

that strength decline in older adults is much more rapid than loss of muscle mass,³² and that muscle strength is more important than muscle mass in estimating mortality risk.^{9,34,35} Recently, the European Working Group on Sarcopenia in Older People recommended that the presence of both low muscle mass and low muscle function (strength or performance) be used.³⁶ Thus, to measure not only muscle mass, but also muscle strength, might be important for the evaluation of actual activity, especially in the elderly.

As several reports have suggested differences of body-weight and the prevalence of obesity by birth cohort,^{37,38} there might also be differences of changes in body composition by birth cohort. In addition, although the participants of the present study were randomly selected, they were relatively well-functioning men and women able to participate in the study. Therefore, the results might not accurately represent changes with aging in the general population.

In conclusion, we evaluated 6-year longitudinal changes of body composition in middle-aged and elderly participants. Remarkable decreases of arm and leg LTM in men in the 70s age group, and early decreases of leg skeletal muscle mass already in the 40s age group in women were found. We believe that these results might offer important information with respect to prevention of sarcopenia, and improving the health-related quality of life in older adults.

Acknowledgments

We thank the participants and the staff of the National Institute for Longevity Sciences-Longitudinal Study of Aging.

This work was supported by a Grant-in-Aid for Young Scientists (B) (19790439) from the Ministry of Education, Culture, Sports, Science and Technology.

Disclosure statement

The authors declare no conflict of interest.

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■ プロシーディング 14

地域在住中高年者のプロリン摂取量が知能に及ぼす影響に関する縦断的研究

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要約

【目的】本研究では、地域在住中高年者を対象とし、知能の10年間の経年変化、特に知識量に着目しプロリン摂取量、年齢が及ぼす影響を明らかにすることを目的とした。

【方法】対象者は「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)」の第2次調査に参加した中高年者2,024名(男性1,031名, 女性993名, 40-81歳)。その後、約2年間隔で行なわれた全5回の追跡調査で測定した知能得点(WAIS-R-SF「知識」得点)を目的変数とし、プロリン摂取量(g/1,000kcal/日:3日間の食事記録調査より推定)、第2次調査からの経過年数、年齢の主効果、プロリン摂取量×年齢、プロリン摂取量×経過年数、プロリン摂取量×年齢×経過年数の交互作用項、調整変数(BMI, 抑うつ)を固定効果とし、個人の切片と傾きを変数効果とする線形混合効果モデルを用いて性別に検討した。

【結果】プロリン摂取量と経過年数の交互作用項に着目したところ、男女ともに動物性食品からのプロリン摂取量×年齢×経過年数の交互作用が有意であった($p < 0.0001$)。10年間の知識得点の推移は、男女とも40, 50歳で、動物性プロリンの多摂取群と少摂取群との傾きの差が有意であり、多摂取群の知識得点が高い増加していたが、60, 70歳では、傾きに有意な差は認められなかった。女性の60, 70歳では、プロリン多摂取群で高い得点を維持していた。一方、植物性食品由来のプロリンでは知識得点と有意な関連はなかった。

【考察および結論】本研究で検討したプロリンは、動物性と植物性で知識得点に与える影響が異なっており、体内での利用効率や動態が異なることが示唆された。男女ともに中年者では動物性プロリンを多く摂取すると知識の獲得および維持に有効である可能性が示され、さらに、女性では高齢でも動物性食品よりプロリンを多く摂取することにより高い得点を維持していた。

Key words プロリン摂取量, 知識量, 一般地域住民, 長期縦断研究, 動物性食品

1 目的

高齢期の知的能力を維持することは、高齢者のQOLを支えるだけでなく社会保障や介護の負担の軽減に繋がる重要な課題である。基礎研究より、肉類や魚介類、乳製品に多く含まれるアミノ酸であるプロリンが、アルツハイマー病のミトコンドリア機能障害や細胞アポトーシスを防ぐ可能性が報告されている¹⁾が、一般住民の日常的に摂取するプロリンの量や食品群別寄与率、プロリンと知能との関連は不明である。そこで本研究では、地域在住中高年者の知的能力、特に知識量に着目し、10年間の長期縦断データを用いて、プロリン摂取量、年齢がその

後の知能の経時変化にどのような影響を及ぼすかを明らかにすることを目的とした。

2 方法

1) 対象者

対象者は「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 (National Institute for Longevity Sciences - Longitudinal Study of Aging: NILS-LSA)」^{2,3)}の第2次調査(2000-02年, 以後ベースライン)に参加し、その後、約2年間隔で行なわれた第3次調査(2002-04年)から第7次調査(2010-12年)までの全5回の追跡

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 2013年12月2日 受領 2014年2月28日 受理

調査に1回以上参加した地域在住中高年者である。

本研究ではベースライン時参加者2,259名のうち、認知障害を有する可能性のある者を除外し (MMSE \leq 23), 下記の検査を完了した2,024名 (40~81歳: 男性1,031名, 女性993名) ののべ9,463件のデータを用いた。

尚, NLS-LSAは年齢および性で層化無作為抽出された地域住民を対象とした縦断的コホート調査であり, 国立長寿医療研究センター倫理委員会の承認を得た後, 事前に説明会を行い, 文書による同意の得られた者を対象とし行われている。

2) ベースライン時のプロリン摂取量

独自に構築した「NLS食品アミノ酸成分表2010」⁴⁾を用いて, ベースラインでの3日間食事秤量記録調査⁵⁾結果から, 摂取エネルギー 1,000kcalあたりの動物性プロリン, 植物性プロリンの一日平均摂取量 (g/1,000kcal/日) を推定した。

3) 知識量 (ベースライン, および各追跡調査時)

ウェクスラー成人知能検査改訂版⁶⁾ (Wechsler Adult Intelligence Scale-Revised : WAIS-R) 簡易実施法下位尺度の「知識 (得点範囲 0~29, 一般的な知識量の指標)」を用いた。

4) その他の調整項目 (ベースライン時)

調整変数として, Body Mass Index (BMI: kg/m²), 抑うつ検査得点, 教育年数をモデルに投入した。BMIは, 身長, 体重の測定値より算出した。抑うつ検査には, CES-D (Center for Epidemiologic Studies Depression Scale; 20項目, 4尺度, 得点範囲0-60点) を用いた。教育年数は自記式質問票により回答を得た。

5) 解析方法

プロリン摂取量が知能に及ぼす影響に着目し, ベースラインおよび各追跡調査時に測定した「知識」得点を目的変数とし, 個人の切片と傾きを変量効果とする線形混合効果モデルにおいて, 固定効果の異なる3つのモデルで性別に検討した。モデル1では, 動物性または植物性プロリンの一日平均摂取量 (g/1,000kcal/日), ベースライン調査からの経過年数, ベースライン調査時の年齢, BMI, CES-D得点を投入し, モデル2ではモデル1に教育年数を加え, モデル3ではモデル2に交互作用項としてプロリン摂取量 \times 年齢, プロリン摂取量 \times 経過年数, プロリン摂取量 \times 年齢 \times 経過年数を投入した。

