表1　3年後の自立度の変化

		3年後の自立度								
	初回の移動能力	一人で外出可能	近隣での移動可能	家庭内での移動可能	起きているが移動しない	寝たり起きたり	1日中床ですごす	入院・入所	死亡	不明
男性 65～74歳	一人で外出可能	2656	87	25	9	9		1	94	346
		(82.3)	(2.7)	(0.8)	(0.3)	(0.3)		(0.0)	(2.9)	(10.7)
	近隣での移動可能	27	38	15	4	1	1	1	21	21
		(20.9)	(29.5)	(11.6)	(3.1)	(0.8)	(0.8)	(0.8)	(16.3)	(16.3)
	家庭内での移動可能	3	4	14	9	3	2	1	8	15
		(5.1)	(6.8)	(23.7)	(15.3)	(5.1)	(3.4)	(1.7)	(13.6)	(25.4)
	起きているが移動なし		1		9	3			6	4
			(4.3)		(39.1)	(13.0)			(26.1)	(17.4)
	寝たり起きたり	1			4	5	2		5	7
		(4.2)			(16.7)	(20.8)	(8.3)		(20.8)	(29.2)
	1日中床ですごす				1		3		7	2
					(7.7)		(23.1)		(53.8)	(15.4)
75～84歳	一人で外出可能	1846	260	66	12	29	6	4	206	359
		(66.2)	(9.3)	(2.4)	(0.4)	(1.0)	(0.2)	(0.1)	(7.4)	(12.9)
	近隣での移動可能	58	87	43	9	16	10	1	54	62
		(17.1)	(25.6)	(12.6)	(2.6)	(4.7)	(2.9)	(0.3)	(15.9)	(18.2)
	家庭内での移動可能	7	12	33	12	6	4	2	50	38
		(4.3)	(7.3)	(20.1)	(7.3)	(3.7)	(2.4)	(1.2)	(30.5)	(23.2)
	起きているが移動なし	2		3	11	3	3	1	17	16
		(3.6)		(5.4)	(19.6)	(5.4)	(5.4)	(1.8)	(30.4)	(28.6)
	寝たり起きたり	2		3	2	15	7		32	16
		(2.6)		(3.9)	(2.6)	(19.5)	(9.1)		(41.6)	(20.8)
	1日中床ですごす		1			2	10	1	29	19
			(1.6)			(3.2)	(16.1)	(1.6)	(46.8)	(30.6)
女性 65～74歳	一人で外出可能	2471	210	34	7	7	2	3	34	292
		(80.8)	(6.9)	(1.1)	(0.2)	(0.2)	(0.1)	(0.1)	(1.1)	(9.5)
	近隣での移動可能	69	100	25	4	5	4		14	56
		(24.9)	(36.1)	(9.0)	(1.4)	(1.8)	(1.4)		(5.1)	(20.2)
	家庭内での移動可能	6	10	23	4	3		1	4	17
		(8.8)	(14.7)	(33.8)	(5.9)	(4.4)		(1.5)	(5.9)	(25.0)
	起きているが移動なし		3	3	2				4	9
			(14.3)	(14.3)	(9.5)				(19.0)	(42.9)
	寝たり起きたり	1	2		1	3	1	2	3	3
		(6.3)	(12.5)		(6.3)	(18.8)	(6.3)	(12.5)	(18.8)	(18.8)
	1日中床ですごす					2	2		2	4
						(20.0)	(20.0)		(20.0)	(40.0)
75～84歳	一人で外出可能	1109	407	74	12	13	8	4	49	302
		(56.1)	(20.6)	(3.7)	(0.6)	(0.7)	(0.4)	(0.2)	(2.5)	(15.3)
	近隣での移動可能	88	343	121	31	27	5	9	45	149
		(10.8)	(41.9)	(14.8)	(3.8)	(3.3)	(0.6)	(1.1)	(5.5)	(18.2)
	家庭内での移動可能	9	25	77	23	12	5	1	39	66
		(3.5)	(9.7)	(30.0)	(8.9)	(4.7)	(1.9)	(0.4)	(15.2)	(25.7)
	起きているが移動なし	2		5	21	10	9	1	5	16
		(2.9)		(7.2)	(30.4)	(14.5)	(13.0)	(1.4)	(7.2)	(23.2)
	寝たり起きたり		1	3	5	15	8	1	14	20
			(1.5)	(4.5)	(7.5)	(22.4)	(11.9)	(1.5)	(20.9)	(29.9)
	1日中床ですごす					2	9		18	8
						(5.4)	(24.3)		(48.6)	(21.6)

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クを高くしていた。

IADL(バスや電車を使っての外出、日用品の買い物、食事の支度、身の回り、金銭の管理)は１項目できるごとに男性では前期高齢者で0.535、後期高齢者で 0.605、女性では前期高齢者が 0.235、後期高齢者で 0.413、自立度低下のリスクが低かった。IADL の効果は後期より前期高齢者で、男性より女性で大きかった。

