Table 3 分析変数間の相関係数（Wave 1）

	1	2	3	4	5	6	7	8	9	10	11
1. 年齢											
2. 性	.01										
3. 教育歴	−.03	−.13***									
4. 年収	−.05	−.14***	.11***								
知能											
5. 知識	−.02	−.28***	.49***	.11**							
6. 類似	−.07	−.10*	.48***	.10**	.62***						
7. 絵画完成	−.13***	−.28***	.22***	.09*	.43***	.43***					
8. 符号	−.25***	−.09*	.42***	.12**	.45***	.45***	.38***				
抑うつ											
9. 身体的症状	.09*	.10**	−.03	−.09*	−.09*	−.05	−.15***	−.13***			
10. うつ感情	.04	.07	−.04	−.12**	−.08*	−.04	−.10**	−.13***	.70***		
11. ポジティブ感情a)	.01	.06	−.13***	−.06	−.15***	−.12**	−.13***	−.15***	.35***	.35***	
12. 対人関係	.10*	−.03	−.04	−.08*	−.14***	−.11**	−.11***	−.11**	.49***	.51***	.27***

注. a)逆転項目の処理を行っているため，ポジティブ感情の‘弱さ’を示す値である。
***p<.001, **p<.01, *p<.05

<.001），「傾き」は.151（*SE*.063, p<.05）と推定された（RMSEA=.093, CFI=.912）。このように，知能では負の傾き，抑うつでは正の傾きが有意であったことから，Wave 1 から Wave 3 にかけて，知能は低下し，抑うつは上昇する傾向が示された。しかしながら，各々の傾きの値は切片と比較して低く，知能と抑うつの4年間の変化は，0ではないが，非常に小さいと推測される。

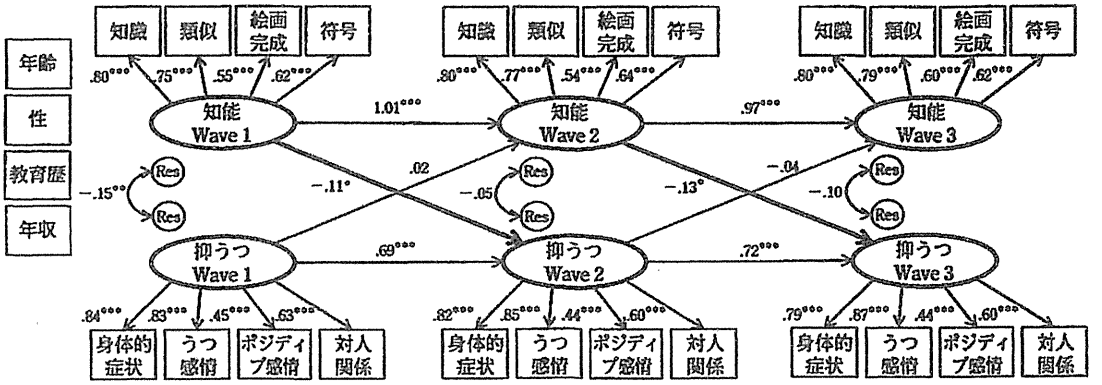
なお，分析対象者のうち，追跡調査である Wave 2・Wave 3 のいずれかにも少なくとも1回参加した者（553名）と，Wave 1 のみに参加した者（172名）において，Wave 1 の得点を比較すると，2回以上の参加者は Wave 1 のみの参加者よりも，全ての知能の下位検査得点が高く（知識：t(723)=4.38, p<.001；類似：t(723)=3.91, p<.001；絵画完成：t(723)=6.60, p<.001；符号：t(723)=4.98, p<.001），全ての抑うつの下位尺度得点が低かった（身体的症状：t(723)=3.99, p<.001；うつ感情：t(723)=4.00, p<.001；ポジティブ感情：t(723)=2.43, p<.05；対人関係：t(723)=4.48, p<.001）。また，CES-D のカットオフポイント（Radloff, 1977; 島ほか, 1985）を用いて，16点以上を「抑うつ有り」，15点以下を「抑うつ無し」に分類すると，「抑うつ有り」の対象者の割合は，Wave 1 で 15.59%，Wave 2 で 11.70%，Wave 3 で 14.93% であった。

2. 基本属性，知能と抑うつの相関関係

Wave 1 における，基本属性，知能の下位検査，及び抑うつの下位尺度の単相関行列を Table 3 に示す。年齢は，知能の2下位検査と有意な負の相関，抑うつの2下位尺度と有意な正の相関を示した。性は，知能の全ての下位検査と有意な負の相関，抑うつの1下位尺度と有意な正の相関を示した。教育歴は，知能の全ての下位検査と有意な正の相関，抑うつの1下位尺度と有意な負の相関を示した。年収は，知能の全ての下位検査と有意な正の相関，抑うつの2下位尺度と有意な負の相関を示した。さらに，知能と抑うつでは，「類似」と「身体的症状」及び「うつ感情」以外の組み合わせにおいて，有意な負の相関が示された。全ての基本属性が知能，抑うつのいずれかの下位検査，下位尺度と有意な相関を示したことから，以下では，これらの基本属性を調整して解析を行うこととした。

3. 知能と抑うつの経時的な相互関係

抑うつがその後の知能に影響するのか，あるいは知能がその後の抑うつに影響するのかを明らかにするために，双方向の因果関係を含む交差遅延効果モデル（Finkel, 1995）を検討した。今回の分析モデルの特徴は以下の通りである（Figure 1 参照）。(1) WAIS-R-SF の4下位検査得点（知識・類似・絵画完成・符号）を観測変数として「知能」という潜在変数を，CES-D の4下位尺度得点（身体的症状・うつ感情・ポジティブ感情・対人関係）を観測変数として「抑うつ」という潜在変数を構成した。その際，各潜在変数から観測変数への影響を示



注．標準偏回帰係数を示す。観測変数間の誤差相関，調整変数（年齢・性・教育歴・年収）からのパスは省略した。
***p<.001, **p<.01. *p<.05

Figure 1　*知能と抑うつの交差遅延効果モデル（Full モデル）*

す非標準化係数には，3時点における等値制約を課した。潜在変数間の相関係数を資料に示す。(2)「知能」から2年後の「抑うつ」，「抑うつ」から2年後の「知能」への双方向の経時的な因果関係を設定した。その際，同一観測変数の各時点間における誤差相関と，各時点の潜在変数間の誤差相関をモデルに組み込んだ。(3)基本属性（年齢・性・教育歴・年収）から「抑うつ」及び「知能」に対する影響を設定することにより，これらの基本的な属性を調整した。

なお，モデルを構築する際には，Perrino et al. (2008)，Fukukawa et al. (2004) を参考にした。また，分析の際は，追跡調査における欠損値を考慮して，完全情報最尤推定法による推定を行った。完全情報最尤推定法は，観測されたデータを全て用いて情報を有効に利用する推定法であり，推定値のバイアスがなく，漸近効率がよい（他の方法よりも真値からの2乗誤差が小さい）ことから，多くの欠損値を含む場合に有効な手法である（荘島・清水，2004）。

Figure 1に，「知能」と「抑うつ」の双方向の因果関係を組み込んだ交差遅延効果モデル（Full モデル）の結果を示す。適合度は，CFI=.970，RMSEA=.034であり，モデルが全体として妥当であることが示された。モデルの特徴を以下に示す。まず，基本属性から「知能」，「抑うつ」に対する影響では，年齢から「知能」のWave 1 と Wave 3 (β=−.098, p<.01；β=−.072, p<.001)，性から「知能」のWave 1 (β=−.173, p<.001)，教育歴から「知能」のWave 1 と Wave 2 (β=.575, p<.001；β=−.068, p<.05)，年収から「抑うつ」のWave 1 (β=−.108, p<.01) への標準偏回帰係数が有意であった（図中省略）。また，全ての時点において，知能，抑うつともに，観測変数の因子負荷量は.40以上の有意な係数を示した。さらに，「知能」のWave 1からWave 2，Wave 2からWave 3への係数は高い値を示しており，各2年間で非常に安定していると推測された。なお，「知能」のWave 1からWave 2へのパスにおける標準偏回帰係数は1を超えていた。室橋 (2006) は，単方向のパスは，値の絶対値が1を超える場合があると説明している。今回のモデルでは多重共線性が認められなかったことから，1.01という標準偏回帰係数は，従属変数「知能（Wave 2)」に対して，独立変数「知能（Wave 1)」が非常に高い予測精度を持つことにより，生じた結果であると推測される。

「知能」から2年後の「抑うつ」，「抑うつ」から2年後の「知能」という交差パスに着目すると，「知能（Wave 1)→抑うつ（Wave 2)」，「知能（Wave 2)→抑うつ（Wave 3)」の係数が有意であり (β=−.11, p<.05；β=−.13, p<.05)，「知能」は2年後の「抑うつ」に負の影響を及ぼすことが示された。しかしながら，「抑うつ（Wave 1)→知能（Wave 2)」，「抑うつ（Wave 2)→知能（Wave 3)」の係数はいずれも有意ではなかった (β=.02, ns；β=−.04, ns)。

4.「知能→抑うつ」モデル，「抑うつ→知能」モデルの検討

次に，Perrino et al. (2008)，高比良ほか (2006)，Fukukawa et al. (2004) を参考に，知能からその後の抑うつへの影響と，抑うつからその後の知能への影響を比較するために，以下の検討を行った。(1)「抑うつ」から2年後の「知能」への係数を0に制約し，「知能」から2年後の「抑うつ」の係数のみを推定する「知能→抑うつ」モデルを検討した。その際，「知能」→「抑うつ」のWave 1からWave 2，Wave 2からWave 3の係数に等値制約を課し，「知能」から2年後の「抑うつ」への影響

Table 4 「知能→抑うつ」モデル，「抑うつ→知能」モデルとFullモデルの比較

モデル	CFI	RMSEA	AIC	χ^2	$\Delta\chi^2$ vs Full モデル
「知能→抑うつ」モデル	.970	.034	811.808	$\chi^2(304)=551.808^{***}$	$\chi^2(3)=2.496^{ns}$
「抑うつ→知能」モデル	.969	.034	821.615	$\chi^2(304)=561.615^{***}$	$\chi^2(3)=12.303^{**}$
Full モデル	.970	.034	815.312	$\chi^2(301)=549.312^{***}$	—