解析には, SAS9.3を用い, 有意水準は5%とした。

3 結果

表1にベースライン時の対象者特性および平均参加回数, 平均最終追跡年数を示した。線形混合効果モデルでの解析結果を表2に示す。

モデル1において, 男女ともに「知識」得点の経年変化に対して動物性プロリン摂取量では有意な主効果を示したが, 植物性プロリン摂取量では有意な関連はなかった (表2)。モデル2では, 「知識」得点と有意な関連があった動物性プロリン摂取量の回帰式に, 教育年数を投入した。男性では, プロリン摂取量および年齢の主効果の有意性が消失した。女性ではプロリン摂取量の主効果は有意であったが, 年齢の主効果は消失した。交互作用項を投入したモデル3では, 男女ともに動物性プロリン摂取量 \times 経過年数および動物性プロリン摂取量 \times 年齢 \times 経過年数の交互作用が有意であった ($p < 0.0001$)。すなわち, 10年間の「知識」得点の推移に対して, 動物性プロリン摂取量の与える影響は経過年数や年齢によって異なることが示された。そこで, 「知識」得点の経年変化の推計値を算出するため, モデル3の回帰式に, 動物性プロリン摂取量の平均+1SD値を多摂取群, 平均-1SDを少摂取群とした摂取量の多寡とベースライン時の各年齢 (40, 50, 60, 70歳) を代入し, ベースライン時と10年後の「知識」の得点を推計した (図1)。調整変数には平均値を代入した。

「知識」得点の10年間の推計値から, 男性の40, 50歳では, 動物性プロリン多摂取群と少摂取群との傾きの差が有意であり, 多摂取群の「知識」得点がより増加していた。女性でも40, 50歳で, 同様に両者の傾きに有意差がみられた。男女ともに60, 70歳では, 傾きに有意差は認められなかった。女性では, 60, 70歳においてプロリン多摂取群が高い得点を維持していた。

一方, 植物性食品由来のプロリンでは「知識」得点と有意な関連はみられなかった。

4 考察および結論

本研究で検討したプロリンは, 動物性食品より多く摂取することにより10年間で「知識」得点をより増加させた。動物性と植物性食品由来のプロリンでは, 「知識」得点の経年変化に与える影響が異なっていた。この結果から, プロリン単体の効果ではなく, 食品や代謝産物に含ま

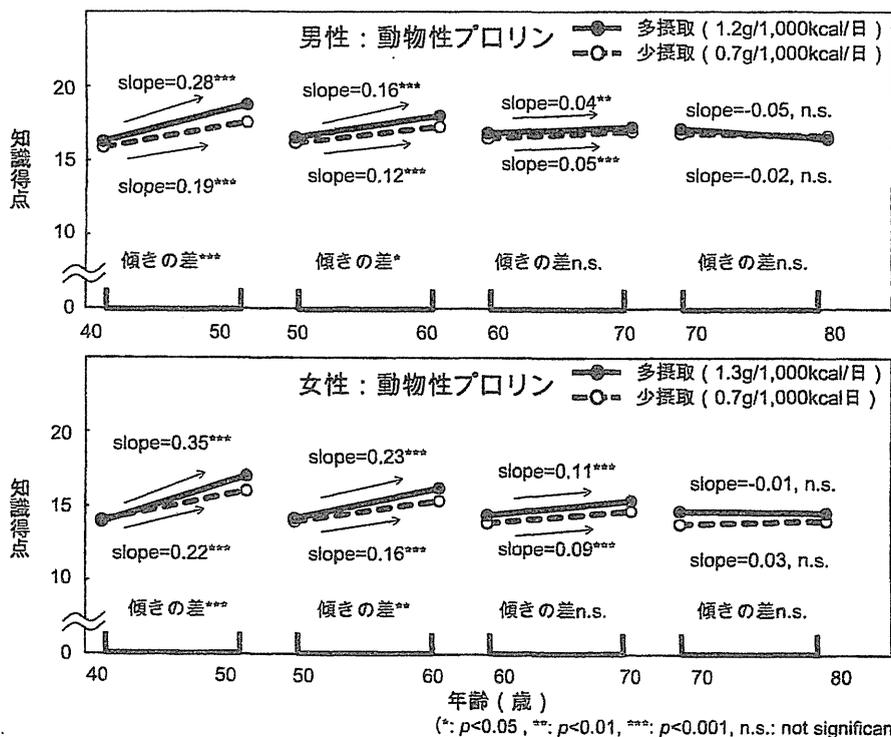
□ 表1 ベースライン時の対象者の特性

		男性 n=1,031	女性 n=993
年齢群	人数 (%)		
40～49歳		249 (24.2%)	238 (24.0%)
50～59歳		269 (26.1%)	267 (26.9%)
60～69歳		265 (25.7%)	253 (25.5%)
70～81歳		248 (24.0%)	235 (23.6%)
年齢	歳	59.3 ± 11.3	59.5 ± 11.1
身長	cm	165.1 ± 6.5	151.9 ± 6.0
体重	kg	63.1 ± 9.4	52.6 ± 8.1
BMI	kg/m ²	23.1 ± 2.8	22.8 ± 3.2
教育歴	年	12.4 ± 2.9	11.5 ± 2.5
CES-D		7.2 ± 6.5	7.5 ± 6.9
栄養素等摂取量 (1日平均摂取量)			
エネルギー	kcal	2,292 ± 392	1,868 ± 327
たんぱく質	g	86.5 ± 16.3	72.8 ± 14.1
動物性たんぱく質	g	46.4 ± 13.5	38.1 ± 11.1
脂質	g	59.6 ± 16.6	52.6 ± 15.1
動物性脂質	g	30.0 ± 11.6	25.2 ± 9.9
炭水化物	g	317.2 ± 62.4	268.5 ± 52.9
ナトリウム	g	4736 ± 1099	4057 ± 911
動物性プロリン	g/1,000kcal	0.96 ± 0.25	1.02 ± 0.29
植物性プロリン	g/1,000kcal	1.06 ± 0.22	1.16 ± 0.24
ウェクスラー成人知能検査改訂版			
推定IQ		109 ± 13	105 ± 13
下位検査得点			
知識		16.6 ± 5.2	13.9 ± 5.5
類似		14.5 ± 5.4	13.6 ± 5.3
絵画完成		12.1 ± 3.1	10.9 ± 3.7
符号		53.4 ± 15.1	54.3 ± 16.3
平均参加回数		4.69 ± 1.78	4.67 ± 1.79
平均最終追跡期間		7.81 ± 3.64	7.77 ± 3.67

□ 表2 プロリン摂取が知能の経年変化に及ぼす影響：線形混合効果モデルの結果

		動物性プロリンでの解析						植物性プロリンでの解析†		
固定効果		モデル1		モデル2		モデル3		モデル1		
		F 値	p 値	F 値	p 値	F 値	p 値	F 値	p 値	
男性	ベースライン時のプロリン摂取量	4.94	0.0264	1.67	0.1961	0.03	0.8521	0.00	0.9502	
	ベースラインからの経過年数	55.65	<.0001	55.35	<.0001	2.67	0.1029	55.71	<.0001	
	ベースライン時の年齢	62.85	<.0001	0.00	0.9628	0.29	0.5895	61.01	<.0001	
	調整変数	BMI	1.68	0.1956	0.27	0.6009	0.34	0.5578	1.84	0.1748
		CES-D	11.87	0.0006	10.56	0.0012	6.07	0.0138	11.97	0.0005
		教育年数			420.92	<.0001	420.06	<.0001		
		プロリン摂取量 × 経過年数					71.52	<.0001		
	プロリン摂取量 × 年齢					0.00	0.9498			
	プロリン摂取量 × 経過年数 × 年齢					107.23	<.0001			
女性	ベースライン時のプロリン摂取量	8.65	0.0033	4.80	0.0285	1.47	0.226	0.82	0.3652	
	ベースラインからの経過年数	117.80	<.0001	117.45	<.0001	2.64	0.1045	117.49	<.0001	
	ベースライン時の年齢	88.27	<.0001	1.72	0.1903	2.54	0.1109	84.77	<.0001	
	調整変数	BMI	6.55	0.0105	5.03	0.025	4.92	0.0266	6.22	0.0127
		CES-D	6.90	0.0087	6.69	0.0097	4.39	0.0362	6.75	0.0094
		教育年数			181.67	<.0001	181.44	<.0001		
		プロリン摂取量 × 経過年数					59.04	<.0001		
	プロリン摂取量 × 年齢					2.58	0.1081			
	プロリン摂取量 × 経過年数 × 年齢					71.69	<.0001			