表２　自立度低下に関連する健康状態（男性）

	前期高齢者 (n=2,787)			後期高齢者 (n=2,223)		
初回調査時に治療中の病気						
脳卒中	**6.628**	**(3.536-**	**12.422)**	**3.004**	**(1.705-**	**5.295)**
高血圧	1.256	(0.852-	1.850)	0.995	(0.777-	1.273)
心臓病	1.246	(0.713-	2.178)	1.228	(0.905-	1.665)
がん	1.270	(0.390-	4.138)	1.537	(0.686-	3.448)
糖尿病	1.573	(0.898-	2.757)	**1.607**	**(1.091-**	**2.367)**
骨折	**4.303**	**(1.224-**	**15.129)**	**2.398**	**(1.044-**	**5.509)**
胃腸病	1.302	(0.719-	2.357)	**1.477**	**(1.043-**	**2.091)**
肺や気管支の病気	**2.164**	**(1.129-**	**4.149)**	1.381	(0.908-	2.101)
関節や筋肉の病気	1.348	(0.804-	2.261)	1.287	(0.956-	1.733)
観察期間中の新規発症(新規発症、初回時治療ともない人に対するrisk)						
脳卒中	**11.049**	**(5.381-**	**22.687)**	**4.273**	**(2.429-**	**7.519)**
高血圧	1.350	(0.700-	2.604)	1.137	(0.751-	1.720)
心臓病	**3.185**	**(1.748-**	**5.804)**	1.599	(0.996-	2.567)
がん	**3.011**	**(1.400-**	**6.476)**	**2.737**	**(1.473-**	**5.084)**
糖尿病	1.599	(0.567-	4.509)	1.844	(0.982-	3.462)
骨折	**11.306**	**(3.241-**	**39.442)**	**2.468**	**(1.033-**	**5.898)**
胃腸病	0.650	(0.202-	2.086)	1.610	(0.930-	2.787)
肺や気管支の病気	**2.399**	**(1.123-**	**5.123)**	**2.265**	**(1.372-**	**3.741)**
関節や筋肉の病気	1.651	(0.883-	3.086)	**1.497**	**(1.026-**	**2.184)**
目・耳・歯の障害						
目が見えにくい	**2.496**	**(1.359-**	**4.583)**	**2.356**	**(1.658-**	**3.348)**
耳が聞こえにくい	**2.914**	**(1.709-**	**4.969)**	**1.563**	**(1.149-**	**2.126)**
歯の具合が悪い	**2.315**	**(1.466-**	**3.655)**	**1.886**	**(1.402-**	**2.538)**
睡眠障害						
30分以内に寝付けない	1.211	(0.768-	1.909)	**1.493**	**(1.136-**	**1.960)**
夜中に目が覚める	0.940	(0.619-	1.427)	**1.701**	**(1.324-**	**2.185)**
早朝目が覚める	1.118	(0.688-	1.817)	**1.612**	**(1.207-**	**2.153)**
睡眠剤を使用している	1.574	(0.863-	2.873)	1.301	(0.904-	1.871)
IADL	**0.535**	**(0.433-**	**0.661)**	**0.605**	**(0.511-**	**0.717)**

表３　自立度低下に関連する健康状態（女性）

	前期高齢者 (n=2,734)			後期高齢者 (n=1,627)		
初回調査時に治療中の病気						
脳卒中	1.240	(0.430-	3.577)	0.692	(0.288-	1.662)
高血圧	**1.342**	**(1.025-**	**1.759)**	1.099	(0.877-	1.378)
心臓病	**2.028**	**(1.354-**	**3.039)**	1.250	(0.911-	1.713)
がん	0.409	(0.055-	3.022)	1.382	(0.339-	5.629)
糖尿病	1.402	(0.837-	2.351)	**1.595**	**(1.050-**	**2.423)**
骨折	1.906	(0.777-	4.677)	1.148	(0.611-	2.156)
胃腸病	1.478	(0.919-	2.376)	**1.509**	**(1.034-**	**2.202)**
肺や気管支の病気	1.310	(0.641-	2.678)	1.228	(0.687-	2.197)
関節や筋肉の病気	**1.705**	**(1.252-**	**2.322)**	**1.397**	**(1.073-**	**1.821)**
観察期間中の新規発症（新規発症、初回時治療ともない人に対するrisk）						
脳卒中	**6.048**	**(2.672-**	**13.691)**	**3.080**	**(1.325-**	**7.162)**
高血圧	0.987	(0.597-	1.631)	0.647	(0.410-	1.022)
心臓病	**1.971**	**(1.059-**	**3.668)**	1.141	(0.693-	1.878)
がん	**2.949**	**(1.374-**	**6.330)**	1.650	(0.624-	4.364)
糖尿病	2.121	(0.966-	4.658)	1.337	(0.602-	2.970)
骨折	**3.526**	**(1.459-**	**8.523)**	**2.070**	**(1.117-**	**3.839)**
胃腸病	1.555	(0.755-	3.202)	1.006	(0.575-	1.760)
肺や気管支の病気	1.214	(0.420-	3.509)	2.350	(0.995-	5.552)
関節や筋肉の病気	**2.143**	**(1.470-**	**3.125)**	**2.348**	**(1.678-**	**3.284)**
目・耳・歯の障害						
目が見えにくい	**2.513**	**(1.627-**	**3.881)**	**1.894**	**(1.284-**	**2.792)**
耳が聞こえにくい	**2.177**	**(1.265-**	**3.747)**	1.354	(0.950-	1.931)
歯の具合が悪い	**1.895**	**(1.266-**	**2.837)**	**1.910**	**(1.396-**	**2.614)**
睡眠障害						
30分以内に寝付けない	1.293	(0.974-	1.717)	1.085	(0.851-	1.385)
夜中に目が覚める	**1.327**	**(1.005-**	**1.753)**	**1.506**	**(1.193-**	**1.901)**
早朝目が覚める	1.115	(0.807-	1.541)	**1.402**	**(1.082-**	**1.818)**
睡眠剤を使用している	**1.734**	**(1.231-**	**2.441)**	**1.895**	**(1.421-**	**2.527)**
IADL	**0.235**	**(0.147-**	**0.375)**	**0.413**	**(0.309-**	**0.553)**

生活習慣と自立度低下の関係について、表４、５に示した。何らかの社会活動に参加していることは、まったく参加していない者に比べて自立度低下のリスクを小さくしており、男性では特に給料や謝金を得る仕事や地域活動で自立度低下のリスクの減少が大きく、女性では学習的活動や給料や謝金を得る仕事での自立度低下が少なくなっていた。

身体活動では、男性は後期高齢者でのみ外出等による 30 分以上の歩行を週５日以上している人で歩いていない人に比べて、自立度を低下のリスクが低くなったが、女性では前期高齢者では週の回数を問わず歩行をしている人では自立度低下のリスクが少なく、後期高齢者では週に５回以上の歩行で自立度低下のリスクが小さかった。歩く早さは、同年代と比べて同じくらいに対し、遅い人では性・年齢を問わず、自立度低下のリスクが大きく、速い人ではリスクは小さくなった。１日に 30 分以上の運動や作業では、男女とも週に３回程度以上の実施が行っていない人に比べて自立度低下のリスクの低いことを示している。

食事については、食欲があることは食欲がないに比べて、性・年齢を問わず自立度低下のリ

スクを小さくしていた。他の項目では。男性の前期高齢者で食事の回数が週に３回以上あること、後期高齢者で野菜を１日に２回以上食べることが、女性の前期高齢者で１日に２回以上野菜を食べることが自立度低下のリスクを小さくしていた。