注．CFI＝comparative fit index; RMSEA＝root mean square error of approximation;
AIC＝akaike information criterion
「知能→抑うつ」モデルでは，「知能」→「抑うつ」の Wave 1 から Wave 2，Wave 2 から Wave 3 の係数に等値制約を課し，「抑うつ」→「知能」の係数を 0 に制約した。一方，「抑うつ→知能」モデルでは，「抑うつ」→「知能」の Wave 1 から Wave 2，Wave 2 から Wave 3 の係数に等値制約を課し，「知能」→「抑うつ」の係数を 0 に制約した。
$^{***}p<.001$, $^{**}p<.01$, ns＝not significant

が，Wave 1 から Wave 2，Wave 2 から Wave 3 の時点で同等であると仮定した。(2)「知能」から 2 年後の「抑うつ」への係数を 0 に制約し，「抑うつ」から 2 年後の「知能」の係数のみを推定する「抑うつ→知能」モデルを検討した。その際，「抑うつ」→「知能」の Wave 1 から Wave 2，Wave 2 から Wave 3 の係数に等値制約を課し，「抑うつ」から 2 年後の「知能」への影響が，Wave 1 から Wave 2，Wave 2 から Wave 3 の時点で同等であると仮定した。(3)「知能→抑うつ」モデルと「抑うつ→知能」モデルを，Full モデルと比較した。その際，χ^2 値の差による検定を行った。

「知能→抑うつ」モデル，「抑うつ→知能」モデルの適合度指標，及び Full モデルとの比較を行った結果を Table 4 に示す。双方のモデルにおいて，適合度は良好な値を示した。しかしながら，特に「知能→抑うつ」モデルは，「抑うつ→知能」モデル，Full モデルと比較して AIC が低かったこと，χ^2 値の差を用いた検定の結果，より制約の少ない Full モデルと同等の適合が認められたことから，相対的に当てはまりのよい良好なモデルであると判断された。「知能」から 2 年後の「抑うつ」への係数は有意な値を示した（Wave 1 → Wave 2，Wave 2 → Wave 3 ともに，$\beta=-.12, p<.01$）。

一方，「抑うつ→知能」モデルは，AIC が最も高く，Full モデルの χ^2 値と比べて有意に高い χ^2 値を示したことから，相対的にモデルの適合が低いことが明らかになった。「抑うつ」から 2 年後の「知能」への係数は，有意ではなかった（Wave 1 → Wave 2, Wave 2 → Wave 3 ともに，$\beta=-.00, ns$）。

考　察

本研究では，地域在住高齢者の縦断データを用いて，知能と抑うつの経時的な相互関係について検討を行った。その結果，「知能」は 2 年後の「抑うつ」に負の影響を及ぼすことが示された。しかしながら「抑うつ」から 2 年後の「知能」への影響は認められなかった。

これまで，多くの先行研究において知的な能力と抑うつとの横断的な関連が報告されてきた（e.g., Baune et al., 2007; Ganguli et al., 2006）が，因果関係に関する研究の結果は混在していた（e.g., Barnes et al., 2006; Bielak et al., 2011; Dufouil et al., 1996; Ganguli et al., 2006; Köhler et al., 2010; Perrino et al., 2008; Vinkers et al., 2004; Wilson et al., 2004）。本研究は，双方向の経時的な因果関係を同時に組み込んだ交差遅延効果モデルを用いて検討することにより，知能からその後の抑うつに対する有意な影響を見出し，地域在住の高齢者における知能の水準が，約 2 年後の抑うつを予測する可能性を示した点で有意義であると言える。

これまでにも，知能はサクセスフル・エイジングを支える資源であり（Baltes & Langs, 1997），高齢期の知能は心理的健康に対して重要な影響をもたらすと指摘されてきた（Shifren, Park, Bennett, & Morrell, 1999）。そのメカニズムは，以下の点から説明することができる。例えば，Vinkers et al.（2004）は，高齢者自身の知能低下への気づきそのものが，機能喪失に対する心理的反応としての抑うつを引き起こす可能性があると指摘している。また，高齢者にとって，自身が自立して生活を送ることができるかどうかは，重要な関心事である。従って，知能が低下することにより，生活を統制することに難しさを感じたり，以前のように日常的な問題を解決することができないことを実感したりすることは，抑うつの兆候を発達させ，深刻にする可能性があると推測される（Bierman, Comijs, Jonker, & Beekman, 2007; Perrino et al., 2008）。一方，高齢者の知能の低さが認知的な歪みをもたらす危険性に着目する文献もある。すなわち，高い知能を有することは，ネガティブなライフイベント（疾病や対人関係など）について，ポジティブ・ネガティブの両側面から，多面的に考えることを可能にする（Shifren et al., 1999）。しかしながら，知能が低い場合に

は，ネガティブな次元にのみ焦点づけてしまうことにより，その後，抑うつ状態を引き起こす危険があると報告されている（Shifren et al., 1999; Zwahr, Park, & Shifren, 1999）。さらに，高齢者の知能の低さは，行動の計画を立てて，遂行する能力とも関連することから，余暇の活動や対人関係を制限する可能性があり，それが抑うつに影響する可能性も指摘されている（Fisher, Segal, & Coolidge, 2003）。本研究で確認された結果は，このような知能から抑うつへの影響のメカニズムを反映していると考えられ，今後は，知能からその後の抑うつへの影響の間に，日常生活動作（ADL：Activity of Daily Living）や認知スタイル，余暇の活動状況等の媒介変数を組み込んだモデルの検討が必要であると考えられる。

一方，今回の交差遅延効果モデルでは，抑うつがその後の知能に及ぼす有意な影響は認められなかった。これまでの高齢者を対象とした縦断研究では，抑うつがその後の知能を低下させるという報告がある（Köhler et al., 2010; Barnes et al., 2006; Wilson et al., 2004）一方で，抑うつから知能への影響はないとする文献（Ganguli et al., 2006; Vinkers et al., 2004; Dufouil et al., 1996; Perrino et al., 2008）もあり，それらの結果は混在していた。この状況を考慮すると，双方向の因果関係を考慮した場合には，抑うつが2年後の知能の低さの直接的なリスク因子にならない可能性を示す本研究の結果は意義深いと考えられる。しかしながら，今回の結果に関しては，主に研究デザインの点から以下のようにも推察されることから，解釈には慎重になるべきであろう。まず，今回のモデルでは「知能」のWave 1からWave 2，Wave 2からWave 3への係数がいずれも高値を示し（Figure 1），潜在成長曲線モデルを用いた検討においても，「知能」の変化を示す傾きの値は小さく，約2年の間隔で評価された4年間の知能の変化は非常に少ないと推測された。この点に関して，中高年者の知能の変化はゆっくりと進行するために，2，3年間の短い研究期間で捉えることは難しい可能性（Schaie & Willis, 2002）が指摘されている。本研究では，知能低下の個人差の大きい高齢者（Schaie, 2005; Wilson et al., 2002）を対象としているが，彼らは地域在住者であり，複数回の施設型の調査に参加することが可能であることからも，比較的健康度の高い集団と言える。従って，そのような高齢者における知能の低下を捉えたり，その個人差に影響する因子を検討するためには，さらに調査の間隔を広げた長期的な追跡が必要となる可能性がある。実際に，抑うつの高さがその後の知能を低下させるという可能性を示唆する報告は，本研究よりも長期的な追跡を行っている研究によるものであった（Köhler et al., 2010; Barnes et al., 2006; Wilson et al., 2004）。交差遅延効果モデルの限界として，タイムラグの適切さを評価できない点が指摘されていることからも（Piccinin, Muniz, Sparks, & Bontempo, 2011），本研究で示された，抑うつはその後の知能の低さに影響しないという結果は，2年という比較的短い間隔での因果関係モデルを検討したものであることに，留意が必要である。

また，本研究では，各々の調査の時点における抑うつの状態を連続変量で扱っている。従って，今回の結果は，一時点における抑うつの相対的な高さが，その2年後の知能の低さには影響しないことを示すものである。しかしながら，一時的な抑うつではなく，慢性的な抑うつこそが知能の低下に関連するという報告がある（Köhler et al., 2010）。また，本研究のベースラインでは，約16%の高齢者が臨床的なカットオフポイントにより「抑うつ有り」に分類されており（結果の1.），この数値は，先行研究をレビューして，地域在住の高齢者の抑うつの罹患率が約15%であると報告した，Blazer（2003）とほぼ一致していた。このような臨床的に定義される抑うつ罹患が，その後の知能の低下に影響を及ぼす可能性もある（Wilson et al., 2004）。従って，今後は，抑うつの持続性や抑うつ罹患の可能性を組み込んだモデルの解析を行う必要があると考えられる。

現在，日本は5人に1人が65歳以上という超高齢社会を迎えており，2035年には3人に1人が65歳以上の高齢者となる社会が到来すると推計されており（内閣府，2012），高齢者が知能を維持しながら，抑うつに罹患することなく生活するための基礎的なデータを蓄積することは，社会的にも学術的にも有用である。その点で，本研究の強みは，先行研究（ほとんどが抑うつから知能へ，あるいは知能から抑うつへという，単一方向の検討であった）の結果が一貫していなかった，知能と抑うつの相互関係について，知能と抑うつを繰り返し測定した大規模縦断データを用いて，双方向の因果関係の検討を行ったことであろう。さらに，今回示された，知能が約2年後の抑うつに影響を及ぼす可能性があるという結果からは，以下の重要な示唆を得ることができる。例えば，Bierman et al.（2007）は，認知機能の水準と抑うつとの関連を検討し，重度（poor）や疾患（Alzheimer's disease）のレベルではなく，平均（average）から中程度（moderate）の認知機能低下を示す高齢者の抑うつが最も高くなる傾向があることを示している。すなわち，知的な能力は，特に，初期の緩やかな低下において，抑うつに大きな影響を及ぼす傾向があると考えられる。本研究では，認知症既往のない地域在住者を対象としており，今回の解析モデルは，追跡調査にも参加した，より心身状態の健康な高齢者の特徴を反映している。この点を考慮すると，本研究で得られた結果は，知的水準が比較的良好な集団における，相対的な知能の低さや知能の初期の低下が，その後の抑うつを増大する可

能性を示していると言えよう。従って，地域在住の高齢者における，これらの緩やかな知能の低下に対して，その維持・向上を目指すための介入プログラムを実施することは，抑うつ予防にとって有効であると考えられる。また，知能を構成する側面には，情報処理の能力など，加齢によるネガティブな影響を受けやすい能力が含まれる（Kaufman & Lichtenberger, 1999）。高齢者自身がその事実を受け入れ，知能低下への対処法として，補償をともなう選択的最適化（selective optimization with compensation：SOC；Baltes, 1997），すなわち，従来よりも狭い領域を探索したり（選択），その狭い領域で適応の機会を増やしたり（最適化），機能の低下を補う新たな方法や手段を獲得したり（補償）できるような支援を行うことも，高齢者の抑うつの軽減に対して効果的であると考えられる。

