594 men and 573 women, whose ages ranged from 40 to 79 at the time of the 1st wave. The 1st and 4th waves were from November 1997 to April 2000, and June 2004 to July 2006, respectively.

2.2. Measurements of Bone Mineral Density. Areal bone mineral densities (aBMD) were measured using Hologic QDR4500, both at the 1st and 4th wave. Only one DXA scanner was used. Data on the right femoral neck (Figure 1) and the lumbar spine (L2–4) were used for the analysis. Coefficients of variance of the DXA instrument for aBMD were 1.3% (femoral neck), 1.0% (trochanter), and 0.9% (L2,1–4) [19]. ABMD is equivalent to BMC divided by an area, so the following formula was used for the theoretical calculation: aBMD (g/cm^2) = BMC (g)/Area (cm^2). Therefore, not only aBMD values but also those of BMC and the area measured were used for the analysis in the three different regions above. The annual change rates (CR) were calculated by the following formula. CR (%) = (the values in the 4th−the values in the 1st)/the values in the 1st × 100/6. The CRs of aBMD, BMC, and the area measured were calculated and described separately by the age stratum of 40s, 50s, 60s, and 70s and by sex. All who were 40 to 49 years at baseline belonged to the 40's age stratum, and so forth. Data are presented as the mean ± SD, including those in figures. The study protocol was approved by the Committee on Ethics of Human Research of the National Institute for Longevity Sciences. Written informed consent was obtained from each subject.

2.3. Statistical Analyses. The statistical analyses were made to test for significance of change (versus no change) in each subgroup defined by age decade and sex, using paired t-tests. Also, the trend analyses according to the increase of the age stratum were made for each subgroup using a general linear model procedure. Gender difference was checked for each subgroup. All analyses were conducted using SAS Ver. 8.2 (SAS Institute, Cary, NC, USA).

3. Results

Characteristics of subjects were shown in Table 1.

The change rates (CR) from the first to fourth what were expressed as an annual rate. Mean variation between the two DXA measurements was 6 years.

3.1. Femoral Neck Region. ABMDs significantly decreased in all age strata both in women (−1.1 ± 1.1% in 40s, −1.2 ± 0.9% in 50s, −1.0 ± 0.9% in 60s, and −0.8 ± 1.1% in 70s, all $P < 0.01$) and in men (−0.4 ± 0.8% in 40s, −0.5 ± 0.7% in 50s, −0.6 ± 0.9% in 60s, and −0.6 ± 1.0% in 70s, all $P < 0.01$) (Figures 2(a) and 2(b)). These declines were caused not merely by the decrease of BMC in most of the age strata (in women, −0.7 ± 1.4% in 40s, −0.8 ± 1.2% in 50s, and −0.4 ± 1.2% in 60s, all $P < 0.01$, and in men, −0.2 ± 0.9% in 50s and −0.2 ± 1.1% in 70s, with $P < 0.01$ and $P < 0.05$, resp.), but also by the constant or significant increase of the area measured (in women, 0.4 ± 1.1% in 40s, 0.5 ± 1.1% in 50s, 0.6 ± 1.2% in 60s, and 0.5 ± 1.5% in 70s, all $P < 0.01$, and in men, 0.4 ± 0.6% in 40s, 0.3 ± 0.8% in 50s, 0.4 ± 0.8% in 60s, and in 0.4 ± 0.8% in 70s, all $P < 0.01$). This trend was the same in both sexes. The change rates (CR) of the aBMD and BMC, however, were different between women and men in their 40s, 50s, and 60s (Table 2). The CR became higher (in absolute value) only in women according to age in aBMD and BMC (P trend = 0.0126 and 0.0027, resp.). As for the CR of the area, no significant trend according to age was observed in both sexes, and no sex difference was observed (Table 2).

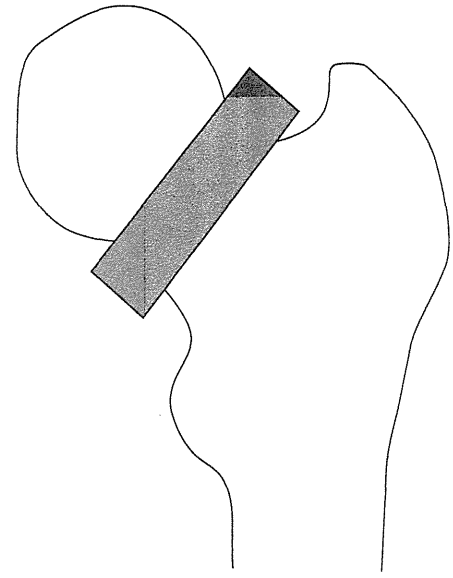

FIGURE 1: Femoral neck region of interest, derived from the Hologic QDR 4500 Operator's Manual.

3.2. Lumbar Spine Region. ABMDs significantly decreased in women in their 40s, 50s, and 60s (−1.1 ± 1.2% in 40s, −1.0 ± 0.9% in 50s, and −0.2 ± 1.1 in 60s, with $P < 0.01$, $P < 0.01$ and $P < 0.05$, resp.) (Figure 3(a)). At earlier ages, these declines were caused by a significant decrease in BMC (−1.2 ± 1.5% in 40s and −1.2 ± 1.2% in 50s, both $P < 0.01$) accompanied by a small but significant decrease in the area. After their 60s, however, no further decrease in BMC occurred, and the small but significant increase of aBMD was caused by the significant increase in the area.

The patterns of aBMD changes were much different in men. BMDs significantly increased in the 50s, 60s, and 70s (0.3 ± 0.8%, 0.5 ± 1.5%, and 0.3 ± 1.0%, all $P < 0.01$) due to

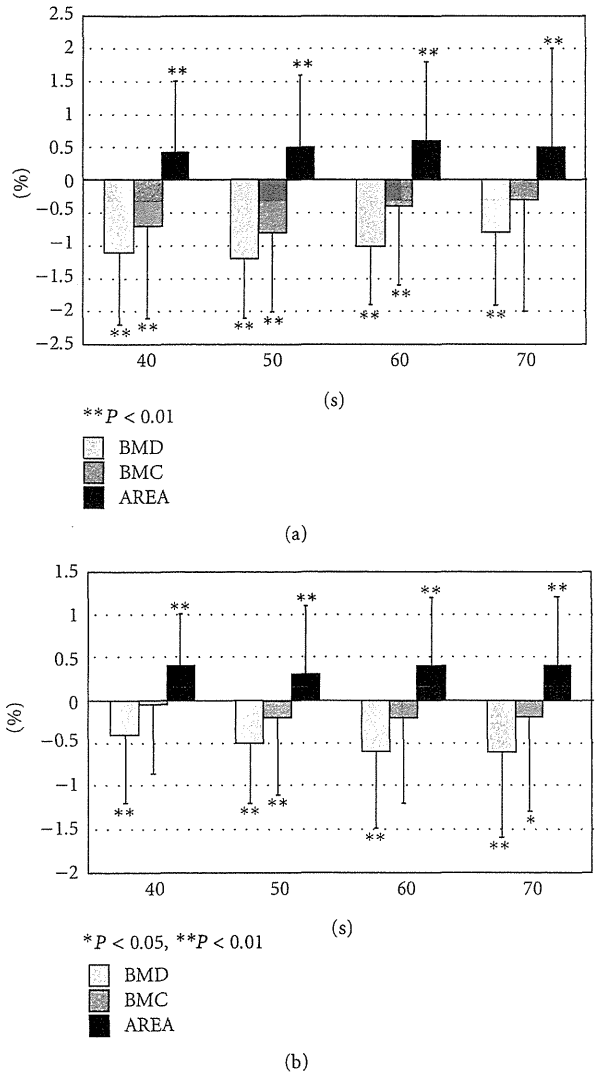

FIGURE 2: (a) Changes in the femoral neck region by age group in women. Results are the mean (±SD) CR of four different age strata. $^{**}P < 0.01$. (b) Changes in the femoral neck region by age group in men. Results are the mean (±SD) CR of four different age strata. $^{*}P < 0.05$, $^{**}P < 0.01$.