飲酒については、男性では毎日飲酒することが飲酒をしないに比べて自立度低下のリスクを小さくしていた。

表４　自立度低下に関連する生活習慣（男性）

		前期高齢者 (n=2,787)			後期高齢者 (n=2,223)		
社会活動							
給料や謝金を得る仕事		**0.465**	**(0.310-**	**0.699)**	**0.691**	**(0.508-**	**0.940)**
収入を得ない作業		0.773	(0.519-	1.152)	**0.620**	**(0.482-**	**0.799)**
地域活動		**0.523**	**(0.341-**	**0.804)**	**0.575**	**(0.439-**	**0.752)**
自分以外の人の用事・世話		0.778	(0.538-	1.123)	**0.535**	**(0.413-**	**0.692)**
学習的活動		0.812	(0.552-	1.194)	**0.741**	**(0.586-**	**0.937)**
身体活動							
歩行	週に1～2回	0.983	(0.592-	1.632)	0.739	(0.532-	1.027)
	週に3～4回	0.904	(0.508-	1.609)	0.809	(0.563-	1.161)
	週に5回以上	0.889	(0.555-	1.424)	**0.570**	**(0.418-**	**0.778)**
歩く速さ							
	遅い	**3.720**	**(2.469-**	**5.604)**	**1.898**	**(1.456-**	**2.472)**
	速い	**0.708**	**(0.429-**	**1.170)**	**0.522**	**(0.378-**	**0.720)**
1日に30分以上の運動							
	週に1～2回	1.256	(0.779-	2.023)	1.049	(0.767-	1.435)
	週に3～4回	1.127	(0.651-	1.952)	0.950	(0.682-	1.322)
	週に5回以上	1.112	(0.687-	1.800)	**0.715**	**(0.523-**	**0.977)**
1日に30分以上の体を動かす作業							
	週に1～2回	0.828	(0.471-	1.456)	0.883	(0.607-	1.284)
	週に3～4回	**0.434**	**(0.232-**	**0.811)**	**0.538**	**(0.366-**	**0.791)**
	週に5回以上	**0.502**	**(0.303-**	**0.830)**	**0.483**	**(0.346-**	**0.673)**
食事等							
食事回数が3回以上		**0.363**	**(0.177-**	**0.746)**	1.123	(0.522-	2.418)
肉・魚・大豆が1日に2回以」		0.907	(0.617-	1.334)	1.127	(0.863-	1.471)
野菜を1日に2回以上		0.927	(0.604-	1.423)	**0.707**	**(0.521-**	**0.959)**
食欲がある		**0.511**	**(0.291-**	**0.896)**	**0.466**	**(0.314-**	**0.690)**
緑茶の飲用							
	1日に1～3杯	0.573	(0.257-	1.279)	1.540	(0.664-	3.568)
	1日に4杯以上	**0.428**	**(0.200-**	**0.915)**	0.965	(0.423-	2.200)
飲酒	週に1～3回	**0.503**	**(0.256-**	**0.989)**	0.785	(0.532-	1.161)
	週に4～6回	0.749	(0.415-	1.352)	0.651	(0.400-	1.059)
	毎日	**0.499**	**(0.326-**	**0.763)**	**0.766**	**(0.589-**	**0.995)**
喫煙	以前吸っていた	0.957	(0.597-	1.532)	1.001	(0.749-	1.340)
	吸っている	1.102	(0.735-	1.652)	1.113	(0.839-	1.476)

表５　自立度低下に関連する生活習慣（女性）

		前期高齢者 (n=2,734)			後期高齢者 (n=1,627)		
社会活動							
給料や謝金を得る仕事		**0.620**	(0.440-	**0.873)**	**0.639**	(0.449-	**0.909)**
収入を得ない作業		**0.677**	(0.489-	**0.938)**	0.801	(0.614-	1.044)
地域活動		**0.689**	(0.491-	**0.967)**	**0.624**	(0.467-	**0.835)**
自分以外の人の用事・世話		0.931	(0.711-	1.220)	0.802	(0.635-	1.013)
学習的活動		**0.601**	(0.461-	**0.782)**	**0.522**	(0.416-	**0.656)**
身体活動							
歩行	週に1～2回	**0.569**	(0.389-	**0.831)**	0.993	(0.709-	1.393)
	週に3～4回	**0.570**	(0.385-	**0.844)**	0.756	(0.527-	1.083)
	週に5回以上	**0.463**	(0.323-	**0.663)**	**0.715**	(0.520-	**0.983)**
歩く速さ							
	遅い	**4.036**	(2.996-	**5.437)**	**1.723**	(1.331-	**2.231)**
	速い	**0.669**	(0.456-	**0.983)**	**0.518**	(0.386-	**0.697)**
1日に30分以上の運動							
	週に1～2回	**0.554**	(0.384-	**0.799)**	**0.707**	(0.527-	**0.949)**
	週に3～4回	0.704	(0.477-	1.040)	**0.529**	(0.364-	**0.769)**
	週に5回以上	**0.470**	(0.310-	**0.711)**	**0.699**	(0.513-	**0.952)**
1日に30分以上の体を動かす作業							
	週に1～2回	0.671	(0.360-	1.249)	1.143	(0.682-	1.916)
	週に3～4回	**0.416**	(0.228-	**0.758)**	0.800	(0.490-	1.305)
	週に5回以上	**0.357**	(0.213-	**0.597)**	0.738	(0.475-	1.148)
食事等							
食事回数が3回以上		1.126	(0.342-	3.707)	0.780	(0.363-	1.674)
肉・魚・大豆が1日に2回以」		0.895	(0.676-	1.183)	0.934	(0.731-	1.193)
野菜を1日に2回以上		**0.588**	(0.415-	**0.833)**	0.892	(0.628-	1.268)
食欲がある		**0.344**	(0.223-	**0.531)**	**0.562**	(0.349-	**0.906)**
緑茶の飲用							
	1日に1～3杯	0.933	(0.315-	2.764)	0.747	(0.303-	1.839)
	1日に4杯以上	0.750	(0.260-	2.168)	0.587	(0.244-	1.411)
飲酒	週に1～3回	0.945	(0.596-	1.500)	**0.593**	(0.363-	**0.968)**
	週に4～6回	0.383	(0.092-	1.589)	1.118	(0.539-	2.320)
	毎日	0.820	(0.350-	1.917)	0.775	(0.389-	1.545)
喫煙	以前吸っていた	**3.240**	(1.037-	**10.122)**	1.088	(0.378-	3.133)
	吸っている	1.570	(0.840-	2.933)	1.362	(0.680-	2.730)