本研究の限界としては，以下の点が挙げられる。第一に，今回用いた追跡データには欠損値が多く含まれている。死亡により，追跡調査に参加しなかった高齢者が存在すること，Wave 1のみの参加者よりも，追跡調査にも参加した高齢者において，知能が高く，抑うつが低かったことを考慮すると，今回の結果には脱落効果（Schaie, 2005）が含まれており，より健康な心身状態の高齢者の特徴が反映されている可能性に留意する必要がある。従って，知能の著しい低下を示す高齢者における知能と抑うつの相互関係については，今後の検討が必要である。第二に，本研究ではWAIS-R-SFの4下位検査，CESD-Dの4下位尺度を観測変数とし，「知能」，「抑うつ」という潜在変数に集約したモデルの検討を行った。しかしながら，知能の側面によって，抑うつとの相互関係の様相が異なる可能性がある。また，抑うつに関しても，個々の特徴的な症状により，知能との相互関係が異なるかもしれない。従って，今後は，知能，あるいは抑うつの包括的な傾向だけではなく，各々の側面や内容も考慮に入れた検討が必要である。第三に，本研究では，知能の水準が2年後の抑うつに影響を及ぼすことが示されたが，今回の交差遅延効果モデルでは，知能，抑うつの相対的順位における関係が明らかになったに過ぎない。すなわち「知能の低下がその後の抑うつを増大させるかどうか」，あるいは「高い知能がその後の抑うつを軽減するのか，低い知能がその後の抑うつを増大させるのか」については，検証することができなかった。今後は，知能と抑うつの個人内変化を指標として組み込んだモデル，例えば，2変数の差分スコア間の先行-遅行の因果関係を検証するDual Change Score Model（McArdle & Hamagami, 2001）などを用いた，より詳細な検討が望まれる。

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付記

本研究は，平成22年度科学研究費補助金基盤研究(S)「中高年者のこころの健康についての学際的大規模縦断研究—予防へのストラテジーの展開（課題番号18109007)」，及び平成24年度科学研究費学術研究助成基金助成金（若手研究（B))「中高年期における知能の経時変化とその維持・向上に有効な年代別ストラテジーの構築（課題番号23730640)」により行われた。

NILS-LSAにご参加いただいている愛知県大府市ならびに東浦町の住民の皆様に感謝いたします。

資料 *潜在変数「知能」,「抑うつ」間の相関係数*

	知能 (Wave 1)	知能 (Wave 2)	知能 (Wave 3)	抑うつ (Wave 1)	抑うつ (Wave 2)	抑うつ (Wave 3)
知能 (Wave 1)	—					
知能 (Wave 2)	.970	—				
知能 (Wave 3)	.964	.992	—			
抑うつ (Wave 1)	−.178	−.156	−.182	—		
抑うつ (Wave 2)	−.210	−.201	−.232	.703	—	
抑うつ (Wave 3)	−.235	−.236	−.249	.522	.739	—

注. Fullモデル（結果の3.）の下で計算された潜在変数の相関係数を示す。

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This study examined the reciprocal relationship between intelligence and depressive symptoms over time, in an elderly Japanese sample. Participants (age range=65–79: N=725) were from the first wave of the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). They were tested three times and followed for about 4 years. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D) and intelligence was assessed by the Wechsler Adult Intelligence Scale-Revised Short Forms (WAIS-R-SF). Structural equation modeling with a cross-lagged panel design showed that intelligence was related to subsequent depressive symptoms at every time point, such that poorer cognitive functioning was related to higher depressive symptoms. However, depressive symptoms were unrelated to subsequent intelligence. These findings suggest that intellectual ability may predict depressive symptoms in community-dwelling Japanese elderly adults.

[Keywords] Intelligence, Depression, Elderly adults, Cross-lagged panel design

2013.2.1 受稿，2013.11.6 受理

OPEN

European Journal of Clinical Nutrition (2014) 68, 503–509

www.nature.com/ejcn

ORIGINAL ARTICLE

Serum docosahexaenoic and eicosapentaenoic acid and risk of cognitive decline over 10 years among elderly Japanese

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BACKGROUND/OBJECTIVES: To clarify the association of serum docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) levels with cognitive decline over 10 years.

SUBJECTS/METHODS: This study was part of the National Institute for Longevity Sciences - Longitudinal Study of Aging, and was conducted with 232 male and 198 female Japanese community-dwelling subjects aged 60–79 years in the second wave (2000–2002). Cognitive function was assessed with the Mini-Mental State Examination (MMSE) in both the second and seventh (2010–2012) waves. Fasting venous blood samples were collected in the morning, and serum DHA and EPA levels were measured. Multiple logistic regression analysis was performed among participants with an MMSE score $\geqslant 24$ in the second wave ($n = 430$) to estimate the odds ratio (OR) and 95% confidence interval (CI) for MMSE score $\leqslant 23$ or MMSE score decline $\geqslant 4$ 10 years later. These estimates were based on baseline tertiles of serum DHA or EPA levels, and controlled for age, sex, education, MMSE score at baseline, alcohol consumption, current smoking, body mass index and disease history.

RESULTS: Fifteen (3.5%) subjects whose MMSE score was $\leqslant 23$ and 36 (8.3%) subjects whose MMSE score declined to $\geqslant 4$ showed cognitive decline. Multivariate-adjusted OR (95% CI) for the lowest through highest tertiles of serum DHA to MMSE score $\leqslant 23$ or decline $\geqslant 4$ were 1.00 (reference), 0.11 (0.02–0.58) and 0.17 (0.04–0.74), or 1.00 (reference), 0.22 (0.08–0.61) and 0.31 (0.12–0.75), respectively (P for trend = 0.01 or 0.04). Serum EPA was not associated with cognitive decline.

CONCLUSIONS: The study gives some indication that a moderately high level of serum DHA might prevent cognitive decline among community-dwelling elderly Japanese individuals.

European Journal of Clinical Nutrition (2014) **68,** 503–509; doi:10.1038/ejcn.2013.264; published online 8 January 2014

Keywords: DHA; EPA; serum; cognition; Japanese; elderly

INTRODUCTION

An estimated two million people in Japan suffer from dementia and this number will likely increase as the population ages.[1] The essential n-3 polyunsaturated fatty acids (PUFA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) that constitute the predominant long-chain PUFAs of membrane phospholipids in mammalian brains and neural tissues, are crucial for maintenance of brain function.[2]

Fish consumption, particularly fatty fish, and intake of marine n-3 PUFA, DHA and EPA are thought to play a protective role against age-related cognitive decline.[3] However, results of cross-sectional and longitudinal studies examining the association between fish or n-3 PUFA intake and cognitive performance have been inconsistent, with some studies showing that high intake of n-3 PUFA was associated with better cognitive performance[4–6] and other studies showing no association.[3,5] One possible reason for these inconsistent results is the limited ability of dietary assessments to quantify blood levels of fatty acids (FA). Blood FA biomarkers can be measured to indicate differences in their delayed response to short- and long-term dietary intakes.[7,8] Studies using n-3 series PUFA in the blood have shown that higher concentrations of DHA in erythrocyte membranes,[9] DHA in plasma phosphatidylcholine[10] and plasma EPA[11] are associated with a lower risk of cognitive decline or Alzheimer's disease. Recently, lower red blood cell EPA and DHA levels were reported to be correlated with smaller brain volumes in elderly subjects without clinical dementia.[12] Furthermore, it has been proposed that FAs in the blood are associated with cognitive function.[13] However, other studies focusing on dementia not only reported no difference in DHA in plasma cholesterol esters and phospholipids,[14] but also reported significantly higher DHA in plasma phospholipids[15] or cholesteryl esters.[16,17] Hence, results of studies examining the association between blood FA and cognitive performance have been inconsistent.

Mean DHA and EPA intake/serum DHA/EPA levels among Caucasian subjects are substantially lower than those of Japanese subjects.[18–21] The effect of serum DHA/EPA levels on cognitive function may vary among Japanese subjects, and the association between serum DHA and EPA levels and cognitive decline among Japanese subjects remains unclear. In addition, studies that examined the effectiveness of serum DHA/EPA levels on cognition in Japanese subjects with high serum DHA/EPA levels would explain one of the reasons that DHA/EPA supplementation trials in Caucasians, in whom serum DHA/EPA levels were substantially low, demonstrated essentially no effect from DHA on cognitive impairment.[22,23] We considered that the duration of these intervention studies examining the effectiveness of DHA/EPA on cognitive performance were relatively short, and

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Received 6 February 2013; revised 29 October 2013; accepted 6 November 2013; published online 8 January 2014

long-term effectiveness of DHA/EPA intake on cognitive performance would be easier to clarify among Japanese subjects because they are naturally exposed to higher DHA/EPA concentrations. No study in Japan and only a few studies among Asians have reported the association between blood FA and cognitive impairment.[24,25]

To clarify the effectiveness of serum DHA and EPA levels on cognitive decline among the Japanese whose DHA and EPA intake/serum DHA/EPA levels are higher than among Caucasians, and who are naturally exposed to high DHA/EPA concentrations, the present longitudinal study was carried out in elderly community-dwelling Japanese subjects and examined the associations of serum DHA and EPA levels with cognitive decline.

SUBJECTS AND METHODS

Participants

Data for this survey were collected as part of the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA). In this project, the normal aging process has been assessed over time using detailed questionnaires and medical checkups, anthropometric measurements, physical fitness tests and nutritional examinations. Participants in the NILS-LSA included randomly selected age- and sex-stratified individuals from the pool of non-institutionalized residents in the NILS neighborhood areas of Obu City and Higashiura Town in Aichi Prefecture. The first wave of the NILS-LSA was conducted from November 1997 to April 2000 and comprised 2267 participants (1139 men, 1128 women; age range, 40–79 years). Details of the NILS-LSA study have been reported elsewhere.[26]

The second wave of the NILS-LSA was conducted from April 2000 to May 2002 and comprised 2259 participants (1152 men, 1107 women; age range, 40–82 years). Among these participants, 1351 (690 men, 661 women) were also included in the seventh wave of the NILS-LSA, which was conducted from July 2010 to July 2012. The mean (±s.d.) interval between the second and seventh wave for each participant was 10.2 (±0.4) years.

Exclusion criteria were as follows: (1) those who were <60 years in the second wave ($n=868$), as cognitive function tested by the Mini-Mental State Examination (MMSE) was assessed only among participants aged 60 or older; (2) those who had an MMSE score ⩽23 in the second wave ($n=10$); and (3) those who did not complete either the alcohol intake assessments or the self-reported questionnaire ($n=43$). A total of 430 Japanese (232 men, 198 women) who had been between 60 and 79 years in the second wave of the NILS-LSA were available for analysis.