†: 植物性プロリン摂取量の主効果は、モデル1の解析方法においても「知識」得点に対して有意な影響が認められなかった。そのため、それ以降のモデルでの検討を行わなかった。



□ 図1 動物性プロリン摂取量の違いでの「知識」得点推計値の10年間の経年変化 (上段：男性, 下段：女性) 線形混合効果モデルを用いて推定した。モデル3の回帰式にプロリンは「平均±1SD値」の2値を、年齢はベースライン時40, 50, 60, 70歳の年齢、経過年数はベースラインと10年を代入し、2時点の知能の得点を推計した。

れる生体機能を有するプロリン含有ペプチドの種類や量が、動物性と植物性食品で異なるためと推測した。ヒトでのジペプチド、トリペプチドの吸収メカニズムが明らかになりつつあり⁷⁾、生体機能を有するトリペプチドの効果が期待されている。例えば、乳製品に含まれるラク トトリペプチド（プロリン2分子含有）はACEの働きを阻害し、血圧上昇を抑制する⁸⁾特定保健用食品として承認されている。血管病変の進展抑制は認知症予防と関連することが示されており、認知機能の低下抑制への貢献が期待される。また、コラーゲンペプチドもプロリンやヒドロキシプロリンなどを多く含んでいる。このペプチド（Pro-Hyp）は生体内で線維芽細胞の増殖に関与しているとの報告⁹⁾があり、脳神経、特に海馬神経の修復、形成による認知機能維持の可能性がある。

副解析として、同モデルに動物性食品摂取量（g/1,000 kcal/日）を主効果として投入し「知識」得点への影響を検討したところ、有意な関連は認められなかった。このことから、プロリン含有ペプチドを特異的に含む牛乳やコラーゲンなどの摂取が、中高年期の知識の獲得・維持に有効である可能性が示唆された。

プロリンは、体内で合成されるため非必須アミノ酸に分類されているが、プロリン含有ペプチドは特定の食品にのみ含まれている可能性があり、たんぱく質合成のためのアミノ酸供給源としてだけでなく、特定の生理作用を有する分子として食事から摂取する必要があると考えられる。

しかし、今回の解析では、動物性プロリンを多く含む食品に含まれる他の栄養成分や他因子の関与について否定できない。さらに、「NILS食品アミノ酸成分表2010」はたんぱく質摂取量の94.5%をアミノ酸摂取量で説明する事が可能であるが、アメリカの農務省（USDA: United States Department of Agriculture）の食品成分値のデータや改訂日本食品アミノ酸組成表（昭和61年公表）の古いデータを一部転載していること、置き換え法を用いていることなどから、真のアミノ酸摂取量を推定するには限界がある。また、成分表に記載されているアミノ酸含有量は、季節変動や産地などを考慮したものではないため、推定される摂取量は誤差を含むことも考慮すべ

きである。

結論として、本研究では、男女ともに中年期に動物性プロリンを多く摂取すると知識の獲得および維持に有効である可能性が示された。さらに、女性では高齢でも動物性食品よりプロリンを多く摂取することにより高い得点を維持していた。

付記

本研究の一部は学術研究助成基金助成金（課題番号24790634）により行われた。

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Longitudinal study of effects of proline intake on intellectual decline in community-dwelling middle-aged and elderly Japanese subjects

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The aim of this study was to elucidate the effect of proline intake and age on age-related changes in intelligence (amount of knowledge) over a 10-year period.

Subjects comprised a total of 2,024 middle-aged and elderly individuals (1,031 men, 993 women; 40-81 years) who participated in the 2nd survey (baseline) of the “National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA)” as well as at least one of the five follow-up surveys until the 7th survey. Animal- and plant-derived proline intakes (g/1,000 kcal/day) was estimated based on the 3-day dietary records at baseline. The amount of knowledge at baseline and follow-up survey was determined using the “Information” subscale of the Wechsler Adult Intelligence Scale-Revised short form (WAIS-R-SF). Using the “Information” score at each point as the objective variable, the effects of proline intake, the years from baseline, age at baseline, their interaction terms, and moderator variables (BMI, CES-D score) were investigated by sex using a linear mixed-effects model.

As for changes in “Information” score over the 10-year period, significant differences in slope were seen between the high and low animal proline intake groups at ages 40 and 50 in both sexes, with the scores increasing more greatly in the high animal proline intake group. Women aged 60 and 70 who were in the high proline intake group had maintained high scores. On the other hand, no significant relationships were observed between plant-derived proline intake and “Information” score.

Proline exerts different effects on “Information” score depending on whether it is derived from animals or plants.

Key words proline intake, intelligence, community-dwelling, longitudinal study, animal food

日本骨粗鬆症学会雑誌
オステオポロシス ジャパン

Vol.22, No.3, 2014

Osteoporosis Japan

第15回日本骨粗鬆症学会

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膝関節の変形および痛みと身体組成との関連

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はじめに

変形性膝関節症(膝 OA)は、高齢期に QOL や身体機能低下をきたす原因となる運動器疾患の一つである。膝 OA の痛みの増悪因子として肥満はよく知られているが、DXA などによる身体組成を含めた詳細な検討は少ない。そこで、膝関節変形ならびに痛みと身体組成の関連を明らかにするため、地域在住中高年者対象の大規模コホートにて検討を行った。

1 対象および方法

「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)」¹⁾の第5次調査(2006~2008年)に参加した男女2,337名(平均年齢60.7±12.6歳,男性1,185名,女性1,192名)の4,750膝を対象とした。本研究参加者は愛知県大府市および東浦町の40歳以上の一般住民から無作為に抽出し選定した。調査項目として、膝関節変形は左右別のエックス線膝荷重位正面像についてKellgren-Lawrence分類を基に5段階に分類し、0~I度を正常、II度を軽度変形、III~IV度を重度変形と3群に分類し、調査票にて現在の膝関節痛の有無を左右別に調査した。さらに身体組成の指標としてHologic社製QDR4500を用いて、DXA法にて下肢脂肪量、下肢筋肉量を測定し、下肢脂肪率(=下肢脂肪量/体重×100)、下肢筋肉率(=下肢筋肉量/体重×100)、

下肢筋肉量と下肢脂肪量の比(=下肢筋肉量/下肢脂肪量)、のそれぞれを左右別に算出し、変形の程度により各指標に差があるかどうかについて、男女別および痛みの有無別に検討した。統計解析は一般線形モデルを用い、左右の膝を合わせ年齢を調整した多重比較(Tukey-Kramer法)によりSAS9.1.3にて行った。研究は当センターの倫理委員会の承認のもと、紙面での参加者の同意を得て施行した。