初回調査時に一人で外出可能、家庭内自立、家庭内での移動可能、起きているがあまり動けないのいずれかに該当する人から、寝たり起きたり、１日中床で過ごす、入院・入所のいずれかに移行した場合を寝たきりとして寝たきりへのリスクを検討した。該当者は男性が 5,162 名、女性が 5,018 名であり、寝たきりになった者は男性 213 名、女性 126 名であった。年齢調整した初回の自立度は、一人で外出可能に対して男性では他の３つの自立度では寝たきりのリスクが高かったが、初回の自立度の高低による差はなかった。女性では初回の自立度の影響はなかった(表６)。その他の健康状態や生活習慣の影響については、年齢と初回の自立度で調整した値を示した。初回に治療中の病気では、男女とも糖尿病で寝たきりのリスクが高く、男性では脳卒中、女性では胃腸病、関節や筋肉の病気でもリスクが高くなっていた。観察期間中

の新規発症では、脳卒中、がん、骨折は男女とも寝たきり移行へのリスクが高く、その他に男性では心臓病、糖尿病、肺・気管支の病気が、女性では関節や筋肉の病気で寝たきり移行のリスクが高かった。目・耳・歯の障害は男性では寝たきりの移行の関係はなかったが、女性では目が見えにくい、耳がきこえにくい者で寝たきりへの移行のリスクがそれらの障害のない者に比べ高かった。睡眠に関する障害では、男女とも夜中に目が覚める者でリスクが高く、女性では早朝に目が覚める者、睡眠剤を使用している者でもリスクが高かった。IADLはできる項目が1つ増えるごとに男性では0.579、女性では0.479寝たきりのリスクが低下した。

表6　寝たきりへの移行に関連する健康状態

	男性 (n=5162)			女性 (n=5018)		
初回調査時の自立度						
家庭内自立	**3.048**	**(2.337-**	**3.975)**	0.943	(0.783-	1.136)
家庭内での移動可能	**3.574**	**(2.357-**	**5.419)**	0.732	(0.516-	1.038)
起きているが移動なし	**2.253**	**(1.059-**	**4.793)**	1.220	(0.687-	2.166)
初回調査時に治療中の病気						
脳卒中	**3.716**	**(2.678-**	**5.156)**	1.385	(0.911-	2.107)
高血圧	1.002	(0.831-	1.209)	1.132	(0.977-	1.312)
心臓病	1.216	(0.959-	1.542)	1.145	(0.925-	1.416)
がん	1.244	(0.675-	2.291)	1.557	(0.772-	3.140)
糖尿病	**1.631**	**(1.237-**	**2.151)**	**1.505**	**(1.156-**	**1.958)**
骨折	1.210	(0.632-	2.315)	1.352	(0.905-	2.020)
胃腸病	1.289	(0.980-	1.695)	**1.292**	**(1.006-**	**1.658)**
肺や気管支の病気	1.341	(0.978-	1.838)	1.149	(0.783-	1.686)
関節や筋肉の病気	1.120	(0.889-	1.411)	**1.452**	**(1.230-**	**1.715)**
観察期間中の新規発症(新規発症、初回時治療ともない人に対するrisk)						
脳卒中	**5.673**	**(3.778-**	**8.519)**	**3.911**	**(2.388-**	**6.405)**
高血圧	1.027	(0.742-	1.421)	0.827	(0.624-	1.096)
心臓病	**2.043**	**(1.464-**	**2.851)**	1.351	(0.982-	1.858)
がん	**2.653**	**(1.718-**	**4.095)**	**2.664**	**(1.559-**	**4.551)**
糖尿病	**1.661**	**(1.000-**	**2.760)**	1.588	(0.968-	2.606)
骨折	**3.139**	**(1.662-**	**5.926)**	**2.748**	**(1.821-**	**4.146)**
胃腸病	1.262	(0.820-	1.944)	1.030	(0.713-	1.487)
肺や気管支の病気	**2.488**	**(1.724-**	**3.590)**	1.404	(0.854-	2.311)
関節や筋肉の病気	1.266	(0.938-	1.709)	**1.867**	**(1.506-**	**2.314)**
目・耳・歯の障害						
目が見えにくい	0.978	(0.527-	1.813)	**2.111**	**(1.314-**	**3.390)**
耳が聞こえにくい	0.887	(0.491-	1.602)	**2.399**	**(1.501-**	**3.835)**
歯の具合が悪い	1.338	(0.810-	2.210)	1.108	(0.684-	1.794)
睡眠障害						
30分以内に寝付けない	1.229	(0.997-	1.514)	1.101	(0.941-	1.289)
夜中に目が覚める	**1.344**	**(1.112-**	**1.623)**	**1.334**	**(1.147-**	**1.551)**
早朝目が覚める	1.244	(0.997-	1.553)	**1.214**	**(1.024-**	**1.440)**
睡眠剤を使用している	1.158	(0.880-	1.524)	**1.536**	**(1.278-**	**1.847)**
IADL	**0.579**	**(0.522-**	**0.642)**	**0.479**	**(0.422-**	**0.542)**

生活習慣と寝たきりの関連を表7に示した。社会活動は種類を問わず参加している者で男女とも寝たきりへの移行は低くなっており、特に男性では地域活動や自分以外の人の用事が、女性では学習的活動がリスクを小さくしていた。歩行は1日に30分以上の歩行をまったくしていない人に

比べて、行っている人で頻度に関わらずリスクを低下しており、週あたりの頻度が高いほど、寝たきりへの移行が少なかった。歩く早さは同年代の人と同じくらいの人に比べて、遅い人では寝たきりへの移行のリスクが高く、速い人ではリスクが小さかった。１日に30分以上の運動は運動していない人に比べて男性では週に５回以上のみで寝たきりへの移行のリスクが小さく、女性では頻度にかかわらずリスクは小さいが、頻度が多くなるほどリスクが小さくなった。１日に30分以上の体を動かす作業も運動と同様の傾向であったが、男性では週に３回以上でリスクが小さくなり、寝たきりへの移行のリスクは半分以下になっている。

食事に関連する項目では、野菜を１日に２回以上食べている者では、２回未満の者に比べて寝たきりへの移行のリスクは約 30%低下し、食欲のある者ではない者に比べて寝たきりへの移行のリスクは約半分に低下した。緑茶の飲用は女性では寝たきりへの移行と関連していないが、男性では１日に４杯以上飲む者で寝たきりへの移行のリスクが低下していた。喫煙は女性でのみ、まったく吸っていない者に比べて、以前すっていた者、現在吸っている者での寝たきりへの移行のリスクが高くなっていた。