The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology (No. 369-2). Written informed consent was obtained from all subjects.

Blood sampling and serum FA analysis

Upon enrolment in the second wave of the NILS-LSA, venous blood was collected early in the morning after fasting for at least 12 h. Blood samples were centrifuged at 3500 *g* for 15 min. Serum was separated and frozen at −80 °C before analysis for FA content by a single technician. Serum DHA and EPA were measured by gas-liquid chromatography at a clinical laboratory (SRL, Tokyo, Japan). In brief, total lipids in the serum were extracted using the Folch procedure and FAs were then methylated with BF3/methanol. Transesterified FAs were then analyzed using a gas chromatograph (GC-17A; Shimadzu, Kyoto, Japan) with a capillary column (Omegawax 250; Supelco, Bellefonte, PA, USA). The weights of DHA and EPA (g/ml) as FA concentrations were identified by comparison with known standards. Intra- and inter-assay precision and accuracy values (coefficient of variation (CV)) were 2.7 and 6.9 CV% for EPA, and 1.9 and 6.9 CV% for DHA, respectively.

Assessment of cognitive function

Cognitive function was assessed by the Japanese version of the MMSE through interviews with a trained psychologist or clinical psychotherapist in both the second and seventh waves.[27,28] The MMSE is widely used as a brief screening test for dementia, and scores range from 0 to 30 points, with a higher score indicating better cognitive function. The MMSE includes questions on orientation of time and place, registration, attention and calculation, recall, language and visual construction. We used two different cutoff scores: (1) a decline of at least 4 points in the MMSE score from the second to seventh wave, which has been shown to be meaningful from a clinical point of view,[29–31] and (2) a cutoff score of ⩽23, which is traditionally used to represent 'suggestive cognitive impairment'[27,28] and thus was also used in the main analyses. Among participants in this study with an MMSE ⩾24 in the second wave ($n=430$), (1) 36 (8.3%) who had a decline of at least 4 points in the MMSE score from the second to seventh wave (10 years later), and (2) 15 (3.5%) who had an MMSE score ⩽23 in the seventh wave (10 years later) were classified as showing cognitive decline, respectively. We defined the second wave as baseline, as the MMSE method between the second and seventh wave was consistent, and there were slight modifications of the procedure between the first and second waves.

Nutritional assessments

Nutritional intakes were assessed using a 3-day dietary record after participation in the second wave survey. The dietary record was completed over three continuous days (both weekend days and 1 weekday),[32] and most subjects completed it at home and returned records within 1 month. Food was weighed separately on a scale (1-kg kitchen scales; Sekisui Jushi, Tokyo, Japan) before being cooked or portion sizes were estimated. Subjects used a disposable camera (27 shots; Fuji Film, Tokyo, Japan) to take photos of meals before and after eating. Dietitians used these photos to complete missing data and telephoned subjects to resolve any discrepancies or obtain further information when necessary. Averages for 3-day food and nutrient intakes were calculated according to the fifth edition of the Standard Tables of Foods Composition in Japan and other sources.[32] Alcohol intake in the previous year was assessed using a food frequency questionnaire; trained dietitians interviewed subjects using this questionnaire.

Other measurements

Medical history of heart disease, hypertension, hyperlipidemia, diabetes (past and current), education (⩽9, 10–12 or ⩾13 years of school) and smoking status (yes or no) were collected using self-report questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Serum triacylglycerol levels were measured using enzymatic methods, and total and high-density lipoprotein-cholesterol levels were measured using the dehydrogenase method and direct method at a clinical laboratory (SRL). These measurements were assessed in the second wave.

Statistical analysis

All statistical analyses were conducted using statistical analysis system software version 9.1.3 (SAS Institute, Cary, NC, USA). The confounding variables were age (year, continuous), sex, education (⩽9, 10–12, ⩾13 years), MMSE score at baseline (continuous), alcohol consumption (ml/day), current smoking status (yes or no), BMI (kg/m^2), history of heart disease, hypertension, hyperlipidemia and/or diabetes (yes or no). Differences in proportions and means of covariates according to the MMSE score in the seventh wave (10 years later) were assessed using the χ^2-test or Fisher's exact probability test (if statistical expectation ⩽5) and independent *t*-test, respectively. Comparisons between baseline dietary intakes according to the MMSE score 10 years later were performed by independent *t*-test.

Multiple logistic regression analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (CI) for (1) a decrease in MMSE score of at least 4 points or (2) an MMSE score ⩽23 in the seventh wave according to tertiles of serum DHA or EPA. The lowest tertile category was used as a reference. The independent variables in the first model were age, sex and education. The second model was further adjusted for MMSE score at baseline, alcohol consumption, current smoking status, BMI, history of heart disease, hypertension, hyperlipidemia and/or diabetes. Trend associations were assessed by assigning dummy variables of −1, 0 and 1 to tertiles of serum DHA or EPA. In the logistic regression analysis, we tested goodness-of-fit (Hosmer–Lemeshow test) using the lackfit option and calculated the generalized R^2 (Nagelkerke R^2) measure using the r^2 option. Age, sex and education-adjusted mean MMSE score according to tertiles of serum DHA or EPA were calculated using the PROC GLM procedure. To eliminate the effects of other confounding variables on MMSE score, a subsequent model included MMSE score at baseline, alcohol consumption, current smoking status, BMI, history of heart disease, hypertension, hyperlipidemia and diabetes as covariates. All reported *P* values are two-sided, and a *P* value < 0.05 was considered significant.

RESULTS

Baseline characteristics of subjects according to the MMSE score in the seventh wave (10 years later) and subjects excluded from the analyses are shown in Table 1. Fifteen subjects (3.5%) were classified as showing cognitive decline (MMSE score ⩽23). Compared with subjects with an MMSE score ⩾24, those with an MMSE score ⩽23 were significantly less likely to be educated, significantly older and had a significantly higher BMI. Compared with subjects with both an MMSE score ⩽23 and ⩾24, subjects excluded from the analyses were older, more likely to be current smokers, and more likely to have a history of hyperlipidemia and diabetes. Mean serum EPA or DHA among subjects excluded from the analyses was intermediate between subjects with MMSE score ⩽23 and ⩾24.

Table 2 shows baseline dietary intakes of subjects according to MMSE score 10 years later. Compared with subjects with an MMSE score ⩾24, those with an MMSE score ⩽23 ate significantly less fat and vegetables and significantly more fruits and sweets.

Table 3 shows the ORs and 95% CIs for an MMSE score decline of at least 4 points in the seventh wave (10 years later) according to tertiles of serum FAs. In the age-, sex- and education-adjusted model, serum DHA levels were significantly associated with a decreased prevalence of cognitive decline. After further adjustment for other covariates, the association remained statistically significant. The multivariate-adjusted ORs (95% CIs) for the lowest through highest tertiles of serum DHA were 1.00 (reference), 0.22 (0.08–0.61) and 0.31 (0.12–0.75), respectively (P for trend = 0.004, goodness-of-fit Pr > 0.93, $R^2 = 0.22$). Serum EPA was not associated with cognitive decline.

Table 4 shows mean MMSE scores and ORs (95% CIs) for MMSE score ⩽23 in the seventh wave (10 years later) according to tertiles of serum FAs. Mean MMSE scores according to tertiles of serum FAs were not statistically significant. In the age-, sex- and education-adjusted model, serum DHA levels were significantly associated with a decreased prevalence of cognitive decline. After further adjustment for other covariates, the association remained statistically significant; the multivariate-adjusted OR (95% CI) for the lowest through highest tertiles of serum DHA were 1.00 (reference), 0.11 (0.02–0.58) and 0.17 (0.04–0.74), respectively (P for trend = 0.01, goodness-of-fit Pr > 0.85, $R^2 = 0.32$). Serum EPA was not associated with cognitive decline.

DISCUSSION

This study provides longitudinal evidence that low serum DHA levels were associated with a higher risk of cognitive decline over a 10-year period in community-dwelling Japanese adults aged 60 years and older. This association remained after controlling for baseline MMSE score and other variables. This is the first study to examine the association between serum DHA/EPA levels on cognitive decline among Japanese subjects whose DHA and EPA intake/serum DHA/EPA levels are higher than those seen in Caucasians and in whom ordinary exposure to DHA/EPA concentrations was high.

The ARIC (Atherosclerosis Risk in Communities) and Framingham Study studies, which examined n-3 series PUFA in the blood, showed that higher concentrations of these FAs were associated with a lower risk for cognitive decline.[10,14] Among elderly French subjects, DHA of erythrocyte membranes[9] and plasma EPA[11] have also been shown to be associated with a lower risk for cognitive decline. However, other studies focusing on dementia not only reported no difference in DHA in plasma cholesterol esters and phospholipids,[14] but also reported significantly higher DHA in either plasma phospholipids[15] or cholesteryl esters.[16,17] Hence, the results from studies examining the association between blood FA and cognitive performance have been inconsistent.

However, serum n-3 series PUFA differs markedly in middle-aged Japanese, Japanese-American and Caucasian (American) men.[33] DHA and EPA levels from the blood of Japanese men are

Table 1. Baseline characteristics of subjects according to the MMSE score 10 years later and subjects excluded from the analyses in the NILS-LSA study

	Subjects available for analyses (n = 430)			*Subjects excluded from the analyses*[a] *(n = 715)*[c]
	MMSE ⩽23	*MMSE⩾24*	*P-value*[b]	
Number of subjects	15	415		
MMSE (mean ± s.d.)	27.7 ± 1.4	28.4 ± 1.4	0.04	27.5 ± 2.2
Age (mean ± s.d., years)	70.9 ± 5.9	66.4 ± 5.0	<0.01	71.3 ± 5.5
BMI (mean ± s.d., kg/m^2)	24.4 ± 2.7	22.8 ± 2.7	0.02	22.9 ± 3.3
Alcohol (mean ± s.d., ml/day)	10.2 ± 15.4	8.1 ± 13.5	0.55	7.5 ± 14.7
Female (%)	46.7	46.0	0.96	50.9
Education				
⩽9 years (%)	66.7	31.1	0.01	47.0
10–12 years (%)	6.7	15.7		21.8
⩾13 years (%)	26.7	53.3		31.2
Current smoking status (%)	6.7	15.4	0.35	17.4
History of hypertension (%)	53.3	31.1	0.07	42.5
History of hyperlipidemia (%)	13.3	21.5	0.45	21.9
History of diabetes (%)	6.7	7.2	0.93	12.8
Triacylglycerol (mean ± s.d., mg/dl)	85.9 ± 25.7	120.9 ± 62.1	0.03	117.7 ± 66.6
Total cholesterol (mean ± s.d., mg/dl)	219.1 ± 37.9	219.1 ± 33.7	0.99	216.5 ± 36.1
HDL cholesterol (mean ± s.d., mg/dl)	61.27 ± 16.1	59.9 ± 14.9	0.72	60.7 ± 15.8
Serum EPA (mean ± s.d., μg/ml)	74.9 ± 41.1	81.5 ± 39.7	0.53	77.5 ± 40.9
Serum DHA (mean ± s.d.,μg/ml)	145.0 ± 38.5	162.2 ± 45.2	0.15	157.1 ± 49.4

Abbreviations: BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high density lipid; MMSE, Mini Mental State Examination.
[a]Subjects excluded from the analyses included those who were older than 60 years in the second wave and those who did not participate in the seventh wave.
[b]For continuous variables, independent t-test was used; for categorical variables, χ^2test or Fisher's exact probability test was used. [c]The number of excluded subjects according to the characteristics listed ranged from 672 to 715.