the significant increase of BMC (0.5 ± 1.0% in 50s, 1.0 ± 3.4% in 60s, and 0.4 ± 1.2% in 70s, all $P < 0.01$) (Figure 3(b)). The areas significantly increased in every age stratum (0.1 ± 0.5% in 40s, 0.2 ± 0.5% in 50s, 0.4 ± 1.2% in 60s, and 0.2 ± 0.6% in 70s, all $P < 0.01$). Since the increase of BMD occurred after the 50s, the rates of BMC increase surpassed those of the area. The change rates (CR) of the aBMD, BMC, and area were different between women and men in their 40s, 50s, and 60s (Table 2). And in women the CR increased according to age in aBMD, BMC, and area (P trend <0 .0001, P trend <0.0001, and P trend = 0.0115, resp.). The CR increased in men according to age in aBMD and BMC (P trend= 0.006 and P trend = 0.027, resp.), but not in area (Table 2).

TABLE 1: Characteristics of subjects.

	Women	Men
Age (years)	56.5 ± 9.9	57.9 ± 9.9
Height (cm)		
All	152.2 ± 5.7 (n = 573)	165.4 ± 5.9 (n = 594)
40s	154.9 ± 5.0 (n = 168)	168.7 ± 5.5 (n = 148)
50s	153.3 ± 4.8 (n = 179)	166.3 ± 5.7 (n = 183)
60s	150.4 ± 5.6 (n = 147)	164.0 ± 4.7 (n = 162)
70s	147.0 ± 5.0 (n = 79)	161.0 ± 5.2 (n = 101)
Weight (kg)		
All	53.0 ± 8.0 (n = 573)	62.8 ± 8.5 (n = 594)
40s	54.1 ± 8.0 (n = 168)	66.4 ± 8.8 (n = 148)
50s	53.7 ± 7.4 (n = 179)	63.5 ± 8.1 (n = 183)
60s	53.0 ± 8.0 (n = 147)	61.2 ± 7.8 (n = 162)
70s	49.1 ± 7.9 (n = 79)	58.8 ± 7.5 (n = 101)
BMI (kg/m^2)		
All	22.9 ± 3.2 (n = 573)	22.9 ± 2.6 (n = 594)
40s	22.5 ± 3.3 (n = 168)	23.3 ± 2.6 (n = 148)
50s	22.9 ± 3.2 (n = 179)	23.0 ± 2.5 (n = 183)
60s	23.4 ± 3.1 (n = 147)	22.8 ± 2.7 (n = 162)
70s	22.7 ± 3.1 (n = 79)	22.6 ± 2.5 (n = 101)
BMD at 1st wave		
Femoral neck (g/cm^2)	0.7 ± 0.1	0.8 ± 0.1
Trochanter (g/cm^2)	0.6 ± 0.1	0.7 ± 0.1
Lumbar spine (L2–4) (g/cm^2)	0.9 ± 0.2	1.0 ± 0.2
BMC at 1st wave		
Femoral neck (g)	3.2 ± 0.6	4.0 ± 0.7
Trochanter (g)	6.0 ± 1.3	8.7 ± 1.6
Lumbar spine (L2–4) (g)	38.1 ± 9.3	50.7 ± 10.0
Area at 1st wave		
Femoral neck (cm^2)	4.6 ± 0.3	5.3 ± 0.3
Trochanter (cm^2)	10.2 ± 1.2	12.8 ± 1.4
Lumbar spine (L2–4) (cm^2)	42.3 ± 3.9	51.3 ± 4.5

Values are mean ± SD.

4. Discussion

ABMD is equivalent to BMC divided by an area, but when we encounter cases of BMD decline, we simply consider the decline of the BMC at the measured sites without

TABLE 2: P trend according to age strata and P value of sex difference analyses of subgroup.

		P trend according to age strata		Sex difference analysis			
		women	men	40s	50s	60s	70s
Femoral neck	BMD	0.0126	0.1682	<0.0001	<0.0001	<0.0001	0.0982
	BMC	0.0027	0.2519	<0.0001	<0.0001	0.0298	0.7122
	Area	0.2084	0.9947	0.9436	0.0434	0.0987	0.2391
Lumbar spine	BMD	<0.0001	0.006	<0.0001	<0.0001	<0.0001	0.815
	BMC	<0.0001	0.027	<0.0001	<0.0001	<0.0001	0.4277
	Area	0.0115	0.3383	<0.0001	<0.0001	0.0052	0.0986

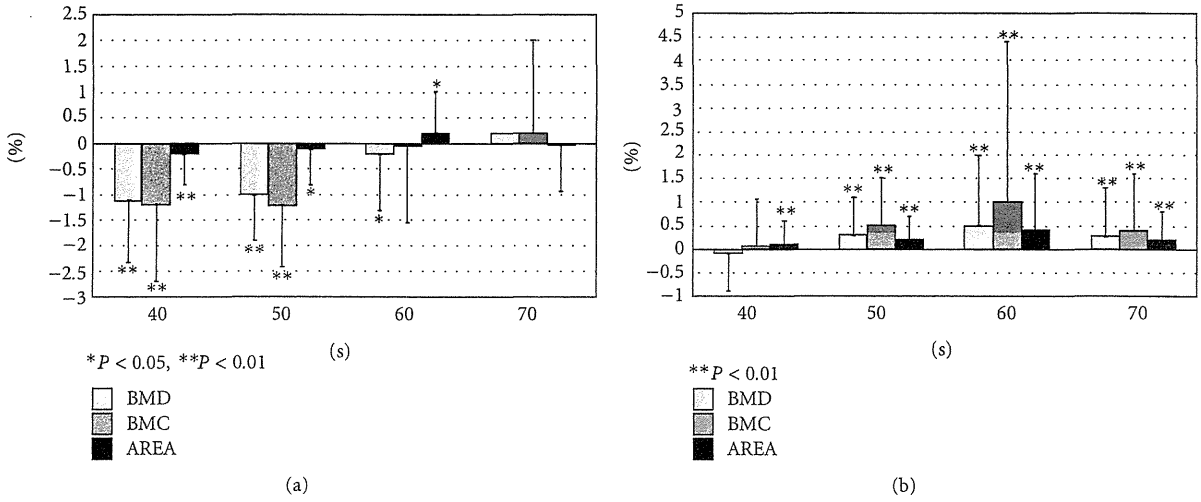

FIGURE 3: (a) Changes in the lumbar spine region by age group in women. Results are the mean (±SD) CR of four different age strata. $*P < 0.05$, $**P < 0.01$. (b) Changes in the lumbar spine region by age group in men. Results are the mean (±SD) CR of four different age strata. $**P < 0.01$.