表７　寝たきりへの移行に関連する生活習慣

		男性 (n=5162)			女性 (n=5018)		
社会活動							
給料や謝金を得る仕事		**0.565**	**(0.447-**	**0.716)**	**0.618**	**(0.492-**	**0.778)**
収入を得ない作業		**0.646**	**(0.534-**	**0.782)**	**0.701**	**(0.592-**	**0.829)**
地域活動		**0.530**	**(0.426-**	**0.660)**	**0.642**	**(0.523-**	**0.788)**
自分以外の人の用事・世話		**0.553**	**(0.453-**	**0.675)**	**0.801**	**(0.685-**	**0.937)**
学習的活動		**0.735**	**(0.611-**	**0.884)**	**0.581**	**(0.500-**	**0.675)**
身体活動							
歩行	週に1～2回	**0.748**	**(0.587-**	**0.955)**	**0.762**	**(0.621-**	**0.935)**
	週に3～4回	**0.735**	**(0.559-**	**0.966)**	**0.615**	**(0.490-**	**0.772)**
	週に5回以上	**0.596**	**(0.472-**	**0.753)**	**0.575**	**(0.469-**	**0.704)**
歩く速さ							
	遅い	**2.390**	**(1.943-**	**2.938)**	**2.544**	**(2.144-**	**3.020)**
	速い	**0.588**	**(0.452-**	**0.764)**	**0.602**	**(0.483-**	**0.750)**
1日に30分以上の運動							
	週に1～2回	1.000	(0.787-	1.270)	**0.607**	**(0.495-**	**0.744)**
	週に3～4回	0.919	(0.708-	1.193)	**0.637**	**(0.503-**	**0.806)**
	週に5回以上	**0.730**	**(0.572-**	**0.933)**	**0.597**	**(0.479-**	**0.745)**
1日に30分以上の体を動かす作業							
	週に1～2回	0.776	(0.594-	1.013)	**0.599**	**(0.448-**	**0.800)**
	週に3～4回	**0.430**	**(0.322-**	**0.574)**	**0.478**	**(0.362-**	**0.632)**
	週に5回以上	**0.412**	**(0.323-**	**0.526)**	**0.416**	**(0.327-**	**0.529)**
食事等							
食事回数が3回以上		0.723	(0.459-	1.138)	0.757	(0.466-	1.232)
肉・魚・大豆が1日に2回以上		1.005	(0.828-	1.221)	0.956	(0.819-	1.117)
野菜を1日に2回以上		**0.716**	**(0.577-**	**0.887)**	**0.748**	**(0.610-**	**0.916)**
食欲がある		**0.535**	**(0.405-**	**0.708)**	**0.502**	**(0.388-**	**0.649)**
緑茶の飲用							
	1日に1～3杯	0.817	(0.500-	1.334)	0.945	(0.548-	1.628)
	1日に4杯以上	**0.577**	**(0.358-**	**0.930)**	0.732	(0.430-	1.246)
飲酒	週に1～3回	**0.709**	**(0.525-**	**0.957)**	0.863	(0.642-	1.161)
	週に4～6回	**0.679**	**(0.481-**	**0.959)**	0.889	(0.503-	1.571)
	毎日	**0.678**	**(0.553-**	**0.832)**	1.015	(0.647-	1.592)
喫煙	以前吸っていた	0.899	(0.719-	1.124)	**1.950**	**(1.058-**	**3.595)**
	吸っている	1.054	(0.856-	1.298)	**1.691**	**(1.124-**	**2.543)**

D．考　察

1）疾病との関連

平成 13 年の国民生活基礎調査によると寝たきりになり介護が必要となった原因で多いものは、脳血管疾患、痴呆、骨折・転倒、高齢による衰弱と報告されている。今回の結果でも脳卒中は特に男性で、既往があること、新規発症とも自立度低下や寝たきりへの移行の大きなリスクとなっている。観察期間中の新規発症では、脳卒中、がん、骨折が男女とも自立度低下を引き起こし、男性では肺・気管支の病気、女性では関節・筋肉の病気も自立度低下を引き起こしている。特に男女とも脳卒中、がん、骨折では新規発症なしに比べ寝たきりへの移行のリスクが２倍以上と高く、男性では心臓病、肺・気管支の病気も寝たきりへの移行のリスクを２倍以上高めている。諸外国の先行研究においても、自立度低下に関連した疾病として高血圧、脳卒中、糖尿病、関節炎があげられており、関連する疾患はほぼ一致している。これらの疾病予防が自立度低下の予防や寝たきりの減少へ有効である。

2）目・耳・歯の障害

自立度の低下については、目・耳・歯のいずれも日常生活で困ることがある場合に自立度低下のリスクが増していたが、寝たきりへの移行については、女性でのみ目と耳の障害で寝たきりへのリスクを増していた。これらの障害による自立度低下の関連を検討することは難しいが、耳の障害については Furner ら(1995)が聞こえにくいことが IADL の低下を招きそのために自立度を低下させていると考察しているが、直接的な関連は弱いようである。また Salive ら(1994)は視覚を測定し、自立度低下との関連を指摘しているが、目の障害については、行動の制約を引き起こしたり、転倒などのリスクを高めることが自立度低下に関連している可能性がある。歯については自立度低下には関連していたが、寝たきりへの移行には影響していなかった。歯の具合が悪く食事が十分に摂取できない場合は、低栄養を引き起こす可能性があるが、３年の間に寝たきりを引き起こすほどの要因にならなかった、または他の補助方法で栄養補給がされていたと推測される。

3）睡眠障害

睡眠に関連する障害は後期高齢者や女性において、自立度低下のリスクを約 1.5 倍にし、女性では寝たきりへの移行もわずかであるが高めていた。睡眠の障害によるリスクの増加は他の要因に比べると小さいが、休養が十分にとれないことの背景には、何らかの疾病や生活習慣の乱れ、精神的ストレスなどが複雑に関連していると考えられる。

4）社会活動

社会活動の質問は週当たりの回数で聞いているが、行っている人数が限られていたため回数には分けず、週に１回以下であっても行っている人を活動ありとし、まったくしていない人と比較した。その結果、活動の種類を問わず行っていることが自立度低下や寝たきりのリスクを減少していた。これはこのような活動により身体活動量が増すことと、社会との関連がとれることの両面からの影響によると推測できる。

5）身体活動

身体活動の減少が自立度低下を引き起こすことは良く指摘されている。男女、年齢で多少の違いはあるものの、１日に 30 分以上の歩行、運動、体を動かす作業などを週に３回以上実施することは自立度低下、寝たきりへの移行のいずれも約半分のリスクに予防できると考えられる。また、自己評価ではあるものの、歩行速度が同年代の人と比べて遅いことは自立度低下や寝たきりのリスクを高め、速いことがリスクを小さくしていることから、ある程度速く歩くことができるだけの下肢の筋力を保持することも重要であろう。