2 結果

対象の特性を表1に示す。男女別および痛みの有無別に、膝関節変形の程度による各指標を比較した結果は、以下のとおりであった。

男性においては、痛みのある例では下肢脂肪率は正常に比べ重度変形で有意に高く($p < 0.05$)、下肢筋肉率、下肢筋肉量と下肢脂肪量の比は、ともに正常に比べ重度変形で有意に低かった(各 $p < 0.05$, 図1A)。一方痛みのない例では下肢脂肪率、下肢筋肉率、下肢の脂肪量と筋肉量の比はいずれも各群間に有意差はなかった(図1B)。女性では、痛みのある例では下肢脂肪率、下肢筋肉率、下肢筋肉量と下肢脂肪量の比のいずれも各群間に有意差はなかったが、下肢筋肉率は重度変形が軽度変形より低い傾向($p = 0.053$)があった(図1C)。一方痛みのない例では、下肢脂肪率は正常に比べ軽度変形で有意に

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表1 対象の特性

	男性 (n=1185)	女性 (n=1192)
年齢 (歳)	60.6±12.5	60.8±12.7
身長 (cm)	166.0±6.6	152.6±6.2
体重 (kg)	64.1±9.3	52.5±8.6
総膝関節数 (膝)	2368	2382
エックス線変形程度別の膝関節数		
正常 (痛みのある膝%)	1524 (7.5)	1300 (10.5)
軽度変形 (痛みのある膝%)	765 (11.5)	859 (20.7)
重度変形 (痛みのある膝%)	79 (50.6)	223 (57.0)
BMI (kg/m ²)	23.2±2.7	22.5±3.3
下肢脂肪量 (kg)	2.1±0.6	2.8±0.8
下肢筋肉量 (kg)	7.4±1.2	5.2±0.8
下肢脂肪率 (%)	3.3±0.6	5.3±1.0
下肢筋肉率 (%)	11.6±0.9	10.0±0.9
下肢筋肉量と脂肪量の比	3.7±1.1	2.0±0.5

平均±SD

高く ($p < 0.05$), 下肢筋肉率では各群間に有意差はなかったが, 下肢筋肉量と下肢脂肪量の比は正常に比べ軽度変形で有意に低かった ($p < 0.01$, 図1D)。

3 考 察

膝 OA の増悪因子として肥満はよく知られているが, DXA などによる身体組成を含めた詳細な検討は多くなく, これまでの国内外における報告のほとんどは女性についての検討である。わが国では, DXA 法を用いた膝 OA 例女性 30 名と健常女性 50 名の比較で, 体脂肪率は膝 OA 例のほうが健常群より大きかったが, 除脂肪量は両群に有意な差を認めなかったとする報告²⁾や, Bioelectrical impedance 法を用いた, 下肢除脂肪率が膝 OA 群で正常群より低かったとする戸田らの報告³⁾, 年齢, BMI, 腰椎骨密度が一致した対照群との比較で, 下肢除脂肪量は膝 OA 群で有意に低下し, 脂肪量は有意差がなく, 膝 OA 群で進行度の高い側の脂肪量は低い側に比べ有意に高かったとする報告⁴⁾がある。また海外においても, DXA 法で体脂肪量, 体脂肪率, 体筋肉量は

膝 OA 群のほうが正常群より高かったが, 体筋肉率は膝 OA 群のほうが低かったとする Johnston Country Osteoarthritis Project での報告⁵⁾や, Bioelectrical impedance 法を用いた, 体除脂肪量は MRI 計測での脛骨軟骨量と正, 軟骨欠損と負の関連があり, 体脂肪量は脛骨軟骨量と負の関連があったとする報告⁶⁾, あるいは, 骨格筋量はエックス線関節裂隙幅と正の関連があったが, 脂肪量とは一定の関連を認めなかった⁷⁾など, 本報告と同様の報告がある。しかしながら, 性別や痛みの有無別に行った検討は, 渉猟したかぎりこれまでにはなかった。われわれの検討では正常例との比較において, 男性では痛みのある例にて重度変形例で下肢の脂肪の割合が高く筋肉の割合が低く, 一方女性では痛みのない例にて軽度変形例で脂肪の割合が高く筋肉の割合が低くなっていた。

ま と め

地域在住中高年者を対象とした大規模コホートにて, 膝関節の変形と身体組成との関連を検討した。両者の関連は, 痛みの有無を考慮した

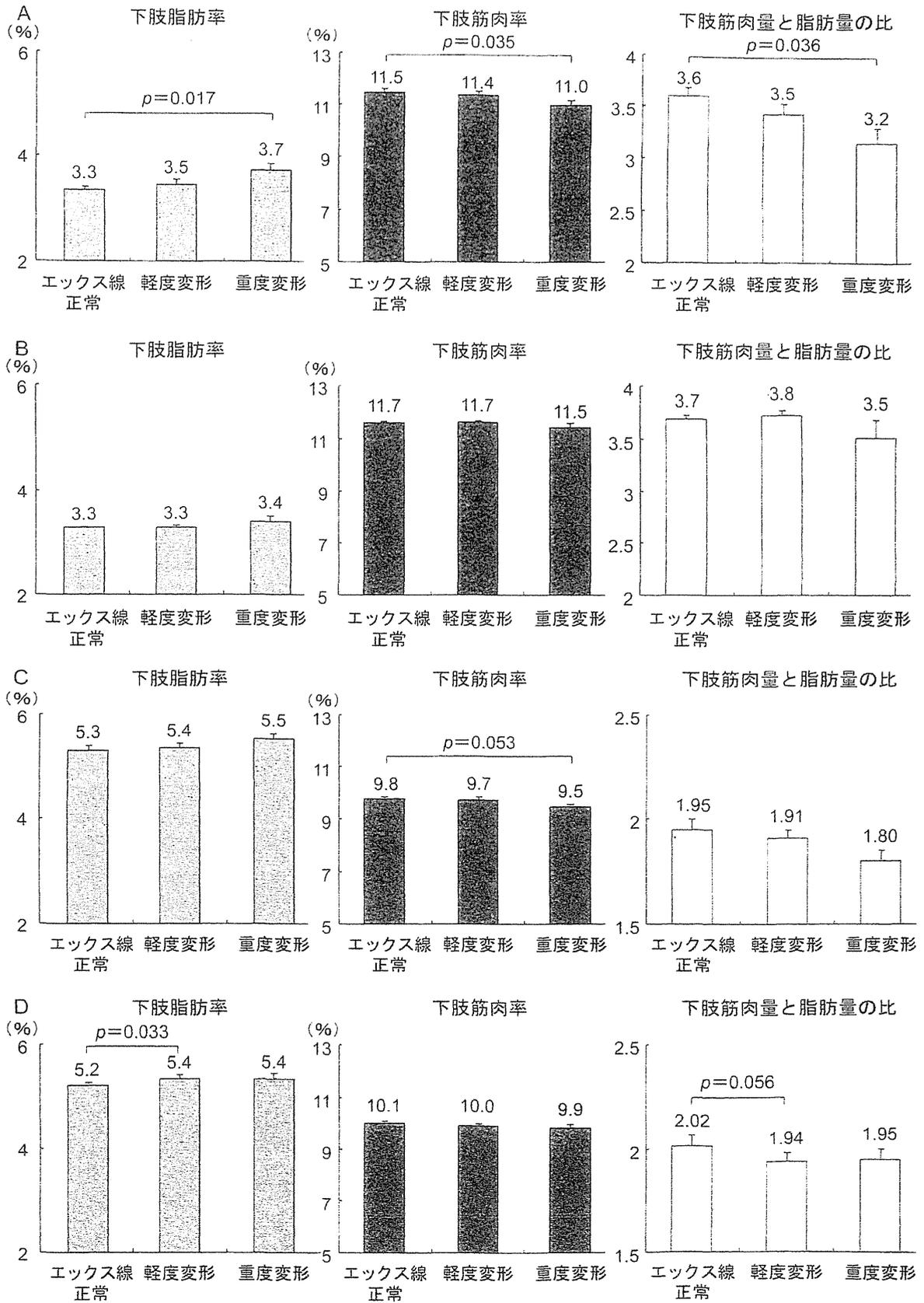


図1 エックス線膝変形の程度による各指標の比較
 年齢を調整した多重比較 (Tukey-Kramer 法) にて
 A: 痛みのある男性例, B: 痛みのない男性例, C: 痛みのある女性例, D: 痛みのない女性例