Table 2. Baseline dietary intakes of subjects according to the MMSE score 10 years later in the NILS-LSA study

	MMSE≤23	*MMSE≥24*	*P-value*[a]
Number of subjects	15	415	
Energy (mean ± s.d., kcal/day)	2270.0 ± 371.5	2095.9 ± 394.8	0.85
Protein (mean ± s.d., energy%)	14.7 ± 1.5	15.7 ± 2.0	0.22
Fat (mean ± s.d., energy%)	21.5 ± 6.0	23.5 ± 4.3	0.03
Saturated fat (mean ± s.d., g/day)	16.2 ± 5.2	15.4 ± 5.1	0.85
Polyunsaturated fat (mean ± s.d., g/day)	12.2 ± 2.7	12.9 ± 3.6	0.25
DHA (mean ± s.d., mg/day)	543.0 ± 250.4	590.3 ± 1.4	0.07
EPA (mean ± s.d., mg/day)	302.5 ± 155.6	321.3 ± 383.0	0.11
Cereals (mean ± s.d., g/day)	475.0 ± 145.2	469.9 ± 139.5	0.74
Beans (mean ± s.d., g/day)	79.2 ± 35.6	72.8 ± 49.9	0.14
Vegetables (mean ± s.d., g/day)	283.9 ± 81.3	336.0 ± 130.5	0.04
Fruits (mean ± s.d., g/day)	259.8 ± 209.7	175.7 ± 129.1	0.002
Fish and shellfish (mean ± s.d., g/day)	113.6 ± 63.5	102.2 ± 50.3	0.16
Meats (mean ± s.d., g/day)	40.9 ± 23.8	56.7 ± 32.4	0.18
Eggs (mean ± s.d., g/day)	46.9 ± 29.5	46.7 ± 25.7	0.39
Milk and dairy products (mean ± s.d., g/day)	213.1 ± 120.5	165.6 ± 128.6	0.83
Sweets (mean ± s.d., g/day)	71.7 ± 53.8	38.3 ± 38.6	0.04

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination. [a]Independent *t*-test was used.

Table 3. ORs and 95% CIs for MMSE scores that declined at least 4 points during 10 years according to tertiles of serum fatty acids

	Tertiles of serum fatty acids			
	T1 (low)	*T2*	*T3 (high)*	*Trend P*[a]
EPA (range, μg/ml)	14.1–59.2	59.2< – 90.4	90.4< – 31.8	
Number of subjects MMSE score declined ≥4/≤3	12/129	13/129	11/136	
Age, sex, and education-adjusted OR (95% CI)[b]	1.00 (reference)	1.18 (0.50–2.79)	0.86 (0.35–2.09)	0.70
Multiple-adjusted OR (95% CI)[b,c]	1.00 (reference)	1.10 (0.44–2.75)	0.69 (0.27–1.76)	0.83
DHA (range, μg/ml)	59.3–138.5	138.5< – 175.6	175.6< – 354.6	
Number of subjects MMSE score declined ≥4/≤3	21/118	6/138	9/138	
Age, sex, and education-adjusted OR (95% CI)[b]	1.00 (reference)	0.23 (0.09–0.60)	0.35 (0.15–0.81)	0.003
Multiple-adjusted OR (95% CI)[b,c]	1.00 (reference)	0.22 (0.08–0.61)	0.31 (0.12–0.75)	0.004

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination; OR, odds ratio. [a]On the basis of multiple logistic regression analysis, assigning dummy variables − 1, 0, 1 to tertiles of serum fatty acids. [b]Adjusted ORs and CIs were based on multiple logistic regression analysis. [c]Adjusted for age (year, continuous), sex, education (≤9, 10–12, ≥13 years), MMSE score at baseline (continuous), alcohol consumption (ml/day), current smoking status (yes or no), body mass index (kg/m^2), and history of heart disease, hypertension, hyperlipidemia and diabetes (yes or no).

Table 4. Mean (s.e.) MMSE score and ORs (95% CIs) for MMSE scores ≤23 10 years later according to tertiles of serum fatty acids

	Tertiles of serum fatty acids				
	T1 (low)	*T2*	*T3 (high)*	*ANCOVA P*	*Trend P*[a]
EPA (range, μg/ml)	14.1–59.2	59.2< – 90.4	90.4< – 31.8		
Age, sex and education-adjusted MMSE score[b]	27.78 (0.15)	27.53 (0.15)	27.77 (0.15)	0.44	0.99
Multiple-adjusted MMSE score[b,c]	27.79 (0.15)	27.57 (0.15)	27.72 (0.15)	0.43	0.74
Number of subjects with MMSE ≤23/MMSE ≥24	4/137	9/133	2/145		
Age, sex and education-adjusted OR (95% CI)[d]	1.00 (reference)	2.76 (0.78–9.72)	0.51 (0.08–2.91)		0.11
Multiple-adjusted OR (95% CI)[c,d]	1.00 (reference)	2.92 (0.74–11.54)	0.52 (0.08–3.24)		0.13
DHA (range, μg/ml)	59.3–138.5	138.5< – 175.6	175.6< – 354.6		
Age, sex and education-adjusted MMSE score[b]	27.48 (0.15)	27.89 (0.15)	27.70 (0.15)	0.18	0.29
Multiple-adjusted MMSE score[b,c]	27.47 (0.15)	27.90 (0.15)	27.68 (0.15)	0.17	0.32
Number of subjects with MMSE ≤23/MMSE ≥24	10/129	2/142	3/144		
Age, sex, and education-adjusted OR (95% CI)[d]	1.00 (reference)	0.16 (0.03–0.78)	0.26 (0.07–0.98)		0.02
Multiple-adjusted OR (95% CI)[c,d]	1.00 (reference)	0.11 (0.02–0.58)	0.17 (0.04–0.74)		0.01

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Examination; OR, odds ratio. [a]On the basis of the general linear model or multiple logistic regression analysis, assigning dummy variables − 1, 0, 1 to tertiles of serum fat [b]Adjusted MMSE scores (mean ± s.e.) were based on the general linear model. [c]Adjusted for age (year, continuous), sex, education (≤9, 10–12, ≥13 years), MMSE score at baseline (continuous), alcohol consumption (ml/day), current smoking status (yes or no), body mass index (kg/m^2), and history of heart disease, hypertension, hyperlipidemia and diabetes (yes or no). [d]Adjusted ORs and CIs were based on multiple logistic regression analysis.

significantly higher than those from the blood of Caucasian men.[33] Mean (± s.d.) serum EPA and DHA concentrations in our sample of subjects with an MMSE ⩾24 were 81.5 (± 39.7) and 162.2 (± 45.2) μg/ml, respectively. On the other hand, among cognitively healthy adults aged 70–79 years living in England, these plasma levels were 39.1 (± 3.1) and 70.7 (± 2.9) μg/ml, respectively.[34]

The biological mechanisms through which serum DHA exerts beneficial effects on cognition can be divided into vascular and non-vascular pathways. In terms of vascular pathways, the beneficial effects of DHA and EPA are well known, including blood pressure reduction[35] and pronounced effects on eicosanoid production[36] and two cardiovascular risk factors that may lead to cognitive decline.[37] In terms of non-vascular pathways, DHA is highly concentrated in membrane phospholipids of brain gray matter, and it has particular effects on membrane properties and cell signaling.[38] The precise mechanism of its effect, however, is unknown, although deficits in DHA could contribute to inflammatory signaling, apoptosis or neuronal dysfunction in the elderly.[39]

In terms of serum DHA levels, the multivariate-adjusted ORs for MMSE score decline of at least 4 points, and MMSE ⩽23 after 10 years were 1.00 (tertile 1, reference), 0.22 (0.08–0.61) and 0.31 (0.12–0.75) (*P* for trend = 0.004), or 1.00 (tertile 1, reference), 0.11 (0.02–0.58) and 0.17 (0.04–0.74) (*P* for trend = 0.01), respectively. Statistical significance was confirmed, but a dose–response relationship between serum DHA levels and cognitive decline was not observed. One of the possibilities for this finding is that serum DHA concentrations in our sample were substantially higher than the levels seen in Caucasian subjects,[33] and these higher blood levels of DHA might be above the threshold level to detect any effect on cognitive decline. In most previous studies of Caucasians, the mean DHA blood levels were in the lowest tertile seen in this study.[33,34] In addition, DHA/EPA supplementation trials in Caucasian subjects whose serum DHA/EPA levels were substantially lower demonstrated essentially no benefit of DHA on cognitive impairment.[22,23] One of the reasons these intervention studies failed might be due to the short duration used to examine the effectiveness of DHA/EPA on cognitive performance. In contrast, Japanese subjects, who have a normally high exposure to high DHA/EPA concentrations, might show different findings. No previous studies that we are aware of have examined serum DHA levels and cognitive decline among the people whose serum DHA/EPA levels were high. Hence, we cannot compare our findings with previous studies.[24,25] Our study presents the possibility that low DHA levels formed over time in blood are a risk factor for cognitive decline rather than that high DHA levels are a protective factor against cognitive decline among the population whose ordinary exposure to DHA/EPA concentrations is high.

Although the precise reason that the OR of the highest tertile in serum DHA was higher than that of the second tertile is unknown, we believe that one possible explanation is that the number of cases was too small. In fact, multiple-adjusted MMSE scores after 10 years according to tertiles of serum DHA were 27.47 (tertile 1), 27.90 (tertile 2) and 27.68 (tertile 3) and did not reach statistical significance (ANCOVA $P = 0.17$, P for trend = 0.32) because the number of cases was too small and no differences in MMSE scores could be detected. To address the small number of subjects, we performed subanalyses to examine the relationships between baseline serum DHA concentration and follow-up MMSE score using Pearson's correlation coefficients ($n = 430$). Even after controlling for age at baseline, no significant positive correlations between serum DHA concentrations and MMSE score at follow-up were observed (partial correlation coefficient $r = 0.029$, $P = 0.55$).