6）食　事

栄養と自立度の関連は多くの場合、BMI や体重変化と関連で検討されている。今回の調査では、詳細な食事内容をチェックしていないが、食欲があるものでは、ない者に比べて自立度低下や寝たきりへの移行のリスクが約半分になっている。食欲を維持できることが、身体活動量が多いことなど他の要因とも関連している可能性はあるが、食事量が多くなり低栄養を予防していることも考えられる。食事内容に関しては、食事の回数が３回以上は男性前期高齢者の自立度低下を、野菜を１日に２回以上食べることは男性後期高齢者と女性の前期高齢者の自立度低下、及び男女とも寝たきりへの移行を少なくしていた。簡易な食事では野菜の摂取が少なくなりがちなため、野菜の摂取頻度が質の良い食事を反映していると推測できる。

E．結　論

脳卒中、骨折、がんなどの予防、１日 30 分以上の身体活動を週に３日以上実施、歩く速さを速く維持すること、野菜を１日２回以上食べるような食生活、食欲をあるようにすることが自立度の低下や寝たきりへの移行のリスクを小さくする可能性が示された。

F．健康危険情報

特になし

G．研究発表

1．論文発表

なし

2．学会発表

なし

H．知的財産権の出願・登録状況

なし

Ⅳ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧

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日本老年医学会雑誌（印刷中）.

14) 岩佐　一, 鈴木隆雄, 吉田祐子, 吉田英世, 金　憲経, 古名丈人, 杉浦美穂
地域在宅高齢者における記憶愁訴の実態把握：要介護予防のための包括的健診（「お達者健診」）についての研究(3).
日本公衆衛生雑誌（印刷中）.

Original Article

Increased Plasma 8-Isoprostane Levels in Hypertensive Subjects: the Tsurugaya Project

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To examine the relationship between 8-isoprostane and blood pressure, we measured plasma 8-isoprostane concentration and home blood pressure levels in an elderly Japanese population. Our study population comprised 569 subjects aged 70 years and over who were not receiving antihypertensive medication. On the basis of their blood pressure values, the participants were classified into three groups: normotensive (home blood pressure <135/85 mmHg), hypertensive (home blood pressure 135/85–160/90 mmHg), and severely hypertensive (home blood pressure ≧160/90 mmHg). The mean plasma 8-isoprostane level in the severely hypertensive group (21.1±5.2 pg/ml) was significantly higher than that in the normotensive (20.2±4.9 pg/ml) or hypertensive (19.7±5.1 pg/ml) group, and this result was unchanged when we adjusted for possible confounding factors such as age, sex, use of vitamin A, C or E supplements, smoking status, drinking status, body mass index, use of non-steroidal anti-inflammatory drugs, history of diabetes, hypercholesterolemia, home heart rate and serum creatinine level. Thus, the level of plasma 8-isoprostane appears to be elevated in older subjects with severe hypertension. (*Hypertens Res* 2004; 27: 557–561)

***Key Words*: hypertension, oxidative stress, isoprostanes, home blood pressure measurement, elderly**

Introduction

Data from a number of animal experiments and *in vitro* studies in humans support the hypothesis that increased oxidative stress may be related to elevated blood pressure (BP) (*1*, *2*).

However, few studies have investigated the relationship between 8-isoprostane and hypertension in a large sample of human subjects (*3*).

Isoprostanes are chemically stable lipid peroxidation products of arachidonic acid, and their quantification provides a novel approach to the assessment of oxidative stress *in vivo* (*4*). Isoprostanes are detectable in plasma and urine under normal conditions (*5*), and their levels increase during oxidative stress (*6*).

Recently, self-measurement of BP at home (home BP measurement) has been reported to have better reproducibility (*7*, *8*) and prognostic value (*9*) than BP measurement in clinics.

Our objective was to clarify the relationship between plasma 8-isoprostane concentration and home BP measurement in elderly people.

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This study was supported by a Grant-in-Aid for Scientific Research (13557031) and a grant for JSPS Research (14010301) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, by Research Grants (2002, 2003) from the Japan Atherosclerosis Prevention Fund, and by a Health Science Grant on Health Services (H13-kenko-008) and a grant for Comprehensive Research on Aging and Health (H13-choju-007, H13-choju-023) from the Ministry of Health, Labour and Welfare of Japan.

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Received October 8, 2003; Accepted in revised form May 7, 2004.

Methods

Study Participants

Our study population comprised subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. At the time of the study, there were 2,730 individuals aged 70 years and older living in Tsurugaya. We invited all of these individuals to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status, and 1,179 of them did so, giving their informed consent for analysis of the data. The protocol of this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine. We excluded subjects whose plasma 8-isoprostane levels had not been measured ($n=29$). Home BP data were obtained from 968 of the remaining subjects, who collected their own data on more than 3 days during the 4-week study period. This criterion was based on our previous observation that average BP values for the first 3 days did not differ significantly from those obtained during the entire study period (*7*). Furthermore, since antihypertensive medication *per se* would affect the degree of oxidative stress, we excluded subjects who were receiving antihypertensive medication (*10*). Therefore, the study population comprised 569 subjects (mean age 75.2±4.6 years; men: 45%).

Home BP Measurements

We used the following procedure to ascertain the accuracy of the home BP measurement. First, physicians informed the population about home BP recording and taught them how to measure their own BP. The daily measurement was made within 1 h of awakening and before breakfast, with the subject seated and having rested for at least 2 min. In subjects receiving antihypertensive drugs, home BP was measured before taking the drugs. The home BP of an individual was defined as the mean of all measurements obtained for that person. The mean (±SD) number of home BP measurements was 15.3±10.2 (range, 3–48).

BP-Measuring Device

Home BP was measured with an HEM747IC device (Omron Life Science Co. Ltd., Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic pressures. This device has been validated previously (*11*), and satisfies the criteria of the Association for the Advancement of Medical Instrumentation (*12*).

8-Isoprostane Measurement

Total (esterified plus free) 8-iso-prostaglandin (PG) $F_{2\alpha}$ concentrations were assayed in plasma by a specific enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, USA) (*13*, *14*).