incorporating the change of the area (or size), which may represent the change of the shape in the region. The present study demonstrated that in the femoral neck, the aBMD decline in aging occurs not only due to the decline of BMC, but also due to the increase in the area, for both men and women. In fact, the increase of the femoral neck area represents the physiological compensating effect of the weakened bone tolerance [4, 20–23], caused by BMC decline. This may be one of the reasons for the dissociation between the strength of the bone and aBMD values. The widening (or enlargement) of the femoral neck in elderly persons has been demonstrated by the hip structure analyses of DXA [10, 13–15], by computed tomography [23–26], or utilizing both [27, 28]. The annual change rates of aBMD in our study in the femoral neck region were around −1% in women (Figure 2(a)) and 0.5% in men (Figure 2(b)). This is almost equal to the level of the large population-based cohort in Hiroshima Japan, −1.14% in women, and −0.38% in men [29]. In the lumbar spine, however, a sexual difference was observed in the changes of aBMD and those of BMC or the area as well. The increase in BMC together with the area may be explained by the osteophyte formation found to be more marked in elderly men [7, 9]. This type of change, osteophyte formation, occurs also in women but later. The significant area increase in women may derive from the osteophyte formation in advanced age. The reason for the significant decrease in the areas in women in their 40s and 50s is unclear at the moment. More detailed studies, using CT scans, are warranted to elucidate the mechanism of the sex difference in the spinal region.

From this perspective, the meaning or significance of aBMD change should be diverse depending on the sites measured and gender. Moreover, the apparent decrease of aBMD may not simply represent the weakness of that measured region (e.g., in the femoral neck), since the greater diameter can make the cylindrical structure stronger [21].

The limitation of this study is that the measurements were carried out by the ordinary DXA method without using elaborate software like hip structure analysis or CT. DXA has an inherent inaccuracy [30–32]. If body composition or weight changed during the followup, it is possible that BMD is inaccurately measured, namely, it may be over- or underestimated. Also, the size measuring by DXA was not very accurate for volumetric analysis. But our method disclosed the differences among sites and between sexes, particularly in terms of longitudinal effect, which have been little investigated.

The strength of our study is its random selection of our samples from people in the local community with very little bias in the process. NILS-LSA is one of the few major epidemiological studies investigating the aging mechanism that is designed to select subjects in a completely random manner. The results of this study should therefore reveal characteristics of the entire Japanese population.

In summary, we investigated the meaning of aBMD changes in aging through separate analyses of BMC and area change. The results revealed that the significance of aBMD changes were very divergent among the sites measured, and between sexes. This may explain the dissociation of aBMD change and bone strength, which encourages one to be more cautious when interpreting the meaning of aBMD change.

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第53回日本老年医学会学術集会記録
〈若手企画シンポジウム2：サルコペニア―研究の現状と未来への展望―〉

1. 日常生活機能と骨格筋量，筋力との関連

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1. 日常生活機能と骨格筋量，筋力との関連

下方　浩史[1)]　安藤富士子[2)]

要　約　サルコペニアは高齢者の日常生活機能を低下させ，健康長寿の障害となる．われわれは無作為抽出された地域在住中高年者コホートのデータを使用して，日常生活機能と筋力，筋量との関連について検討した．男女ともに40歳以降，握力，下肢筋力は年間約1パーセントずつ低下していた．どの年代でも男性は女性よりも筋力が強く，80代の男性の筋力は40代の女性の筋力にほぼ等しかった．筋力の低下は女性の日常生活機能により大きな影響を与える可能性がある．一方，四肢の筋量は男性では加齢とともに低下するが，女性では加齢による低下はほとんどなかった．このことは女性では筋肉の量的な変化よりも，質的な変化が問題になっていることを示している．日常生活機能は筋肉のパフォーマンスの影響を受け，握力と歩行速度で推定することが可能であった．高齢者の脆弱を予防するためには，これらの評価によりハイリスクの集団を見つけることが重要であろう．

Key words：サルコペニア，日常生活機能，筋量，筋力，老化

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はじめに

老化に伴う筋量減少（サルコペニア）は，高齢者のADLを低下させ，健康長寿を実現の大きな障害となる[1)2)]．しかし，老化に伴う筋量減少の実態は明らかでなく，またサルコペニア自体の簡便な基準がない．臨床の現場や住民調査などで使用できる簡便なサルコペニアの基準が必要である．これらの検討を一般住民のコホートのデータを使用して行った．

研究方法

対象は「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」第5次調査参加者で，40歳から88歳までの無作為抽出された地域在住中高年者2,419名（男性1,200名，女性1,219名）である[3)]．上腕囲，臍高腹囲，大腿囲，下腿囲を身体指標として計測し，また体力の指標として，普通歩速度，速歩速度，上体起こし，膝伸展筋力，脚伸展パワー，握力を計測した．日常生活機能として健康関連QOL尺度であるSF36の身体機能項目を用いた．サルコペニア指標として，Dual-energy X-ray absorptiometry（DXA）（QDR 4500, Hologic）によって四肢除脂肪・除骨重量測定し，これを四肢筋量とした．Baumgartnerら[1)]の方法に準じ，四肢筋量（kg）を身長（m）の二乗で除した値をSkeletal Muscle Index（SMI）とし，サルコペニアの指標とした．その判定基準には同じQDR 4,500で測定したSanadaら[4)]によるYAM（Young Adult Mean：18～40歳）の－2SD（男性6.87 kg/m^2，女性5.46 kg/m^2）を用いた．

サルコペニアの性・年代別頻度

DXAによるSMIでの診断基準で求めたサルコペニアの有無を，性・年齢別の分布をみた（図1）．男性では25.0パーセントが，女性では24.2パーセントがサルコペニアであり，全体の割合には性差はなかった．年代別の検討では，男性では加齢とともにサルコペニアの頻度は高くなっていたが（p trend<0.0001），女性では有意な加齢変化はなかった．男性のSMIの平均値±SDは7.42±0.83 kg/m^2，女性は5.96±0.73 kg/m^{2}であり，男性の方が有意に高い値であった（p<0.0001）．男性では加齢とともにSMIは低下していたが（p trend<0.0001），女性では有意な加齢変化はなかった．男女ともに年齢が高いほど握力は低下していた（p trend<0.0001）．男性の方が低下率は大きかったが，80代でも女性の40代の握力よりも大きかった．膝伸展筋力についても握力と同様に，