場合、男女で異なっていた。

【CO1】本演題に関連して、筆頭著者に開示すべき利益相反はありません。

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Prevalence of knee pain, lumbar pain and its coexistence in Japanese men and women: The Longitudinal Cohorts of Motor System Organ (LOCOMO) study

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Received: 9 July 2013 / Accepted: 9 September 2013 / Published online: 9 November 2013
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Abstract The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008 through a grant from the Ministry of Health, Labour, and Welfare of Japan to integrate information from several cohorts established for the prevention of musculoskeletal diseases. We integrated the information of 12,019 participants (3,959 men and 8,060 women) in the cohorts comprising nine communities located in Tokyo (two regions: Tokyo-1 and Tokyo-2), Wakayama [two regions: Wakayama-1 (mountainous region) and Wakayama-2 (seaside region)], Hiroshima, Niigata, Mie, Akita, and Gunma prefectures. The baseline examination of the LOCOMO study consisted of an interviewer-administered questionnaire, anthropometric measurements, medical information recording, X-ray

radiography, and bone mineral density measurement. The prevalence of knee pain was 32.7 % (men 27.9 %; women 35.1 %) and that of lumbar pain was 37.7 % (men 34.2 %; women 39.4 %). Among the 9,046 individuals who were surveyed on both knee pain and lumbar pain at the baseline examination in each cohort, we noted that the prevalence of both knee pain and lumbar pain was 12.2 % (men 10.9 %; women 12.8 %). Logistic regression analysis showed that higher age, female sex, higher body mass index (BMI), living in a rural area, and the presence of lumbar pain significantly influenced the presence of knee pain. Similarly, higher age, female sex, higher BMI, living in a rural area, and the presence of knee pain significantly influenced the presence of lumbar pain. Thus, by using the data of the

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LOCOMO study, we clarified the prevalence of knee pain and lumbar pain, their coexistence, and their associated factors.

Keywords Nation-wide population-based cohort study · Epidemiology · Prevalence · Knee pain · Lumbar pain

Introduction

Musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), are major public health problems among the elderly; these diseases can affect activities of daily living (ADL) and quality of life (QOL), and can lead to increased morbidity and mortality. According to the recent National Livelihood Survey by the Ministry of Health, Labour, and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities and subsequently require support for ADL, whereas falls and osteoporotic fractures are ranked fifth [1]. Studies have reported increased mortality after osteoporotic fractures at the hip and other sites [2]. An estimated 47,000,000 individuals (21,000,000 men and 26,000,000 women) aged ≥ 40 years will eventually be affected by either OA or OP [3].

Considering that the population of Japan is aging rapidly, a comprehensive and evidence-based prevention strategy for musculoskeletal diseases is urgently needed. However, only a few prospective, longitudinal studies designed to develop such a strategy have been conducted. Therefore, little information is available regarding the incidence of disability and the prevalence and incidence of musculoskeletal disorders, including knee pain, and lumbar pain, and their associated factors in Japan. The absence of such epidemiological data hampers the rational design of clinical and public health approaches for the diagnosis, evaluation, and prevention of musculoskeletal diseases.

Several cohorts have focused on the prevention of OP, knee OA (KOA), lumbar spondylosis (LS) or disability caused by musculoskeletal diseases. However, since the prevalence of the musculoskeletal diseases has been reported to be high [3], the extent of the population at risk after excluding those who had the target disease at the baseline seems to be small. To identify epidemiological indices, especially the incidence of musculoskeletal diseases and/or disability, a large number of subjects is required. In addition, to determine the regional differences in epidemiological indices, we need a survey of cohorts across Japan.

The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008 by the members of the committee for 'the prevention of knee and back pain and bone fractures in a large cohort of regionally

representative residents from across Japan,' through a grant from the Ministry of Health, Labour, and Welfare of Japan (Director, Noriko Yoshimura). This study aimed to integrate the information of several cohorts established for the prevention of musculoskeletal diseases from 2000 onwards, and to initiate a follow-up examination using the unified questionnaire from 2006 onwards in Japan.

In the present paper, by using the integrated information at the baseline of the LOCOMO study, we tried to confirm the prevalence of clinical symptoms of musculoskeletal diseases, such as knee pain and lumbar pain and their characteristics.

Materials and methods

Participants

Participants in the cohorts were residents of nine communities located in Tokyo (two regions: Tokyo-1, principle investigators (PIs): Shigeyuki Muraki, Toru Akune, Noriko Yoshimura, Kozo Nakamura; Tokyo-2, PIs: Yoko Shimizu, Hideyo Yoshida, Takao Suzuki), Wakayama [two regions: Wakayama-1 (mountainous region) and Wakayama-2 (sea-side region); PIs: Noriko Yoshimura, Munehito Yoshida], Hiroshima (PI: Saeko Fujiwara), Niigata (PI: Go Omori), Mie (PI: Akihiro Sudo), Akita (PI: Hideyo Yoshida), and Gunma (PI: Yuji Nishiwaki) prefectures [4]. Figure 1 shows the location of each cohort in Japan, and Fig. 2 provides the timeline of the LOCOMO study. Residents of the nine regions were recruited from resident registration lists in the relevant region. Data for the 12,019 participants were collected and registered as an integrated cohort. Numbers of participants in the LOCOMO study classified by regions of each cohort are shown in Table 1. The smallest cohort consisted of 826 individuals in Wakayama-2, and the largest consisted of 2,613 individuals in Hiroshima.

All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (nos. 1264 and 1326), the Tokyo Metropolitan Institute of Gerontology (no. 5), Wakayama (no. 373), The Radiation Effects Research Foundation (RP03-89), Niigata University (no. 446), Mie University (no. 837 and no. 139), Keio University (no. 16–20), and National Center for Geriatrics and Gerontology (no. 249). Safety of the participants was ensured during the examination and during all other study procedures.