For total 8-iso-$PGF_{2\alpha}$ measurement, peripheral venous blood was collected in ethylenediaminetetraacetic acid 2Na (EDTA2Na)- and EDTA4Na-coated cold polyethylene tubes containing indomethacin, an inhibitor of cyclooxygenase, and aprotinin, an inhibitor of kallikreins, to prevent any *in vitro* formation of 8-iso-$PGF_{2\alpha}$. After collection, blood samples were immediately cooled at 4°C and transferred to the laboratory within 4 h. In the laboratory, the samples were centrifuged at $3,000\times g$ at 4°C for 10 min. The plasma fraction was removed and stored at −80°C for later 8-isoprostane assay. The antiserum used in this assay has 100% cross-reactivity with 8-isoprostane, 0.2% with $PGF_{2\alpha}$, $PGF_{3\alpha}$, PGFI, and PGF_2 and 0.1% with 6-keto $PGF_{2\alpha}$. Both the intra-assay and interassay variabilities were within 6%. The detection limit of the assay was 4 pg/ml .

Classification of Subjects

On the basis of BP values, participants were classified into three groups: normotensive, home BP <135/85 mmHg; hypertensive, home BP 135/85–160/90 mmHg; and severely hypertensive, home BP ≧160/90 mmHg.

Data Analysis

Variables were compared by the *t*-test, analysis of variance, the χ^2 test, or analysis of covariance, as appropriate.

We used the following confounders as covariates: age, sex, use of vitamins A, C or E, use of non-steroidal anti-inflammatory drugs (NSAIDs), smoking habit, drinking habit, body mass index (BMI), history of diabetes or hypercholesterolemia, home heart rate (HR) and serum creatinine level. These factors were chosen because it is known that some lifestyle-related factors, such as obesity (*3*), smoking (*15*), supplementation with vitamins A, C or E (*16*), or use of NSAIDs (*17*), and disease conditions such as diabetes (*18*) or hypercholesterolemia (*19*) can affect the plasma 8-isoprostane level. We defined diabetes as a free blood glucose level of 200 mg/dl or over, or current use of antidiabetic medication. Similarly, we defined hypercholesterolemia as a level of total cholesterol of 220 mg/dl or over, or current use of lipid-lowering agents. The drug information was confirmed by a well trained pharmacist. The level of statistical significance was set at $p<0.05$. Data are given as the mean± SD. All statistical analyses were performed with SAS software, version 8.02.

Results

Descriptive Data for Plasma 8-Isoprostane

Table 1 shows the descriptive data for plasma 8-isoprostane.

Table 1. Descriptive Data for Plasma 8-Isoprostane

		N	Plasma 8-isoprostane	*p* value
Sex	Men	258	20.4±4.9	0.09*
	Women	311	19.7±5.0	
Age	70–79 years	462	20.0±5.0	0.43*
	80 years–	107	20.4±5.1	
Use of vitamins A, C or E supplements	With	74	19.7±5.1	0.47*
	Without	495	20.1±5.1	
Smoking	Current	76	20.7±4.9	0.046**
	Ex	165	20.6±4.8	
	Never	319	19.6±5.2	
Drinking	Current	227	20.0±5.0	0.63*
	Ex or Never	337	20.0±5.1	
Diabetes	With	46	21.0±4.4	0.16*
	Without	523	20.0±5.1	
Hypercholesterolemia	With	243	19.7±5.2	0.11*
	Without	326	20.3±4.9	
Use of NSAIDs	With	92	20.7±4.9	0.18*
	Without	477	19.9±5.1	

NSAIDs, non-steroidal anti-inflammatory drugs. * *t*-test; ** ANOVA.

Table 2. Baseline Characteristics

	Normotensive	Hypertensive	Severely hypertensive	*p* value
N	286	205	78	
Age	74.6±4.0	76.1±5.1	75.1±4.8	0.002*
Sex (% men)	47.6	42.0	46.2	0.46†
Use of vitamins A, C, or E supplements (%)	14.7	11.7	10.3	0.46†
Current smokers (%)	12.2	14.2	15.4	0.82†
Current drinkers (%)	37.4	41.5	44.9	0.18†
Diabetes (%)	8.0	7.8	9.0	0.95†
Hypercholesterolemia (%)	40.9	42.9	48.7	0.037†
BMI	22.9±3.1	24.1±3.5	24.5±3.1	<0.001*
Systolic blood pressure (mmHg)	120.6±9.7	144.1±7.0	167.3±12.4	<0.001*
Diastolic blood presure (mmHg)	70.5±6.5	77.5±7.7	90.8±8.1	<0.001*
Home heart rate (beat/min)	65.2±7.9	65.2±8.1	67.8±8.9	0.03*
Use of NSAIDs	15.7	17.6	14.1	0.75†
Serum creatinine (mg/dl)	0.76±0.20	0.76±0.44	0.73±0.15	0.71*

Normotensive: home blood pressure <135/85 mmHg; Hypertensive: home blood pressure 135/85–160/90 mmHg; Severely hypertensive: home blood pressure ≧160/90 mmHg. BMI, body mass index; NSAIDs, non-steroid anti-inflammatory drugs. * ANOVA; † χ^2 test.

The plasma 8-isoprostane level tended to be higher in men, elderly subjects and subjects with diabetes. Similarly, subjects who were using vitamin A, C or E supplements showed a lower plasma 8-isoprostane level than those who were not. Current smokers and ex-smokers showed higher levels of plasma 8-isoprostane than subjects who had never smoked.

Baseline Characteristics

Table 2 shows the baseline characteristics of the subjects. The normotensives were the youngest subjects, and the prevalence of diabetes was highest among the severely hypertensive subjects. The proportions of subjects who were taking antihypertensive medication were higher among subjects with severe hypertension or hypertension than among normotensive subjects. Among the three subject groups, the mean BMI was the highest in severe hypertensives. The plasma 8-isoprostane level in severely hypertensive subjects (21.1 pg/ml) was significantly higher than that in hypertensive (20.2 pg/ml) or normotensive (19.7 pg/ml) subjects.