Dietary intakes might belie the association between serum DHA/EPA and MMSE score; for example, subjects with an MMSE score <23 might eat less of the traditional Japanese diet that includes high intakes of fish and rice, or eat more of the western diet that includes high intakes of meat and dairy products[40] compared with subjects with MMSE scores ⩾24. Recently, dietary patterns characterized by a high intake of soybeans, vegetables, algae, and milk and dairy products and a low intake of rice were reported to be associated with reduced risk of dementia in the general Japanese population.[41] However, in our study, subjects with an MMSE score ⩽23 had less intake of DHA (543.0 vs 590.3 mg/day, $P = 0.07$), significantly less intake of fat and vegetables and greater intake of fruits and sweets compared with subjects with an MMSE score⩾24. Fish and shellfish intake between the two groups were not statistically different (113.6 vs 102.2 g/day, in Table 2). To eliminate the effects of dietary intake including sugar, sweets, fruits, fat and vegetables on MMSE decline, we performed multiple logistic regression analysis further adjusted for intakes of sugar, sweets, fruits, fat and vegetables. The association between serum DHA levels and MMSE decline held up even after controlling for these food intakes (data not shown). Hence, no specific dietary pattern or food intake seemed to bias the association between serum DHA/EPA and MMSE score.

Several limitations to the present study warrant consideration. First, we assessed cognitive function only using a general cognitive test, that is, the MMSE. Although the MMSE is widely used as a brief screening test for dementia, it could be affected by demographic variables such as educational level. Among older patients with a college education living in the United States, the MMSE cutoff score of 27 (sensitivity, 0.69; specificity, 0.91) or 28 (sensitivity and specificity, 0.78) has been shown to be better for detecting cognitive dysfunction compared to the value of ⩽23 used in this study (sensitivity, 0.66; specificity, 0.99).[42] Among our Japanese sample, 52% (224/430) had an education level of 13 years or more. Therefore, the MMSE cutoff point of ⩽23 may be inadequate to assess cognitive impairment. On the basis of this limitation, we used the other cutoff score that was (1) a decline of at least 4 points in MMSE score from the second to seventh wave (Table 3) and (2) an MMSE cutoff score of 28 in a subanalysis. The former analysis was consistent with the results when we used the MMSE cutoff point of ⩽23. However, in the latter subanalysis, an MMSE score ⩽27 was seen in 36% of our Japanese sample (118/326) in the seventh wave, although no significant association was observed between serum DHA/EPA levels and cognitive decline (data not shown). Because of the lack of a sufficient number of cases, when the serum DHA levels were divided into quartiles or quintiles, a few categories contained only one case, although there were still statistically significant findings in a few categories (OR of the fourth quartile: 0.21, $P = 0.05$, OR of the third quintile: 0.11, $P = 0.07$, data not shown).

Second, serum FA concentrations were assessed from a single blood sampling. However, Kobayashi *et al.* examined correlations between serum phospholipid FA levels collected twice and FA intake assessed from 7-day weighted dietary records among 87 Japanese men, and reported that a single measurement of serum phospholipids was a useful biomarker of n-3 PUFA.[8] Although that study used serum phospholipids, Ogura *et al.* reported that PUFA levels in plasma and erythrocyte phospholipids were nearly identical among 75 Japanese patients admitted for non-malignant diseases.[43] Third, attrition bias may have affected our results. Compared with included subjects, subjects excluded from the analyses were older, more likely to be current smokers, and more likely to have a history of hyperlipidemia and diabetes. Hence, excluded subjects might have been less healthy than subjects included in the final analysis. However, mean serum EPA or DHA among subjects excluded from the analyses was higher than those among subjects with an MMSE score ⩽23, and our results do not necessarily mean that subjects with lower serum EPA or DHA levels were more likely to drop out during the follow-up period. Fourth, DHA and EPA intake/serum levels among Japanese subjects are substantially higher than those of Caucasian subjects,[18–21] and the tissue n-3/n-6 ratio that would alter

eicosanoid patterns[44] might also differ between these groups. Furthermore, genetic factors, including APOE4, might also modify the metabolism of n-3 PUFA.[45] However, we could not assess the n-3/n-6 ratio or genetic factors in this study.

The main strengths of the present study are as follows: (1) the long average follow-up period of 10 years; (2) the use of an older sample of randomly selected age- and sex-stratified non-institutionalized individuals from the community; and (3) the use of serum FA levels to assess DHA or EPA status. Furthermore, a certain level of serum DHA is modifiable through the consumption of fish or dietary supplements in DHA.[46] Recently, red blood cell levels of DHA plus EPA were reported to be explained by DHA plus EPA intake (25%), heritability (24%) and fish oil supplementation (15%) in the Framingham Heart Study.[47] In our Japanese sample ($n=430$), Pearson's correlation coefficient between serum DHA and DHA intake assessed by a 3-day dietary record was 0.18 ($P<0.01$, data not shown). This finding means that serum DHA levels are an adjustable factor to some extent.

In conclusion, the findings of this study give some indication that a moderately high level of serum DHA among the Japanese, whose DHA and EPA intake/serum DHA/EPA levels are higher than among Caucasians, might prevent cognitive decline among elderly, community-dwelling Japanese individuals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We wish to express our sincere appreciation to the study participants and our colleagues in the NILS-LSA for completing the survey for this study. This work was supported in part by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (22790584 to RO) and Research Funding for Longevity Sciences from the National Center for Geriatrics and Gerontology, Japan (25-22 to RO).

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Geriatrics Gerontology Medline Indexed

Geriatr Gerontol Int 2014; 14: 354–361

ORIGINAL ARTICLE EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Six-year longitudinal changes in body composition of middle-aged and elderly Japanese: Age and sex differences in appendicular skeletal muscle mass

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Aim: Little is known about longitudinal changes of body composition measured by dual-energy X-ray absorptiometry (DXA) in middle-aged and elderly individuals. We evaluated longitudinal changes of body composition, and age and sex differences in appendicular skeletal muscle mass.

Methods: Participants were 1454 community-dwelling Japanese men and women aged 40–79 years. Body composition at baseline and 6-year follow up was measured by DXA.

Results: Fat increased significantly in men of all ages, and in women aged in their 40s and 50s. Among men, arm lean tissue mass (LTM) changed by 0.9%, −0.5%, −1.4% and −3.7%, respectively, for the 40s to the 70s, and decreased significantly in the 60s and 70s. Leg LTM in men changed by −0.4%, −1.3%, −1.7% and −3.9%, respectively, and decreased significantly from the 50s to the 70s. Compared with the preceding age groups, significant differences were observed between the 60s and 70s in arm and leg LTM change in men. Among women, arm LTM changed by 0.7%, 0.2%, 1.6% and −1.5%, respectively, which was significant in the 60s and 70s. Leg LTM decreased significantly in all age groups of women by −2.0%, −2.8%, −2.4% and −3.9%, respectively. With respect to sex differences, leg LTM loss rates were significantly higher in women than men at the 40s and 50s.

Conclusions: Longitudinal data suggest that arm and leg LTM decreased markedly in men in their 70s, and leg LTM had already decreased in women in their 40s. **Geriatr Gerontol Int 2014; 14: 354–361.**

Keywords: aging, appendicular skeletal mass, body composition, longitudinal study.

Introduction

Significant changes in body composition occur with aging, and these changes greatly affect health and physical function. Cross-sectional studies have suggested that skeletal muscle mass decreases with age,[1–3] and that fat mass increases linearly or curvilinearly with age.[4,5] Sarcopenia, age-associated loss of skeletal muscle mass,[6,7] is correlated with functional impairment and disability.[8,9] In advanced countries, where the elderly population is rapidly growing, the prevention of sarcopenia is important, and changes in appendicular skeletal muscle mass with aging need to be clarified to develop appropriate measures for sarcopenia.

Metter *et al.* reported that the relationship between muscle quality and age is dependent on how muscle is estimated, and on whether subjects are studied cross-sectionally or longitudinally.[10] Most studies dealing with body composition changes with aging have been cross-sectional, and their results might not reflect actual changes with aging. There have been some longitudinal reports of body composition using dual-energy X-ray absorptiometry (DXA)[11–14] or other methods,[15,16] but the number of participants and their age range were limited. With respect to evaluation, previous studies have reported that DXA is an accurate method for measuring body composition.[17–19] To date, there have been no

Accepted for publication 20 May 2013.

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large-scale, population-based studies using DXA to evaluate longitudinal changes of body composition from middle age. In the present study, 6-year longitudinal changes in body composition measured by DXA were examined, and sex and age group differences in appendicular skeletal muscle mass changes were evaluated in middle-aged and elderly Japanese individuals.

Methods

Study sample

The data of the present study were collected as part of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA). NILS-LSA is a population-based, prospective cohort study of aging and age-related diseases with follow up of the participants every 2 years. Participants in the NILS-LSA were randomly-selected age- and sex-stratified individuals selected from the pool of independent residents in the NILS neighborhood, Obu City and Higashiura Town, Aichi Prefecture, in central Japan. The age at the first wave ranged from 40 to 79 years. Details of the NILS-LSA have been given elsewhere.[20] A total of 2258 men and women took the examination by DXA at the first wave (from April 1998 to March 2000) of NILS-LSA. Among them, a total of 1469 participants (748 men and 706 women) underwent the evaluation by DXA in the fourth wave (from June 2004 to July 2006). We used the data of the participants who attended both investigations. There were various reasons why the participants could not be followed up; for example, transfer to another area, drop out for personal reasons, or death. Participants who used androgen and estrogen drugs were excluded. The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all participants.

Anthropometric variables

Bodyweight was measured to the nearest 0.1 kg using digital scales, height was measured to the nearest 0.1 cm using a stadiometer, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Body composition

Body composition, fat mass, lean tissue mass (LTM), and bone mineral content (BMC) at baseline and 6-year follow up were assessed by DXA (QDR-4500; Hologic, Madison, OH, USA). LTM is equal to the fat-free mass minus BMC. Arm and leg LTM compartments were examined. Absolute change in each body composition measure was calculated as follow-up value minus baseline value. Percentage of change in each body composition measure was calculated as follows:

$$\text{Percent change} = (\text{absolute change value}/\text{baseline value}) \times 100$$

Total physical activity

Participants responded to a self-administered questionnaire, and were interviewed according to an assessment method for leisure time and on-the-job physical activity within the last 12 months by trained interviewers.[21] Each activity was classified into four categories according to the intensity as determined by metabolic equivalent scores by duration in minutes. The total physical activity score was calculated by summing physical activity scores during leisure time, on the job, sleep and residual time.