Data collection

The baseline examination of the LOCOMO study consisted of the following: an interviewer-administered questionnaire,

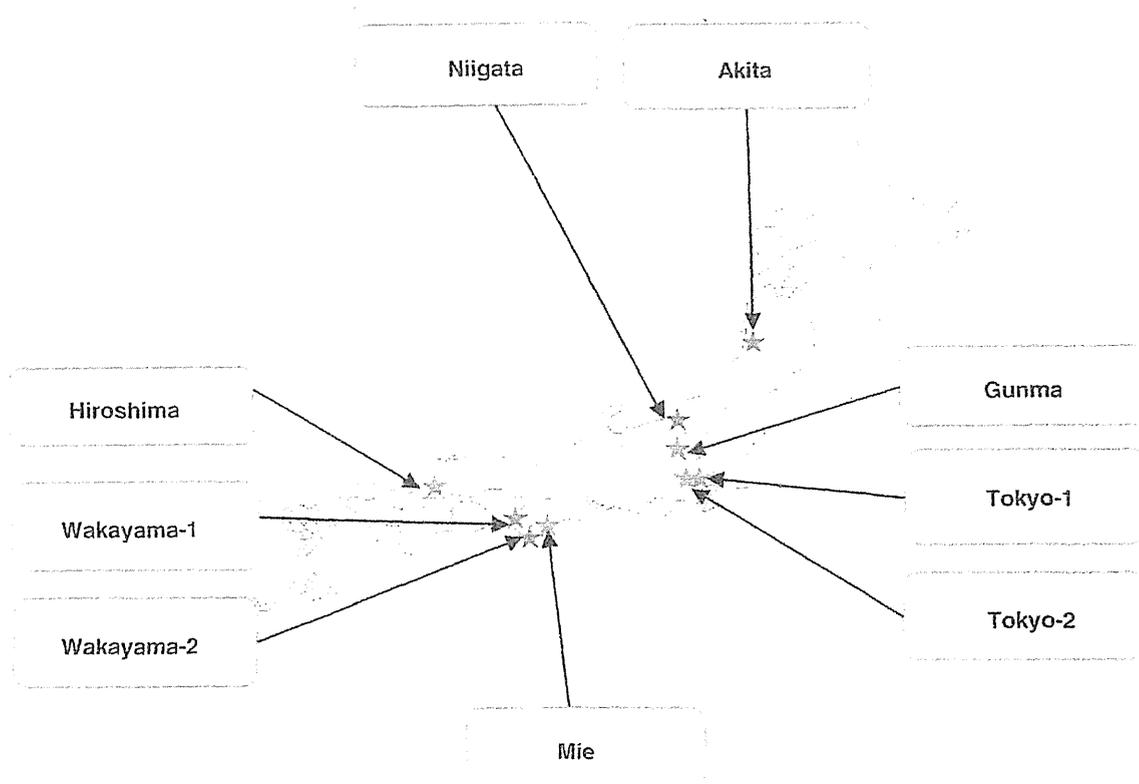


Fig. 1 Locations of the nine different regions from which the study cohorts were derived

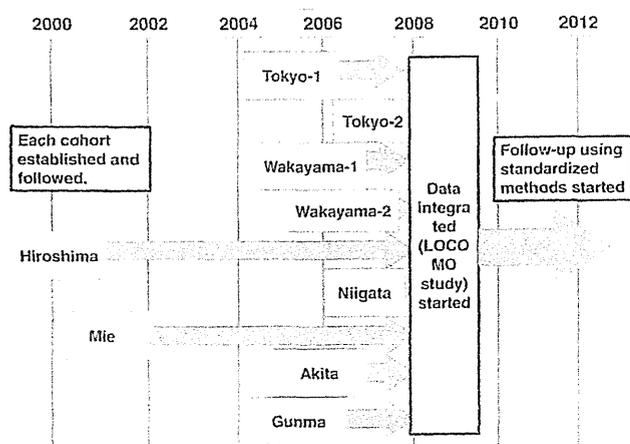


Fig. 2 Timeline of the LOCOMO study

Table 1 Numbers of participants in the LOCOMO study classified by regions of each cohort

Regions of each cohort	Start year	Total	Men	Women
Tokyo-1	2005	1,350	465	885
Tokyo-2	2008	1,453	59	1,394
Wakayama-1 (mountainous)	2005	864	319	545
Wakayama-2 (seaside)	2006	826	277	549
Hiroshima	2000	2,613	794	1,819
Niigata	2007	1,474	628	846
Mie	2001	1,175	423	752
Akita	2006	852	366	486
Gunma	2005	1,412	628	784
Total		12,019	3,959	8,060

anthropometric measurements, medical information recording, radiography, and bone mineral density (BMD) measurement.

Interviewer-administered questionnaire

A questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS) [5], and some new items were added to the modified questionnaire. Knee symptoms were evaluated using

the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [6]. Health-related QOL was evaluated using the European QOL-5 dimensions instrument (EuroQOL EQ5D) [7] and the Medical Outcomes Study 8-item Short Form (SF-8) [8]. The study staff recorded all the medications administered and their doses.

Anthropometric measurements

Anthropometric factors were measured by well-trained medical nurses. Body mass index [BMI: weight in

kilograms/(height in meters)²] was calculated on the basis of the current height and weight. Hand grip strength was measured using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested, and the higher value was used to characterise the maximum muscle strength of the subject. Walking speed was determined by recording the time taken by a subject to walk a determined distance, such as 5 or 6 m, at his/her usual speed. The ability to rise from a chair without using the arms (chair stand) and the ability to perform 5 chair stands was evaluated. The time required to complete the tasks was recorded.

Medical information

Medical information was obtained by experienced medical doctors in each cohort. All participants were questioned about pain in both knees by asking the following questions: ‘Have you experienced right knee pain on most days (and continuously on at least one day) in the past month, in addition to the current pain?’ and ‘Have you experienced left knee pain on most days (and continuously on at least one day) in the past month, in addition to the current pain?’ Subjects who answered ‘yes’ were considered to have knee pain. Lumbar pain was determined by asking the following question: ‘Have you experienced lumbar pain on most days (and continuously on at least one day) in the past month, in addition to the current pain?’ Subjects who answered ‘yes’ were considered to have lumbar pain.

In some cohorts (Tokyo-1, Wakayama-1, and Wakayama-2), the participants completed the modified Mini-Mental Status Examination-Japanese version [9] for evaluating cognitive function. Physicians explained any unclear sections of this questionnaire to the participants and assessed the cognitive status on the basis of the completed questionnaire.

Radiography and radiographic assessment

In several cohorts (Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, Niigata, and Mie), the radiographic examination of knees and/or spine was performed to evaluate the OA or fractures. Plain radiographs were obtained for both knees in the antero-posterior view with weight-bearing and foot map positioning and for the spine in the antero-posterior and lateral views.

The severity of OA was radiographically determined according to the Kellgren-Lawrence (KL) grading system as follows [10]: KL0, normal joint; KL1, slight osteophytes; KL2, definite osteophytes; KL3, narrowing of joint cartilage, and large osteophytes; and KL4, bone sclerosis, narrowing of joint cartilage, and large osteophytes. In the LOCOMO study, joints exhibiting disc-space narrowing alone and no large osteophytes were graded as KL3. In each

cohort, radiographs were examined by a single, experienced orthopaedic surgeon who was masked to the clinical status of the participants. If at least one knee joint was graded as KL2 or higher, the participant was diagnosed with radiographic KOA. Similarly, if at least one intervertebral joint of the lumbar spine was graded as KL2 or higher, the participant was diagnosed with radiographic LS.

BMD measurement

In the Wakayama-1, Wakayama-2, and Hiroshima cohorts, BMD of the lumbar spine and proximal femur was measured using dual energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination.

OP was defined on the basis of the World Health Organization (WHO) criteria. Specifically, OP was diagnosed when the BMD T scores were lower than the mean lumbar peak bone mass—2.5 SDs [11]. In Japan, the mean BMD of the L2–L4 vertebrae among both young male and female adults has been measured using Hologic DXA [12]. In the present study, lumbar spine BMD < 0.714 g/cm² (for both men and women) and femoral neck BMD < 0.546 g/cm² (men) or < 0.515 g/cm² (women) were considered to indicate OP.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the Chi square test. Differences in continuous variables were tested for significance using analysis of variance for comparisons among multiple groups or Scheffe’s least significant difference test for pairs of groups. To test the association between the interaction between the knee pain and lumbar pain, a logistic regression model was used. First, the presence of knee pain was used as an objective variable (0: absence, 1: presence) and age (+1 year), gender (men vs. women), BMI (+1 kg/m²), regional differences (0: rural areas including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo-1, Tokyo-2, and Hiroshima), and lumbar pain (0: no, 1: yes) were used as explanatory variables. Then, lumbar pain was used as an objective variable, and knee pain was used as an explanatory variable in the identical model. All *p* values and 95 % confidence intervals (CI) of two-sided analysis are presented.