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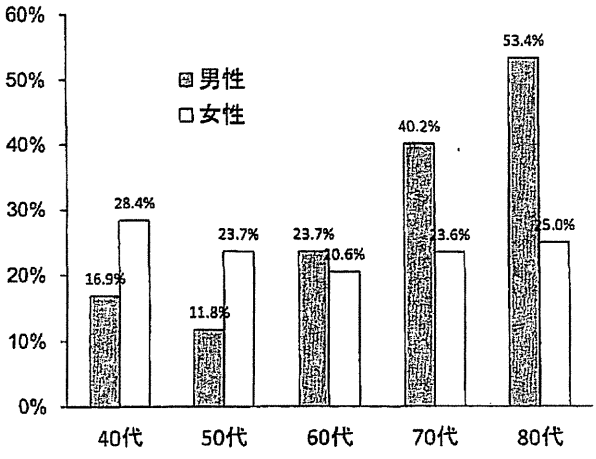

図1　サルコペニアの性・年代別頻度
DXAによるSMIでの診断基準（YAMの－2SD）での判定を行った．男性では加齢とともにサルコペニアの頻度は高くなっていたが（p　trend<0.0001），女性では有意な加齢変化はなかった．

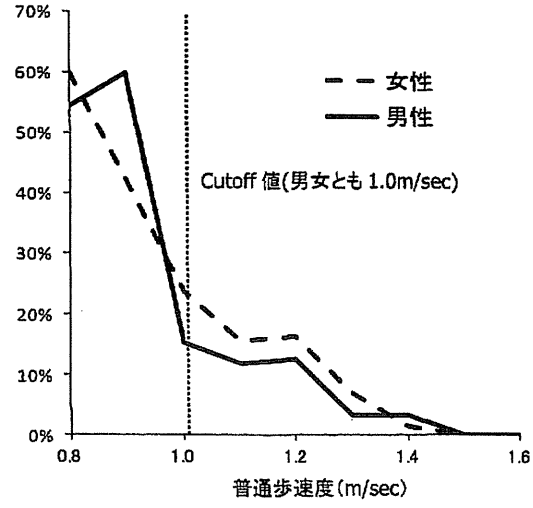

図2　普通歩速度と数百メートル以上歩くことに困難を感じる割合（65歳以上）

男女ともに加齢とともに低下していた．男性の方が低下率は大きかったが，男性の80代でも女性の40代とほぼ同じ値であった．

SMIに影響を与える変数を求めるとともに，SMIを推定するための簡便な式の作成を行うために，SMIと身体測定値，アルブミンとの相関解析を行った．SMIは上腕囲，下腿囲，大腿囲，腹囲BMIと強い正の相関があったがアルブミンとは相関はなく，体脂肪率とは弱い正の相関が認められた．SMIと最も相関が強かったのはBMIであり，相関係数は男性で0.77，女性で0.73と高かった．周囲長では女性で下腿囲が最も相関が強く，男性では上腕囲，下腿囲，大腿囲で相関係数はほぼ同じ値となった．

65歳以上の男女について，年齢，BMI，下腿からSMIを推定する重回帰式の作成を試みた．その結果，以下の回帰式を得ることができた．

男性：SMI＝－0.1026×年齢＋0.1341×BMI＋0.6034×下腿囲＋2.5653（r^2＝0.651）

女性：SMI＝－0.0413×年齢＋0.0513×BMI＋0.4438×下腿囲＋0.5509（r^2＝0.558）

骨格筋量，筋力と日常生活機能

65歳以上の男女についてサルコペニアの有無とSF36での身体機能との関連を検討した．男性では一部の項目でサルコペニアがあると身体機能は低下していたが，その差は大きくなかった．女性ではサルコペニアによる身体機能の有意な低下はなかった．身体機能の障害の有無とSMIとの関連については，男性では身体機能の障害の有無によるSMIの差はいくつかの項目で認められたものの，その差はそれほど大きくはなかった．女性では身体機能の障害の有無によるSMIの差はほとんどなかった．

65歳以上の男女について，身体機能と歩行や筋力などの体力との正準相関係数を求めて，体力のどの項目が身体機能と関連しているのかを検討した．その結果，男女とも普通歩速度が身体機能にもっとも関連しており，筋力では脚伸展パワーの影響が男性でもっとも大きかったが，握力は男女ともに身体機能に大きな影響が与えていた．

一般住民で日常生活に影響が出るような障害は，SF36の中強度の身体活動項目に困難を感ずる障害と考え，中強度の項目のうち「数百メートル以上歩くこと」を身体機能の指標とすることとした．「数百メートル以上歩くこと」が困難になれば，日用品の買い物にも支障が生じ，独立した生活を送ることが困難となる．体力，身体計測値がどの程度まで低下すると身体機能が低下するのか，身体機能との関連が認められた項目のうち，簡便に測定できるものについてカットオフ値を求めた．図2に示すように，普通歩速度は男女ともに1 m/secよりも遅くなると身体機能が低下する割合が大きく増加した．握力に関しては，普通歩ほどカットオフ値ははっきりしなかったが，男性で25 kg，女性で20 kgをカットオフ値とした．身体計測値については，女性ではSMIが低い部分でのカットオフ値は決められなかった．男性ではカットオフ値は5.5 kg/m²であった．BMIは女性では値

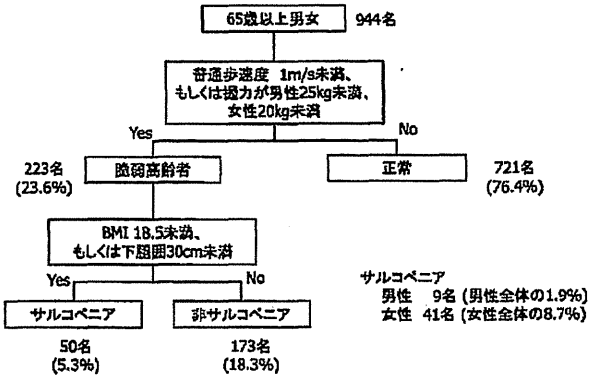

図3　サルコペニアの簡易基準案と，一般住民での分布

が小さいほど，つまりやせているほど身体機能は良くなっており，カットオフ値は決められなかったが，男性では19 kg/m²がカットオフ値であった．下腿囲も同様に女性ではカットオフ値は決められなかったが男性では30 cmであった．

サルコペニアの簡易基準の作成

サルコペニアの簡易基準の作成は，体力や身体計測値から中強度の身体機能に支障が生じる可能性のある集団を捉えることを目指した．判定に使用する項目は，簡便な器具で簡単に測定できるものとした．さらに，Muscle performanceとmuscle volumeを分けて考えることとし，Muscle performanceは普通歩速度と握力で評価し，Muscle volumeは測定に高額で放射線被曝を伴う機器が必要なSMIの代わりにBMIと下腿囲で評価することとした．また，各指標のカットオフ値は中強度の身体機能との関連で決めることとし，女性で上記の基準で決められない場合には，従来のやせの基準値や男性の値を参考に決めることとした．