Prevalence of diseases and smoking status

Prevalence of diseases (cerebrovascular disease, heart disease and diabetes mellitus) and smoking status at baseline were determined by a questionnaire.

Statistical analysis

Data were analyzed with the Statistical Analysis System (SAS) release 9.13 (SAS Institute, Cary, NC, USA). Differences between baseline and follow-up characteristics were tested using paired *t*-tests. The χ^2-test was carried out to compare smoking status and disease prevalence between men and women. The participants were analyzed by age decade groups (40s, 40–49 years; 50s, 50–59 years; 60s, 60–69 years; 70s, 70–79 years at baseline). Changes in body composition over time in each age group were tested using paired *t*-tests. Sex and age group differences in arm and leg LTM were analyzed using the general linear model (GLM). Another GLM, with adjustment for confounding factors, the presence of diseases (cerebrovascular disease, heart disease and diabetes mellitus), smoking status and total physical activity at baseline, was also evaluated. Values of $P < 0.05$ were considered to show statistical significance.

Results

Mean ages at baseline were 57.2 ± 9.9 years in men and 56.2 ± 9.9 years in women. The mean follow-up interval was 6.3 ± 0.3 years both in men and women. The participants' anthropometric variables, total physical activity, smoking status and prevalence of diseases at baseline are shown in Table 1.

Weight and height were significantly higher in men than women, and there was no difference in BMI. Total

Table 1 Baseline anthropometric variables, total physical activity, and prevalence of smoking status and diseases

	Men	Women
Weight (kg)	63.4 ± 8.4**	53.6 ± 7.5
Height (cm)	165.3 ± 6.0**	152.3 ± 5.5
BMI (kg/m^2)	23.2 ± 2.5	23.1 ± 2.9
Total physical activity (*10^3*METS*min/y)	705.3 ± 93.5**	736.5 ± 68.8
Smoking status (%)		
Never	22.9**	90.5
Past	41.0**	2.6
Current	36.1**	7.0
Prevalence of disease (%)		
Cerebrovascular disease	2.0*	0.7
Heart disease	9.9	7.8
Diabetes mellitus	7.1*	3.1

Values for anthropometric variables and total physical activity are mean ± standard deviation. Differences between men and women were evaluated by *t*-test or χ^2-test. Significantly different from women, $^{**}P < 0.01$, $^{*}P < 0.05$. METS, metabolic equivalents.

physical activity was significantly greater in women than in men. There were significant differences in smoking status, and prevalence of cerebrovascular disease and diabetes between men and women.

Table 2 shows changes in body composition by age groups in men. A significant weight increase was observed from the 40s to 60s age groups, but not for the 70s age group. There were significant increases in fat for all age groups. A significant decrease in BMC was observed in the 70s age group. Total LTM increased in the 40s and 50s age groups, and decreased in the 70s age group. Arm LTM increased in the 40s age group, and decreased in the 60s and 70s age groups. Leg LTM decreased significantly from the 50s to the 70s age group.

Table 3 shows changes in body composition by age groups in women. Significant increases in weight in the 40s and 60s age groups, and in fat in the 40s and 50s age groups were observed. There were significant decreases in BMC in all age groups. Total LTM increased significantly in the 60s age group. Arm LTM increased significantly in the 60s age group and decreased in the 70s age group. Leg LTM decreased significantly in all age groups.

Figure 1 presents the percentage change of arm (a) and leg (b) LTM in men. Percentage changes of arm LTM were 0.9%, −0.5%, −1.4% and −3.7%, respectively. Compared with the preceding age group, there were significant differences between the 40s and 50s age groups ($P < 0.05$), and between the 60s and 70s age groups ($P < 0.01$) in men. When adjusting for confounding factors, the significant difference between the 60s and 70s age groups continued, but that between the 40s and 50s age groups disappeared in men.

Percentage changes of leg LTM in men were −0.4%, −1.3%, −1.7% and −3.9%, respectively. Compared with the preceding age group, there were significant differences between the 60s and the 70s age groups ($P < 0.01$), and this did not change after adjustment for confounding factors.

Figure 2 presents percentage change of arm (a) and leg (a) LTM in women.

Percentage changes of arm LTM were 0.7%, 0.2%, 1.6% and −1.5%, respectively. Compared with the preceding age group, there was a significant difference between the 60s and the 70s age groups ($P < 0.01$) in women, and this did not change after adjustment for confounding factors.

Percentage changes of leg LTM in women were −2.0%, −2.8%, −2.4% and −3.9%, respectively. There were no differences between the adjacent age groups in women.

With respect to sex differences of arm LTM within the same age groups, men in the 60s and 70s age groups had a relatively greater percentage decrease change than women ($P < 0.01$), and when adjusting for confounding factors, the significant differences persisted. With respect to sex differences of leg LTM within the same age groups, women in the 40s and 50s age groups had a significantly greater percentage decrease change than men ($P < 0.01$), and after adjustment for the confounding factors, the significance of these differences did not change.

Discussion

The present study showed the 6-year longitudinal changes in body composition measured by DXA in men

Table 2 Changes in body composition by age group during the 6-year follow-up period in men

	Age group	Baseline (kg)	Change (kg)	*P*-value	Percent change (%)
Weight	40s	66.8 ± 8.5	1.9 ± 3.4	<0.0001	2.7
	50s	64.4 ± 7.7	1.5 ± 3.2	<0.0001	2.4
	60s	61.5 ± 7.8	1.5 ± 3.7	<0.0001	2.6
	70s	58.7 ± 7.7	0.4 ± 3.2	0.15	0.6
Fat	40s	14.1 ± 4.2	1.1 ± 2.2	<0.0001	8.4
	50s	13.4 ± 3.8	1.2 ± 2.2	<0.0001	10.4
	60s	13.5 ± 3.8	1.3 ± 2.4	<0.0001	11.4
	70s	13.0 ± 3.7	1.0 ± 2.1	<0.0001	8.3
BMC	40s	2.37 ± 0.29	−0.01 ± 0.06	0.09	−0.3
	50s	2.31 ± 0.30	−0.01 ± 0.06	0.07	−0.4
	60s	2.18 ± 0.30	−0.01 ± 0.07	0.05	−0.5
	70s	2.08 ± 0.26	−0.04 ± 0.08	<0.0001	−1.9
LTM	40s	50.4 ± 5.4	0.8 ± 1.6	<0.0001	1.6
	50s	48.6 ± 4.8	0.3 ± 1.6	0.002	0.7
	60s	45.8 ± 4.7	0.2 ± 1.8	0.08	0.5
	70s	43.5 ± 4.8	−0.5 ± 1.8	0.003	−1.3
Arm LTM	40s	5.97 ± 0.75	0.05 ± 0.34	0.03	0.9
	50s	5.73 ± 0.69	−0.04 ± 0.31	0.08	−0.5
	60s	5.35 ± 0.67	−0.08 ± 0.29	0.0002	−1.4
	70s	5.01 ± 0.67	−0.18 ± 0.30	<0.0001	−3.7
Leg LTM	40s	15.89 ± 1.97	−0.05 ± 0.74	0.32	−0.4
	50s	15.08 ± 1.82	−0.21 ± 0.79	<0.0001	−1.3
	60s	14.14 ± 1.69	−0.25 ± 0.89	<0.0001	−1.7
	70s	13.45 ± 1.81	−0.52 ± 0.73	<0.0001	−3.9

$n = 204$ in age group 40s, $n = 234$ in age group 50s, $n = 196$ in age group 60s, $n = 114$ in age group 70s. Values of baseline and change are mean ± standard deviation). Significant changes from baseline were evaluated by paired *t*-test. BMC, bone mineral content; LTM, lean tissue mass.

and women aged 40–79 years. Weight and fat mass increased or did not change in both men and women in all age groups. Among men, marked decreases in both arm and leg LTM were found in the 70s age group. Among women, leg LTM decreased significantly in all age groups. The rates of loss in arm LTM were larger in men than in women in the 60s and 70s, the elderly age groups. In contrast, the rate of loss in leg LTM was larger in women than in men in the 40s and 50s, the early stage, middle-aged groups.

Previous cross-sectional studies suggested that appendicular skeletal muscle mass decreases with age in both sexes.[1,3,22] However, these cross-sectional studies show indirect evidence of age-related changes.[23] There have been several longitudinal studies of body composition measured by DXA. Gallagher *et al.* reported that there were significant decreases in leg skeletal muscle mass, and tendencies for a loss of arm skeletal muscle mass in healthy men and women aged over 60 years during an average 4.7-year follow up.[13] Visser *et al.* showed that, over a 2-year period, appendicular skeletal muscle mass decreased −0.8% in men, but not in women aged 70–79 years, and leg lean soft tissue mass decreased significantly in both sexes.[12] Zamboni *et al.* found that significant losses of leg skeletal muscle were observed in stable-weight, elderly (68–78 years) men and women over a 2-year period.[13] However, in most of these studies, the participants were aged over 60 years. In the present study, we showed the changes in body composition in participants of a wide age range, 40–79 years. In the 60s and 70s age groups, except for the arm LTM in the 60s age group in women, there were significant decreases of arm and leg LTM in men and women. Already in the 40s and 50s age group, there were significant decreases in leg LTM in women.