Results

Table 2 shows the number of participants classified by age and gender. Most participants were aged ≥60 years, and

Table 2 Numbers of participants in the LOCOMO study classified by age and gender

Age strata (years)	Total (%)	Men (%)	Women (%)
≤39	125 (1.0)	49 (1.2)	76 (0.9)
40–49	483 (4.0)	183 (4.6)	300 (3.7)
50–59	963 (8.0)	320 (8.1)	643 (8.0)
60–69	3,170 (26.3)	1,161 (29.3)	2,009 (24.9)
70–79	5,041 (41.9)	1,573 (39.7)	3,468 (43.0)
80–89	2,111 (17.6)	627 (15.8)	1,484 (18.4)
≥90	126 (1.1)	46 (1.2)	80 (1.0)
Total	12,019 (100.0)	3,959 (100.0)	8,060 (100.0)

99.0 % of the participants were aged ≥40 years. Two-thirds of the participants were women, and their mean age was 1 year greater than that of the male participants.

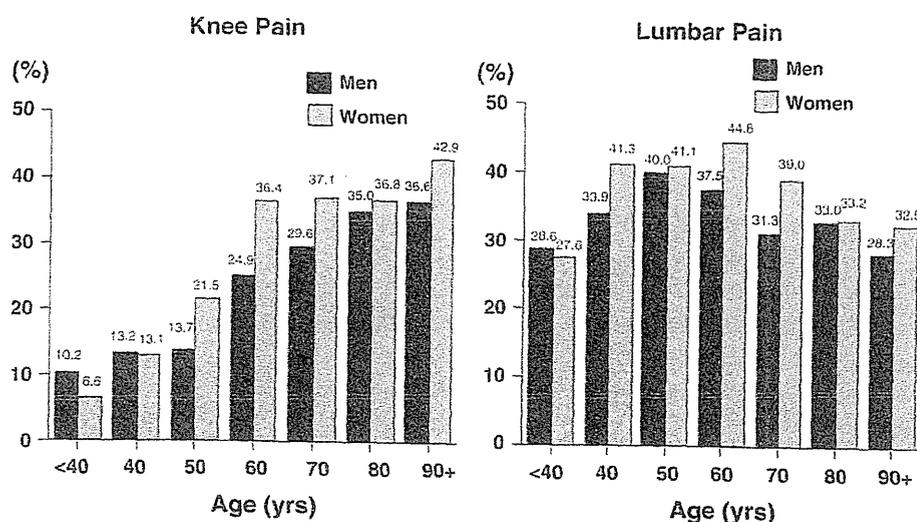
Selected characteristics of the study populations, including age, height, weight, BMI, and proportions of participants who smoked and consumed alcohol are shown in Table 3. The participants were considered as smokers and alcohol consumers if they answered ‘yes’ to the

Table 3 Baseline characteristics of participants in the LOCOMO study classified by age and gender

Variables	Men	Women	<i>p</i> Value (men vs. women)
Age (years)	70.0 (10.6)	71.0 (10.3)	<0.001
Height (cm)	161.1 (6.8)	148.5 (6.4)	<0.001
Weight (kg)	59.3 (9.5)	50.8 (8.6)	<0.001
BMI (kg/m ²)	22.8 (3.0)	23.0 (3.5)	0.007
Smoking (%)	34.0	4.8	<0.001
Drinking (%)	52.4	21.1	<0.001

Values are represented as mean (standard deviation)

BMI body mass index

Fig. 3 Prevalence of knee pain and lumbar pain according to age and gender

question ‘Are you currently smoking/drinking?’ in the self-administered questionnaire. The mean values of age and BMI were significantly higher in women than in men ($p < 0.01$). The proportions of both current smokers and alcohol consumers were significantly higher among men than among women ($p < 0.001$).

By analysing the data at the baseline examination, we determined the prevalence of knee pain and lumbar pain. Figure 3 shows the age-sex distribution of the prevalence of knee pain and lumbar pain. Overall, the prevalence of knee pain was 32.7 % (27.9 % in men, and 35.1 % in women) and that of lumbar pain was 37.7 % (34.2 % in men and 39.4 % in women). The prevalence of pain in both the knee and lumbar region were significantly higher in women than in men ($p < 0.001$). On the basis of the total age and sex distributions derived from the Japanese census in 2010 [13], our results estimate that 18,000,000 people (7,100,000 men and 10,900,000 women) aged ≥40 years would be affected by knee pain and that 27,700,000 people (12,100,000 men and 15,600,000 women) aged ≥40 years would be affected by lumbar pain.

Further, among 9,046 individuals who were surveyed on both knee pain and lumbar pain at the baseline examination in each cohort, the prevalence of both knee pain and lumbar pain was 12.2 % (10.9 % in men and 12.8 % in women). The prevalence of the coexistence of knee and lumbar pain in the participants aged <40, 40–49, 50–59, 60–69, 70–79, and ≥80 years was 4.0, 4.8, 7.4, 13.0, 13.3, and 11.7 %, respectively. (6.1, 5.3, 6.0, 10.0, 11.5, and 13.2 %, respectively, in men and 2.6, 4.6, 8.1, 14.8, 14.2, and 11.0 %, respectively, in women). The prevalence of both knee pain and lumbar pain increased with age in men, whereas that in women reached a plateau at 60–69 and 70–79 years and then declined. On the basis of the total age and sex distributions derived from the Japanese census in 2010 [13], our results estimate that 6,800,000 people

Table 4 Odds ratios (OR) of potentially associated factors for the presence of knee pain/lumbar pain vs. absence of pain

Explanatory variables	Reference	OR	95% confident interval	p
Knee pain (presence vs. absence)				
Age (years)	+1 year	1.045	1.039–1.051	<0.001***
Gender	0: men, 1: women	1.602	1.441–1.780	<0.001***
Region	0: urban area, 1: rural area	2.419	2.152–2.720	<0.001***
BMI (kg/m ²)	+1 kg/m ²	1.141	1.124–1.158	<0.001***
Lumbar pain	0: absence, 1: presence	1.373	1.243–1.515	<0.001***
Lumbar pain (presence vs. absence)				
Age (years)	+1 year	1.018	1.013–1.023	<0.001***
Gender	0: men, 1: women	1.130	1.023–1.248	0.016*
Region	0: urban area, 1: rural area	2.016	1.801–2.256	<0.001***
BMI (kg/m ²)	+1 kg/m ²	1.020	1.003–1.031	0.021*
Knee pain	0: absence, 1: presence	1.375	1.246–1.518	<0.001***

BMI body mass index

* *p* < 0.05, *** *p* < 0.001

(2,800,000 men and 4,000,000 women) aged ≥40 years would be affected by both knee pain and lumbar pain.