European consensus[5]によるサルコペニアの簡易基準を参考に，日本人高齢者におけるサルコペニアの簡易基準の作成を試みた．図3に示すように，まず普通歩速度1 m/sec未満，もしくは握力が男性25 kg未満，女性20 kg未満である場合には脆弱高齢者と判断し，脆弱高齢者のうち，BMI 18.5 kg/m²未満もしくは下腿囲30 cm未満である場合をサルコペニアとした．

今回の検討での対象者についてこの基準を当てはめてみると，65歳以上の男女944名のうち23.6パーセント(223名)が脆弱高齢者であり，さらに全体の5.3パーセント(50名)がサルコペニアと診断された．その内訳は男性9名(男性全体の1.9パーセント)，女性41名(女性全体の8.7パーセント)と女性で割合が高くなっていた．

ここに示したサルコペニアの簡易基準案は，身長，体重，握力計とメジャー，ストップウォッチがあれば実施することができる．スクリーニング検査として有用と思われるが，さらに縦断的なデータを用いて，妥当性の検討を行っていきたい．

まとめ

40歳以上の地域住民2,419名を対象としたDXAによる判定では男性の25.0パーセントが，女性の24.2パーセントがサルコペニアに分類された．男性では加齢とともにサルコペニアの割合は増加していたが，女性では加齢による変化はなかった．サルコペニアの簡易基準の作成は，体力や身体計測値から中強度の身体機能に支障が生じる可能性のある集団を捉えることを目指した．その結果，普通歩速度1 m/sec未満もしくは握力が男性25 kg未満，女性20 kg未満である場合には脆弱高齢者と判断し，脆弱高齢者のうちBMI 18.5 kg/m²未満もしくは下腿囲30 cm未満である場合をサルコペニアとした．65歳以上の男女の5.3パーセントがサルコペニアとされた．

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Association of daily physical performance with muscle volume and strength

Hiroshi Shimokata[1] and Fujiko Ando[2]

Abstract

Sarcopenia disturbs the daily life of elderly people, and hinders healthy aging. We studied the association of daily physical performance with muscle volume and muscle strength in a randomly selected community-living population. Results: Grip power and leg muscle strength decreased about 1% per year after age 40 in both men and women. Muscle strength was greater in men than in women at every age by decade, and muscle strength in men in their 80s was similar to that in women in their 40s. Therefore, the effect of a decrease in muscle strength on daily physical performance was greater in women than men. On the other hand, the muscle volume of all limbs decreased with age in men, but there was almost no decrease in muscle volume in women. These results indicate that qualitative change in muscle was more significant than quantitative change in muscle in women. Daily physical performance was influenced by muscle performance and could be assessed based on grip power and walking speed. To prevent frailty, it may be important to determine the high-risk group for frailty using these assessments.

Key words: *Sarcopenia, Daily physical performance, Muscle volume, Muscle strength, Aging*
(Nippon Ronen Igakkai Zasshi 2012; 49: 195–198)

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認知症の実態と予防の重要性

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第18回日本未病システム学会学術総会

●シンポジウム４「認知症予防の最前線―現在そして将来，どこまでできるか―」

認知症の実態と予防の重要性

下方　浩史[1)]
安藤　富士子[2)]

1. はじめに

認知症にはまだ根本的な治療はなく，病状は長期にわたって慢性に進行して重症に至ることが多い．進行すると徘徊や暴力などの問題行動もみられ，末期には寝たきりとなり，誤嚥性肺炎や褥創などの合併症も生じて，経済的，社会的な負担がきわめて多い．認知症の出現頻度は高齢になるほど高くなるので，わが国の社会の高齢化に伴って今後急速に患者数が増大し，介護や医療への費用負担が急騰することが予想される[1-5]．このため，認知症罹患の実態を把握し，認知症の予防を目指すことはわが国にとっての緊急の課題となっている．

2. 認知症の有病率

認知症の有病率や罹患率に関しての疫学統計が，今後の医療費予測や高齢者の介護・福祉のあり方，医療政策に関して，重要な意味を持つと思われる．しかし，今まで認知症の疫学調査は十分には行われてこなかった．それは認知症という疾患の持つ特殊性により，調査に多くの困難を伴うためである[1-4]．

認知症の有病率は比較的低いので正確な統計データを得るためには対象人数を多くしなければならない．65歳以上の高齢者は日本全体では現在約3,000万人であり，推定有病率の１％の違いが患者数推計では30万人の差となる．例えば，有病率15％を14～16％の信頼区間で得るためには4,898名の対象者が必要である．また，アルツハイマー病，血管性認知症，レビー小体型認知症，前頭側頭葉脳変性などの病型別有病率についての検討を加えるためには，さらに多くの対象者が必要である．

認知症の診断を行うためには専門的知識が必要であり，場合によってはMRIやPETなどの検査や剖検が診断のためには必要となる．認知症患者やその家族は調査に対して消極的なことが多い．認知症は高齢者に多いため，身体機能の低下を認める者が少なくなく，訪問による検査などが必要で，実際の調査が思うようにいかないことも多い．また，認知症の有病率を調べる場合，調査地域の高齢者の年代分布によって有病率が異なる可能性がある．地域在住者を調査しても，問題行動のある認知症患者は施設に入所しているために，有病率が低く出てしまうことも考えられる．

認知症の有病率については1970年代から全国のさまざまな地域において疫学調査が行われてきたが，調査は県や市町村の地域ごとに行われており，最近まで全国規模での調査は行われていなかった．日本初の全国調査は，厚生労働省認知症対策総合事業「認知症の実態把握に向けた総合的研究」として実施された[6]．まず2009年から2010年にかけて全国７ヵ所で65歳以上の住民を対象として行われた（図1）．訪問調査員による１次調査と専門医による２次調査を基本として，さらに頭部MRIによる脳萎縮や血管性病変の評価なども行い，精度の高い診断を目指した．全国での調査結果から2008年の日本の人口を基準にして推定された有病率は12.4～20.2％（平均14.4％）であった．2008年度の65歳以上の全国人口2,822万人から，認知症患者数は406万人と推定された．しかし，施設入所者などを加えればこれよりも患者数はさらに多い可能性がある．従来の方法での患者数推計では208万人とされていたが，患者数は少な