With respect to sex differences, previous cross-sectional[1,5] and longitudinal studies[11,13,14] reported that the rates of decrease in appendicular lean mass were greater for men than for women. The present study showed that the rates of loss in arm LTM were greater in men than in women in the 60s and 70s age groups. However, the rate of loss in leg LTM was greater in women than in men in the 40s and 50s age groups, and no significant sex difference was found in the 60s and 70s age groups. Previous longitudinal studies evaluated the differences using absolute change,[11,12,14] whereas the

Table 3 Changes in body composition by age group during the 6-year follow-up period in women

	Age group	Baseline (kg)	Change (kg)	*P*-value	Percent change (%)
Weight	40s	54.8 ± 7.9	1.2 ± 3.9	<0.0001	2.1
	50s	54.4 ± 6.9	0.3 ± 3.0	0.19	0.5
	60s	53.3 ± 7.1	0.5 ± 2.8	0.02	0.9
	70s	49.9 ± 7.8	−0.2 ± 3.1	0.60	−0.4
Fat	40s	16.5 ± 4.6	1.2 ± 2.6	<0.0001	8.0
	50s	17.2 ± 4.4	0.5 ± 2.3	0.001	3.6
	60s	17.7 ± 4.5	0.3 ± 2.0	0.06	2.1
	70s	16.2 ± 4.7	0.02 ± 2.3	0.95	0.5
BMC	40s	1.98 ± 0.25	−0.11 ± 0.13	<0.0001	−5.6
	50s	1.77 ± 0.26	−0.13 ± 0.10	<0.0001	−3.7
	60s	1.54 ± 0.23	−0.06 ± 0.06	<0.0001	−3.7
	70s	1.36 ± 0.23	−0.06 ± 0.06	<0.0001	−4.4
LTM	40s	36.3 ± 4.2	0.1 ± 1.8	0.24	0.3
	50s	35.5 ± 3.4	−0.1 ± 1.3	0.18	−0.3
	60s	34.0 ± 3.5	0.2 ± 1.2	0.008	0.7
	70s	32.4 ± 3.8	−0.1 ± 1.2	0.34	−0.4
Arm LTM	40s	3.56 ± 0.54	0.02 ± 0.28	0.22	0.7
	50s	3.53 ± 0.44	0.003 ± 0.22	0.85	0.2
	60s	3.43 ± 0.45	0.05 ± 0.23	0.003	1.6
	70s	3.24 ± 0.47	−0.05 ± 0.20	0.02	−1.5
Leg LTM	40s	11.19 ± 1.64	−0.22 ± 0.63	<0.0001	−2.0
	50s	10.88 ± 1.34	−0.31 ± 0.57	<0.0001	−2.8
	60s	10.42 ± 1.33	−0.25 ± 0.48	<0.0001	−2.4
	70s	9.91 ± 1.36	−0.39 ± 0.51	<0.0001	−3.9

$n = 216$ in age group 40, $n = 218$ in age group 50, $n = 177$ in age group 60, $n = 95$ in age group 70. Values of baseline and change are mean ± SD (standard deviation). Significant changes from baseline were evaluated by paired t-test. BMC, bone mineral content; LTM, lean tissue mass.

present study used a relative index, the percent change. In the present study, comparisons using the absolute change in mass were also made, but the results for the sex differences showed almost the same tendency (data not shown). As there were many differences among the studies in the participants' characteristics, race, lifestyle and study design, further examination is required to clarify these differences.

The present study showed that there were significant decreases in leg LTM, but not in arm LTM, among women in the 40s to 60s age groups. Lynch *et al.* reported that, with increasing age, leg muscle quality declined ~20% more than arm muscle quality in women.[24] Based on these results, changes in muscle mass or function might differ between arms and leg muscles in women; decreases were apparent in the leg muscles. Leg muscle mass is closely associated with functional performance[14,25] and, in general, women have significantly less skeletal muscle mass than men.[1,2,23] There were several reports that frailty was higher in women than men in the elderly.[26,27] Therefore, it might be especially important for women to prevent the decrease of leg LTM from middle age. Some studies have suggested the relationship between menopause and loss of muscle mass,[28–30] and that estrone predicted loss of appendicular muscle mass.[31] The early onset of leg LTM decrease of women in the present study might be associated with the menopausal transition.

For evaluating sarcopenia, skeletal muscle mass index (SMI), obtained by dividing appendicular skeletal muscle mass by height squared, is often used.[8] Appendicular skeletal muscle mass was measured as the sum of the LTM for arms and legs. In the present study, both arm and leg LTM significantly decreased at the same time in the 70s age group in men. In contrast, in women, the time of LTM decrease differs in arms and legs. Therefore, in order to evaluate the decrease of muscle mass in women more clearly, it might be better to use leg LTM alone. Further detailed analyses of LTM in women would be necessary in future studies.

Regarding fat mass change, Hughes *et al.* reported that fat mass increased in the elderly, but the increase in women was attenuated with advancing age.[15] Other studies showed that fat mass increased significantly in elderly men and decreased non-significantly in elderly women.[11,12] As in these previous studies, the present

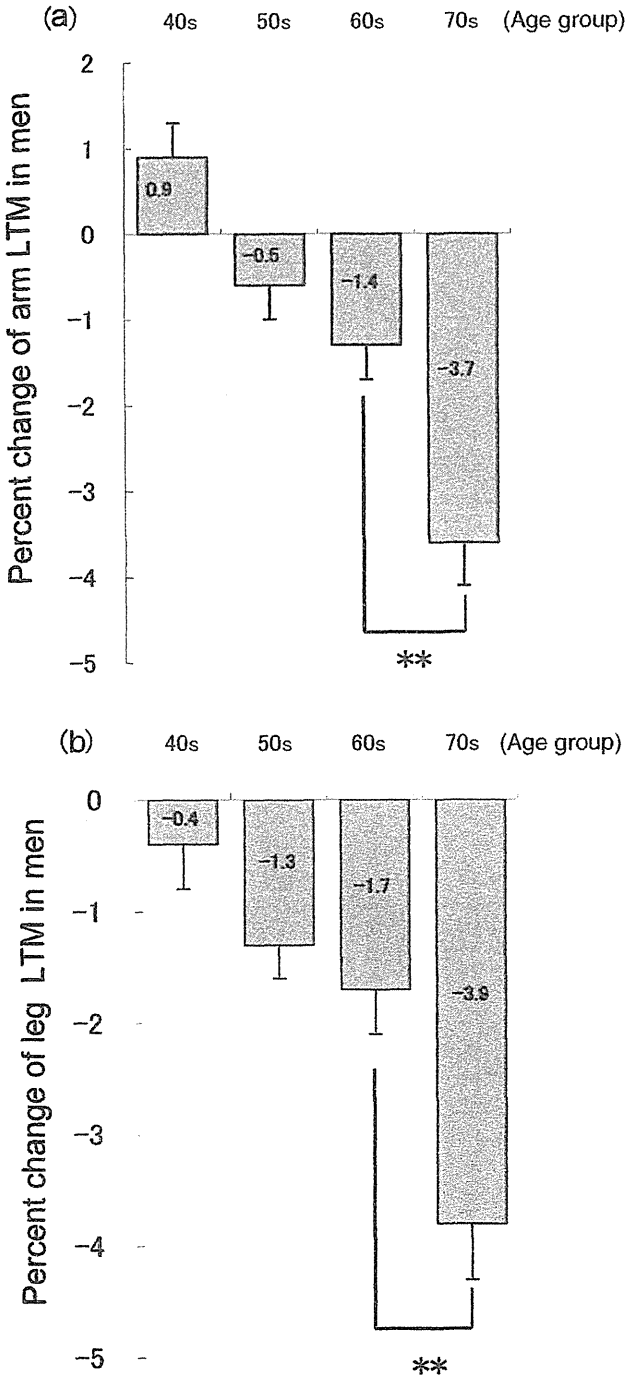

Figure 1 Percentage change of (a) arm and (b) leg lean tissue mass (LTM) during the 6-year follow-up period by age group in men. Values are mean ± standard error of the mean. $^{**}P < 0.01$, compared with the preceding age group adjusting for confounding factors.

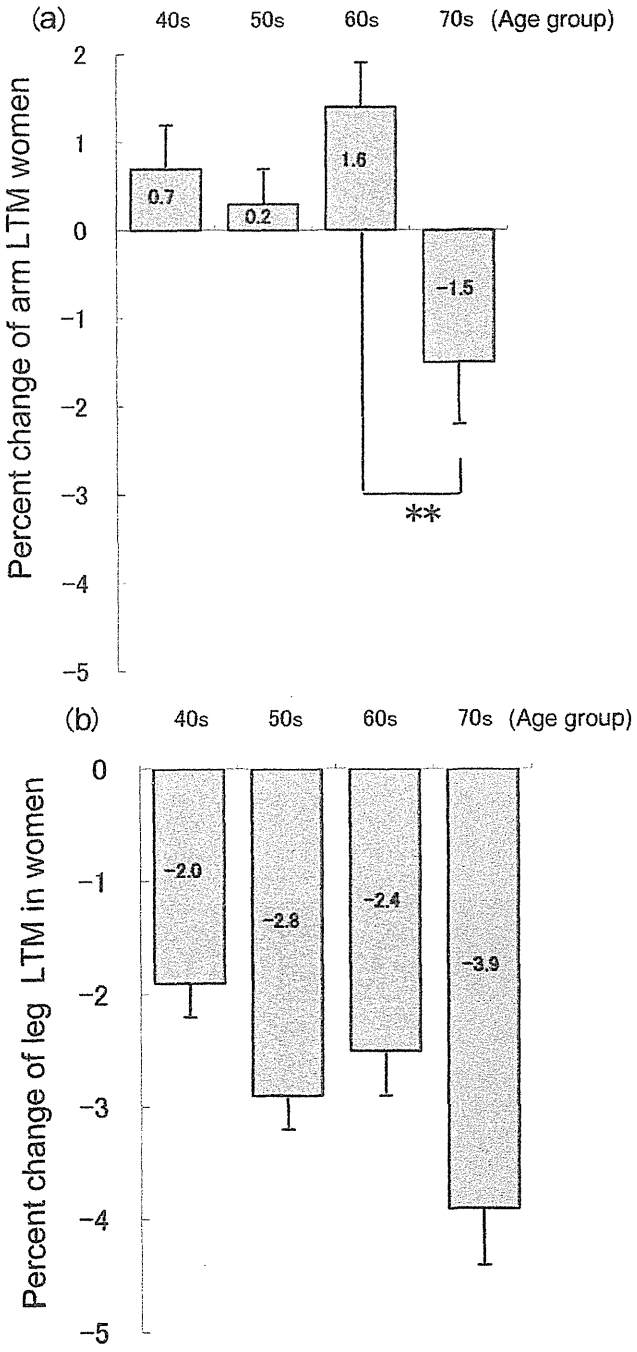

Figure 2 Percentage change of (a) arm and (b) leg lean tissue mass (LTM) during the 6-year follow-up period by age group in women. Values are mean ± standard error of the mean. $^{**}P < 0.01$, compared with the preceding age group adjusting for confounding factors.

study showed that fat mass increased in all age groups in men and that, in women, it increased in the 40s and 50s, but it did not change thereafter.

The strengths of the present study are the large age- and sex-stratified sample size, the wide range of ages and the 6-year follow-up period. This is the first study to report the longitudinal changes of body composition, measured by DXA in 40- to 79-year-old Japanese subjects. With respect to race, so far, no longitudinal study of Asians has been reported, and there has not been sufficient research on racial differences. It will be necessary to clarify racial differences and consider various environmental factors in future studies.

Although loss of muscle mass is associated with decline in strength[32,33] and disability,[8] there were reports