To test the association between the knee pain and lumbar pain, the presence of knee pain was first used as an objective variable (0: absence, 1: presence) and age (+1 year), gender (men vs. women), BMI (+1 kg/m²), regional differences (0: rural areas including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo-1, Tokyo-2, and Hiroshima), and lumbar pain (0: no, 1: yes) were used as explanatory variables. Then, the presence of lumbar pain was used as an objective variable (0: absence, 1: presence) and age (+1 year), gender (men vs. women), BMI (+1 kg/m²), regional differences (0: rural areas including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo-1, Tokyo-2, and Hiroshima), and knee pain (0: no, 1: yes) were used as explanatory variables. Table 4 shows the result of the logistic regression analysis. Higher age, female sex, higher BMI, living in a rural area, and the presence of lumbar pain significantly influenced the presence of knee pain. Similarly, higher age, female sex, higher BMI, living in a rural area, and the presence of knee pain significantly influenced the presence of lumbar pain.

Discussion

In the present study, we integrated the information of individual cohorts established for the prevention of musculoskeletal diseases, and created the nationwide large-scale cohorts comprising the LOCOMO study. By using the data of the LOCOMO study, we found that the prevalence of knee pain was 32.7 % and that of lumbar pain was 37.7 %. Both knee pain and lumbar pain were prevalent in 12.2 % of the total population. In the present study, we also clarified that the factors associated with knee or lumbar

pain were age, sex, body build, and residential characteristics. In addition, the presence of knee pain affected the lumbar pain, and vice versa. This association remained even after the adjustment for the above-mentioned associated factors. To our knowledge, this is the first study to report the frequency of the knee pain and lumbar pain and to estimate the total number of prevalent subjects, by using a large-scale population-based cohort study in Japan.

With regard to musculoskeletal pain, several population-based epidemiological studies have demonstrated that chronic pain is a highly prevalent condition. Soni et al. [14] reported that the prevalence rates of self-reported knee pain using the baseline data in 1,003 participants from the Chingford Women’s Study were 22.97 % in the left knee and 24.80 % in the right knee. The definition of the presence of the knee pain (based on the following two questions: ‘Have you had any knee pain in either knee in the last month?’ and ‘How many days of pain have you experienced in the last month?’) was similar but not identical to our definition used in the LOCOMO study, and the subjects’ age was younger in the Chingford study than in the LOCOMO study. Therefore, we could not compare the prevalence between the Chingford and LOCOMO studies directly. However, at a glance, the prevalence seems to be higher in the Japanese population. This may be due to the fact that the prevalence of KOA (KL grades ≥2) was higher in the Japanese population than that in the Caucasian population [15]. Verhaak et al. [16] reviewed epidemiological studies on chronic benign pain among adults, including subjects aged between 18 and 75 years, and reported that the prevalence ranged between 2 and 40 % of the population. Coggon et al. did not perform a population-based study, but instead conducted a cross-sectional survey comparing the prevalence of disabling low back pain and disabling wrist/hand pain among groups of workers carrying out similar physical activities in different cultural environments in 18 countries including Japan. They

reported that the 1-month prevalence of disabling low back pain in nurses ranged from 9.6 to 42.6 %, and that of disabling wrist/hand pain in office workers ranged from 2.2 to 31.6 % [17]. We could not compare our results to those of Coggon's results directly because of the difference in the characteristics of the targeted population. However, previous reviews and reports demonstrated that the prevalence of the chronic pain varied in the population surveyed, and therefore, estimating the prevalence and number of patients in pain would require a study that comprises various regions with a large number of subjects. Our LOCOMO study contains 12,019 participants from the cohorts consisting of nine communities in different locations in Japan. Therefore, we believe that our estimation of the prevalence of knee pain and lumbar pain is appropriate, and the number of patients was sufficient.

With regard to the characteristics of subjects with chronic pain, Soni et al. [14] reported that among subjects who could be followed up for 12 years, a higher BMI was predictive of persistent knee pain (odds ratio = 1.14) and incident knee pain (odds ratio = 1.10). Verhaak et al. [16] demonstrated that chronic pain generally increased with age, with some studies reporting a peak prevalence between the ages of 45 and 65 years. These results were not consistent with our results. Moreover, we noted that living in a rural area was associated with the presence of knee pain and lumbar pain, which may be due to the difference of the primary occupation in that area. Muraki et al. [18] reported that the presence of KOA and LS was influenced by the primary occupation of the participants. According to their report, the prevalence of higher K/L grades of KOA and LS was significantly higher among agricultural, forestry, and fishery workers than among clerical workers and technical experts [18]. For occupational activities, sitting on a chair had a significant inverse association with K/L grades ≥ 2 for KOA and LS, whereas standing, walking, climbing and heavy lifting were associated with higher K/L grades for KOA [18]. An association between occupational activities and KOA was also observed in several studies [19–21]. Agricultural, forestry, and fishery workers seemed to be more common in rural areas than in urban areas. In addition, occupational activities, such as sitting on a chair, might be observed more commonly in clerical workers than in agricultural, forestry, and fishery workers. These findings might support the regional differences of pain that were observed in the present study. The main focus of the present study was pain, and not OA; however, the most probable diagnosis underlying knee pain among older people was reported to be OA [22].

There are also several reports regarding the coexistence of pain. The above-mentioned Coggon's investigation indicated that the rates of disabling pain at 2 anatomical sites—the lumbar spine and wrist/hand—covaried ($r = 0.76$) [17].

In their cross-sectional study, Smith et al., examined the presence and sites of chronic pain in 11,797 women. The presence of chronic pain was noted in 38 % of women; among them, the percentage of women experiencing chronic pain at 1, 2, 3, 4, and ≥ 5 sites was 23.2, 24.4, 20.0, 14.3, and 18.2 %, respectively [23]. These results showed that chronic pain coexists at other anatomical sites. In the present study, the prevalence of both knee pain and lumbar pain was 12.2 % (10.9 % in men and 12.8 % in women) among the general population. However, among the subjects with lumbar pain, 37.3 % also had knee pain (39.0 % in men and 36.6 % in women). Unfortunately, in the LOCOMO study, we were unable to collect the data regarding pain at anatomical sites other than knee pain and lumbar pain. Nevertheless, the coexistence of pain was commonly noted, which is inconsistent with previous reports.

There were several limitations in the present study. First, the current subjects do not truly represent the entire Japanese population. We should carefully consider this limitation, especially when determining the generalisability of the results. However, the LOCOMO study is the first large-scale population-based prospective study with more than 12,000 participants. Although it does not comprise the whole population of Japan, the number of participants in the cohorts established for the prevention of the musculoskeletal diseases appears to be biggest worldwide. Second, all the items of our survey in the baseline examination were not recorded in all cohorts. For example, radiographic examination of knees was performed only in Tokyo-1, Wakayama-1, Wakayama-2, Niigata, and Mie prefectures and radiographic examination of the lumbar spine was performed only in Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, and Mie prefectures. Third, the radiographic findings for OA assessment using KL scales have not been integrated yet, because of the delay in the standardisation of reading methods of the observers. Radiographs should be assessed by a single observer to omit the inter-observer variability, and if this is impossible, then the inter-observer variability among observers should be tested using the standardised criteria. Therefore, in the present study, we could not evaluate the severity of knee/spinal OA or vertebral fractures for assessing knee pain and lumbar pain. After suitable evaluation of intra-observer and inter-observer variability in the assessment of radiography findings and integration of this information, we hope to re-analyse the factors associated with the presence of chronic pain. Moreover, not only OA and fractures, but also rheumatoid arthritis and spondyloarthritis should be considered as parameters for assessing knee pain and lumbar pain. Although collection of the information on the diagnosis may be difficult on a large scale due to the associated cost, it may be possible to obtain this information in at least two cohorts.