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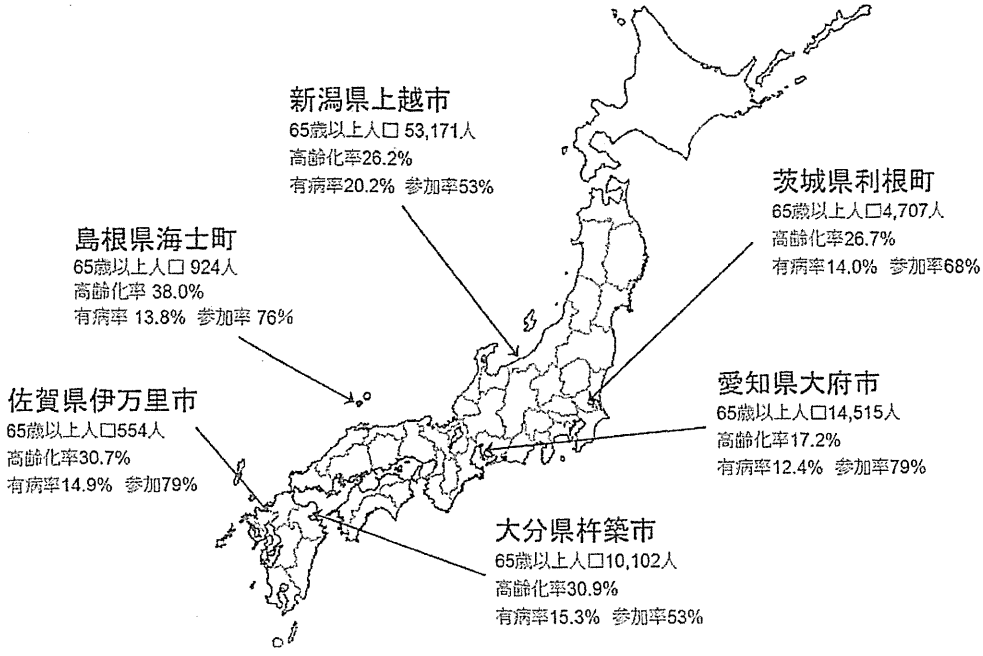
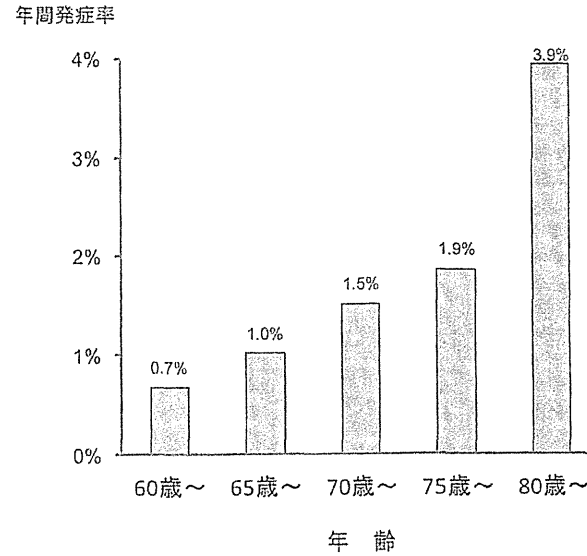


■図 1　認知症有病率全国調査結果（2008 年度日本全国の人口構成に基づく）

くともその約 2 倍存在することになる．

3. 認知症の発症率

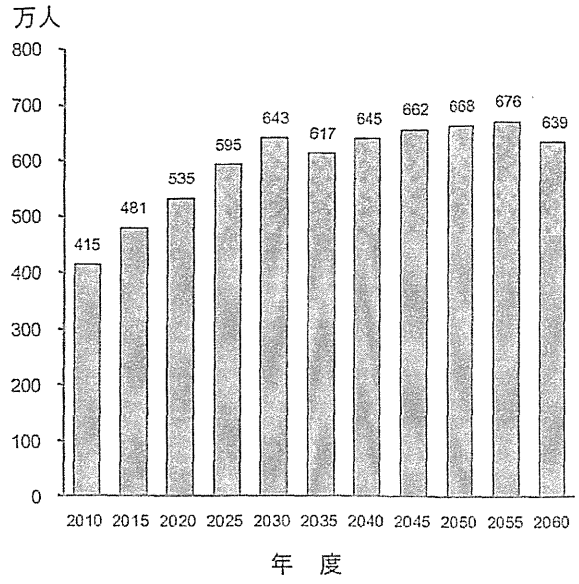
発症率を推定するためには，同一対象集団について複数年にわたっての繰り返しの調査が必要であり，有病率の推定よりも難しく，わが国の疫学調査の結果では認知症の発症率の推定はほとんど行われていない．われわれは，無作為抽出された地域住民を長期にわたって追跡した「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」[7] のデータを用いて 8 年間の縦断的な検討から認知症の発症率の推定を行った（図 2）．その結果では，60 歳以上の地域住民の 1.5 %が毎年認知症となっていた．年齢が高くなるほど発症率は上昇し，80 歳以上では毎年 3.9% が認知症となっていたという結果であった．



■図 2　認知症の年間発症率（「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」の 8 年間の縦断的観察から）

4. 将来推計

人口の高齢化に伴う認知症患者数の将来推計を行ってみた．性別・年齢別の認知症有病率は今回の全国調査の結果を用い，人口推計は国立社会保障・人口問題研究所の平成 24 年度 1 月推計を用いた．2010 年度の 65 歳以上の認知症推定患者数は全体として 415 万人で，



■図3 認知症患者数の将来推計（人口推計は国立社会保障・人口問題研究所の平成24年度1月推計を用いた）

有病率は約14.1パーセントであると推定される．今後，高齢者人口，特に後期高齢者の人口が急増し，患者数は2020年度に535万人，2030年度には643万人と，これからの20年間にアルツハイマー病の患者数は1.5倍に大きく増加すると予測される（図3）．

5. 認知症の経過と予後に関する統計

認知症は長期にわたって慢性に進行していくことが多い．このことが社会に大きな負担となる要因のひとつである．わが国の在宅認知症患者の5年後生命予後調査では，66％～86％の生存率が報告されており[3]，認知症の発症から死亡までの全経過は現在のところ7年から10年程度だと思われる．米国での認知症患者の大規模な追跡調査では，発症からの生存年数は10.5年，診断からの生存年数は5.7年であった[8]．他の研究でも認知症患者の診断後の生存年数は5年から9年であった[9-12]．米国の国立老化研究所（NIA）からの報告では，生存期間は年齢によっても大きく異なり，75歳までに診断されたアルツハイマー病患者の生存年数は診断後7年から10年であったが，85歳以降に診断された場合は3年未満の生存期間であった[13]．しかし今後，介護技術，医療の進歩により死亡までの期間は長くなっていくと思われる．

6. 認知症予防とのその重要性

世界有数の長寿の国であるわが国は急速に高齢化が進み，それとともに認知症患者の数も増大していく．今後15年間で認知症にかかわる介護費用は大きく増加し，年間10兆円に達するとも予想される．高齢化が進む一方で，少子化も進み，介護にかかわることのできる労働人口は激減する．このままでは認知症によって日本の社会が崩壊すると言っても過言ではない．認知症を予防していくことが，今後の日本にとっては極めて重要であろう．

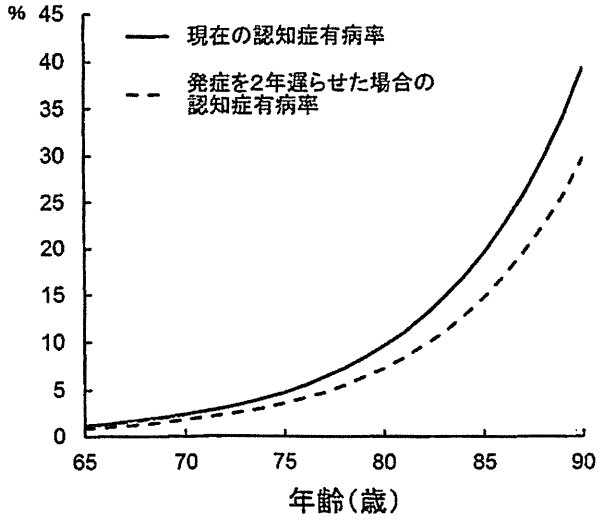
アルツハイマー病予防の切り札としてワクチンの開発が進められている．ワクチンはアルツハイマー病を引き起こすアミロイドβ蛋白の蓄積を予防するような作用を持つとされるが，脳炎などの重篤な副作用も報告されている[14]．また中年以降ではすでにアミロイドβ蛋白は蓄積されてしまっており，ワクチンは30歳以前に使用しなければ効果はないという．たとえワクチンが開発されたとしても，50年後の認知症発症を予防するために，有効性が不明でしかも脳炎などの副作用のリスクがあるワクチンを若者が使用するかどうかは疑問である．

認知症は生活習慣病でもあり，生活習慣の改善である程度の予防が可能である．生活習慣は血管性認知症だけでなくアルツハイマー病の発症と関連している可能性がある．特に食事は毎日の生活の中で繰り返され，影響が大きい．認知症の予防にはビタミンE，ビタミンC，カロテノイドのような抗酸化ビタミンが有用であり，中でも抗酸化作用を持つビタミンEが期待される[15,16]．葉酸やビタミンDの認知症予防作用も明らかにされてきている[17,18]．多価不飽和脂肪酸，特にn-3系のドコサヘキサエン酸（DHA），エイコサペンタエン酸（EPA）は認知症の予防に有用であり[19,20]，またアラキドン酸についても有用性の研究が進んでいる[21]．食事のパターンとしては野菜や魚類をバランス良く摂ることが重要である．適度な飲酒，特にワインが認知症の予防に有用であり[22]，喫煙は多くの研究で認知症の危険因子となることが報告されている[23]．運動によって認知症やアルツハイマー病のリスクを下げることは多くの論文で報告されている[24]．運動が糖尿病，脂質異常症，高血圧症を

予防し，その結果，動脈硬化の進行を遅らせて認知症の発症リスクを下げると考えられるが，運動自体が脳神経のネットワーク機能を強化し，認知症の発症を防ぐという直接的な効果も推測されている．

認知症の素因としての遺伝子多型の研究も進み始めている．しかし危険因子間の相互作用，特に遺伝子と生活習慣との相互作用についてはほとんど研究が進んでいない．例えば食塩の摂取により血圧が高くなる遺伝子多型は，塩分感受性遺伝子多型として知られている．特定の遺伝子多型を持つ人は塩分を多く摂ると高血圧症になりやすく，それが認知症のリスクとなる．このような遺伝子多型とライフスタイル，環境因子との相互作用は数多い．認知症に関連する遺伝子多型は直接に認知症を引き起こすわけではなく，むしろライフスタイルや環境因子の影響を修飾することで認知症の発症に関与するものと考えられる．特定の遺伝子多型の認知症発症寄与率は集団全体の生活習慣などによって異なると考えられ，このために集団が異なれば結果も異なることになり，遺伝子多型の影響について一定の結果が得られにくい．こうした，危険因子相互の作用について明らかにしていくには，大規模な一般住民で追跡を行い，生活習慣や認知機能の変化を継続的に観察する縦断的研究が必要である[25]．

医薬品の開発などで認知症の発症を完全に予防できなくても，仮に2年間だけでも遅らせるようなことが出来れば，各年齢の認知症の有病率は，2歳若い年齢に相当する有病率になると期待できる（図4）．65歳以上の全人口に対して，実際の年齢よりも2歳若い年齢の有病率を使って患者数を計算すると期待患者減少数は33万人，医療費削減効果は2,000億円，介護費用削減効果は7,700億円となる．さらに，家族が介護のために職につけなかったり，本人が病気のため社会参加が出来なかったりした損失も加えると合計の費用削減効果は，年間約2兆円にも達する．こうした経済的な効果を考えると，認知症性疾患の基礎研究，臨床研究へのわが国における研究費の支出は驚くほど少ない．



■図4　年齢別にみた認知症の有病率と認知症の発症を2年遅らせた場合の有病率
期待患者減少数は33万人，医療費削減効果は2,000億円，介護費用削減効果は7,700億円と推定される．

7. 最後に

世界でも類をみない速度で高齢化が進んでいるわが国にとって，認知症患者の増加は大きな社会問題である．今後15年間で認知症にかかわる介護費用は倍増し，年間10兆円に達するとも予想される[5]．高齢化が進む一方で，少子化も進み，介護にかかわることのできる労働人口は激減する．このままでは認知症によって日本の社会が崩壊すると言っても過言ではないかも知れない．一方で，認知症の発症を2年遅らせることができれば，それだけで年間2兆円もの費用が削減できる可能性がある．

日本人で比較的多いと言われる血管性認知症は，喫煙や高脂血症，高血圧，糖尿病などが要因となっており，禁煙や減塩，身体活動，食生活の改善などである程度予防することが可能である．最近ではアルツハイマー病も生活習慣病であると言われ始めており，生活習慣の改善である程度の予防が可能であろう．認知症の素因としての遺伝子多型の研究も進み始めている．こうした研究の推進により高齢者の知的機能を守り，高齢者の社会参画を可能にしていくことが是非とも必要であろう．

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Review Article

Aging-related Genes

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Abstract

Genetic factors affect an individual's maximum possible lifespan. In humans, the average lifespan is about 40 years shorter than the maximum lifespan. Any gene that influences the development of a disease is called a disease-susceptibility gene. The impacts of disease-susceptibility genes on aging and average lifespan would be much stronger than the impacts of aging genes on maximum lifespan. Multiple genes are associated with the aging process and age-related diseases, and gene-to-gene interactions are important, as are gene-environment interactions; the interactive effects of lifestyle are especially important. A broad-scale, long-term longitudinal study that includes detailed examinations of medicine, nutrition, physical activity, and psychology in a community-dwelling population is necessary for comprehensive genetic epidemiological study of aging and age-related diseases. Risk of disease to individuals can be more effectively assessed with data on genetic, lifestyle, and environmental factors. The most appropriate health education, lifestyle modifications, and health examination protocols could be then implemented in an individualized manner to prevent diseases and aging processes based on these personalized risk assessments.

KEY WORDS: aging, gene, epidemiology, longitudinal study, lifespan

Aging and genes

Japan is the world leading country with long living poeple. Nevertheless, until recently, few Japanese people lived more than 100 years. However, the number of centenarians has recently begun to increase rapidly; in 2012, there were 51,376 men and women aged 100 years or older in Japan. It is no longer inconceivable for a regular person to live for 100 years or more.

The lifespan of individual organisms varies based on species. The maximum lifespan for humans is currently 120 years, at most. The maximum lifespan in each species is determined by genes. Do longevity genes that increase maximum life-span exist? If such longevity genes exist, what is the function of these genes in the human body? Perpetual youth and longevity is a dream of people worldwide, and extensive research is currently being performed to clarify the mechanism of aging using new molecular and genetic methodologies [1] to identify for longevity genes.

Search for an aging gene

Progeria (Hutchinson–Gilford progeria syndrome) is a rare genetic disease with symptoms that resemble the acceleration of the regular aging process [2]. The first symptoms manifest in neonates and infants. In one year, a patient with progeria undergoes physical aging equivalent to that requiring over 10 years in an unaffected person. The average lifespan of patients with progeria is about 13 years. The incidence of progeria is very low, at only 1 person in every 4 to 8 million live births. The typical symptoms of progeria are growth insufficiency, a localized scleroderma-like skin condition, wrinkled skin, loss of eyesight, hair loss, atherosclerosis, cardiovascular disease, and renal failure. However, cognitive development and function are usually normal. A point mutation in position 1824 of the lamin A (LMNA) gene has been identified as the cause of progeria [3].

Werner syndrome, also called adult progeria or progenoid syndrome, is another very rare genetic disease characterized by the appearance of premature aging. Symptoms of Werner syndrome are short stature, low body weight, absence of a teenage growth spurt, graying of hair, bilateral cataracts, hoarseness of the voice, and thickening of the skin. These symptoms appear after the age of 10. Patients with Werner syndrome generally die of atherosclerotic disease or cancer sometime between the ages of 40 and 60. In humans, Werner syndrome is an autosomal recessive disorder caused by a point mutation in the WRN gene on chromosome 8 [4]. About 1,200 cases have been reported, and 80% of these patients are Japanese.

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The incidence of Werner syndrome is 3 per 100,000 live births in Japan.

The LMNA and WRN genes, which are responsible for progeria and Wener syndrome respectively, cause pathological aging processes, but do not regulate normal aging processes. The frequency of genotypes unrelated to lifespan did not differ between younger people and older people in a cross-sectional study [5] (***Fig. 1-A***). However, the frequency of certain genotypes changes with aging. A genotype with a high frequency among older people could represent a "longevity genes" that serves to prolong lifespan or to protect against age-related diseases (***Fig. 1-B***). In contrast, a genotype with a lower than average frequency among older people could represent an "aging gene" or a "gene resulting in shorter life expectancy" (***Fig. 1-C***).

Table 1 shows a list of genes associated with longevity based on the findings of a cross-sectional study of age difference in genotype frequency [5]. Most of these genes are related to a molecular pathway involved in nutrient metabolism, especially lipid or glucose metabolism, or in endocrine regulation.

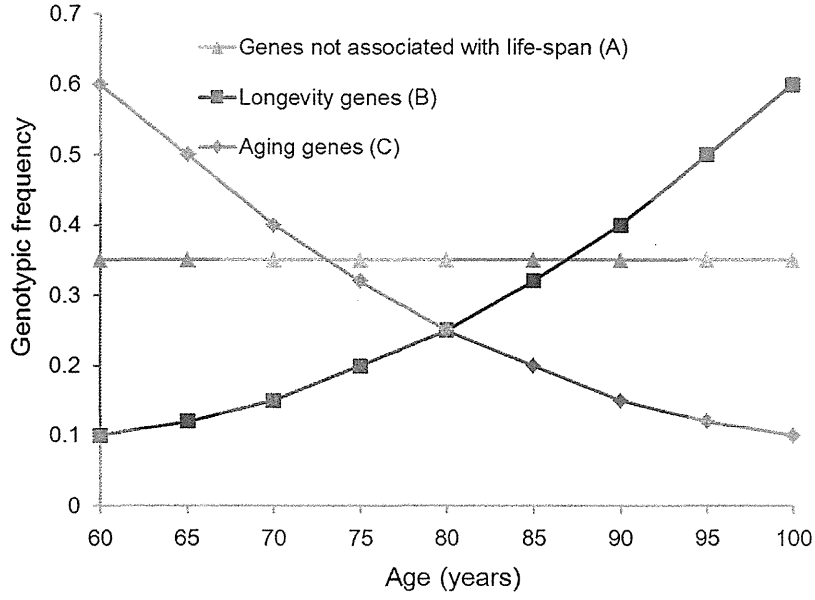

Fig. 1. **Genotypic frequency by age in genes not associated with lifespan (A), longevity genes (B), and aging genes (C) (Modified form Barzilai *et al.*, 2010 [5]).**

Table 1 Genes associated with longevity

Gene	Longevity	Relevant biological action	Chromosomal loci
Klotho (KL gene)	+	Insulin sensitivity, modulation of IGF-I and vitamin D	13q12
Silent mating type information regulation 2 homolog 1 (SIRT1)	+	Regulates epigenetic gene silencing and suppresses recombination of rDNA, associated with insulin action/sensitivity	10q21.3
Catalase (CAT)	+	Antioxidant that protects cells from hydrogen peroxide	11p13
Mammalian target of rapamycin (mTOR)	−	Modulates insulin, IGF, and mitogen function	1P36
IGF-I/insulin (FOXO)	−	Transcription factors that take part in cell growth and differentiation	12q23–23
GH	−	Stimulates growth, production of IGF-I	17 q22-q24
TSHβ	+	Production of TSH	1p13
Thyrotropin receptor (TSHR)	+	Production of T4 and T3	14q31
CETP	+	Facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins	16q21
APOC-3	+	Inhibits lipoprotein lipase and hepatic lipase	11q23.1-q23.2
Adiponectin (AdipoQ)	+	Modulates glucose and fatty acid metabolism	3q27

Modified form Barzilai *et al.*, 2010 [5]

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.

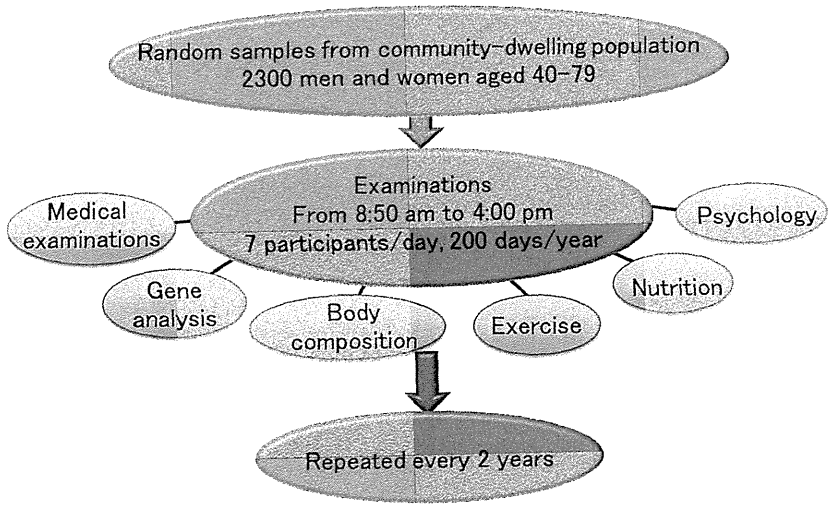

Fig. 2. **Implementation of the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA).**