Table 3. Relationship between Plasma 8-Isoprostane Level and Home BP Levels

	N	Plasma 8-isoprostane (95% C.I.)
All subjects (*N*=569)		
Normotensive	286	19.7 (19.1–20.3)*
Hypertensive	205	20.1 (19.4–20.8)
Severely hypertensive	78	21.0 (19.9–22.2)
p for trends		0.041
Men (*N*=258)		
Normotensive	136	20.4 (19.5–21.2)
Hypertensive	86	20.0 (18.9–21.0)
Severely hypertensive	36	21.7 (20.0–23.4)
p for trends		0.402
Women (*N*=311)		
Normotensive	150	19.1 (18.3–19.9)
Hypertensive	119	20.2 (19.2–21.1)
Severely hypertensive	42	20.6 (19.0–22.2)
p for trends		0.054
Limited population** (*N*=294)		
Normotensive	156	20.3 (19.5–21.0)
Hypertensive	95	20.0 (19.0–21.0)*
Severely hypertensive	43	21.9 (20.4–23.4)
p for trends		0.149

* $p<0.05$ *vs.* Severely hypertensive. ** Subjects without HDL <40 mg/dl, total cholesterol ≧220 mg/dl, triglyceride ≧300 mg/dl or free blood glucose ≧200 mg/dl. Normotensive: home BP <135/85 mmHg; Hypertensive: home BP 135/85–160/90 mmHg; Severely hypertensive: home BP ≧160/90 mmHg. Adjusted for age, sex, use of vitamin A, C or E supplements, smoking habit, drinking habit, body mass index, home heart rate, diabetes, hypercholesterolemia, use of non-steroid anti-inflammatory drugs and serum creatinine level. *N*, number of subjects; C.I., confidence interval; BP, blood pressure; HDL, high-density lipoprotein.

Adjustment for Possible Confounders

Even after adjustment for confounding factors, there was no change in the finding that the plasma 8-isoprostane level in severely hypertensive subjects was higher than that in hypertensive or normotensive subjects (p for trend=0.041) (Table 3).

When we performed separate analyses for men and women, the finding that the plasma isoprostane level among severely hypertensive subjects was higher than that in normotensives or hypertensives was unchanged. Furthermore, even when we excluded the subjects with a high-density lipoprotein (HDL) cholesterol level <40 mg/dl, or with a level of total cholesterol ≧220 mg/dl, or with a high triglyceride level ≧300 mg/dl or a free blood glucose level ≧200 mg/dl , the tendency for the plasma isoprostane level in severely hypertensive subjects to be higher than that in normotensive or hypertensive was also unchanged.

Discussion

The plasma 8-isoprostane level in elderly subjects with severe hypertension was modestly but significantly higher than that in normotensive or hypertensive subjects, even when we adjusted for possible confounders.

Our study had several methodological advantages. First, the use of home BP measurement made it possible to obtain multiple measurements over a long observation period under well-controlled conditions. This approach has been reported to have better reproducibility (*7*, *8*) and prognostic value (*9*) than casual BP measurement, because it avoids observer bias, regression dilution bias (*8*) and the white-coat effect. Second, we adjusted for possible confounders such as age, sex, use of vitamin A, C or E supplements, smoking habit, drinking habit, BMI, use of NSAIDs, history of diabetes, history of hypercholesterolemia, home HR, and serum creatinine level, since these factors could affect the level of 8-isoprostane or BP.

Although many animal experiments have indicated a positive relationship between high BP levels and 8-isoprostane, few studies have supported such a relation in humans (*3*). Keaney *et al.* examined 2,828 subjects in the Framingham Heart Study and measured urinary creatinine-indexed 8-isoprostane as a marker of systemic oxidative stress (*3*). However, they did not find any meaningful positive association between oxidative stress and hypertension.

The difference between their findings and ours may be explained as follows. First, their diagnosis was based on clinic BP measurements, whereas we used home BP measurements. Therefore, our approach may have reduced the number of misclassifications (*8*).

Second, Keaney *et al.* considered that the proportion of individuals with oxidative-mediated hypertension, such as salt sensitivity, may have been too small to drive an association between hypertension and oxidative stress in their sample (*3*). On the other hand, our population comprised elderly Japanese individuals. The proportion of individuals with sodium sensitivity is known to be higher in Japanese than in Caucasian populations (*20*). Similarly, BP becomes salt-sensitive with age (*20*). Therefore, the proportion of subjects with salt sensitivity might have been higher in our subjects than in theirs, and this might have at least partly accounted for the difference between our results and those of Keaney *et al.* (*3*).

Our study also had some limitations. First, most of the participants were sufficiently active and healthy to participate in the survey, and this might have led to small inter-individual differences in the study effects. Second, since this study was a cross-sectional study, we cannot conclude that oxidative stress causes hypertension or that higher BP leads to increased oxidative stress. Third, we used EIA rather than gas chromatography/mass spectrometry, the gold standard for isoprostane analysis, and plasma obtained by centrifuga-

tion was stored at −80°C within 1 to 4 h—rather than immediately—after collection, because large numbers of samples had to be processed in a timely manner. Finally, we used plasma samples rather than urine samples. Although the plasma samples were prepared carefully (peripheral venous blood was collected in polyethylene tubes containing 1 mmol/ml indomethacin, cooled immediately at 4°C and transferred to the laboratory within 4 h; plasma obtained by centrifugation was aliquoted and stored at −80°C for later 8-isoprostane assay in the laboratory), some autoxidation might have occurred.

In conclusion, we have demonstrated that plasma 8-isoprostane levels are elevated in elderly subjects with severe hypertension. This is the first study to clarify the relationship between isoprostanes and hypertension in elderly individuals. However, as the difference in plasma 8-isoprostane levels among the three groups was modest, further study will be needed to clarify the clinical significance of this difference.

Acknowledgements

The authors are grateful to all the participants of the Tsurugaya Project, and to Yoshiko Nakata, Mika Wagatsuma, and Reiko Taneichi for their secretarial assistance.

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Original Article

C-Reactive Protein and Peripheral Artery Disease among Japanese Elderly: the Tsurugaya Project

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We investigated the cross-sectional relationship between ankle brachial index and cardiovascular disease risk factors, including C-reactive protein (CRP), among Japanese elderly, a topic which has had little prior epidemiologic study. Our study population comprised 946 subjects aged at least 70 years in whom both CRP and ankle brachial index were measured. The participants were classified into a low (ankle brachial index<0.9) and normal ankle brachial index group. We found that current smoking, high-density lipoprotein cholesterol <40 mg/dl, a low body mass index (continuous variable), hypertension, diabetes and statin use were all significantly related to a lower ankle brachial index. Higher log-transformed CRP level was significantly related to a lower ankle brachial index after adjustment for the cardiovascular risk factors mentioned above ($p<0.01$). The odds ratios for low ankle brachial index compared to 0–1 risk factors were 5.79 (95% confidence interval [CI]: 2.99–11.20) for 2 risk factors and 17.45 (95% CI: 6.78–49.91) for 3 or more risk factors; independently of other risk factors, the odds ratio for CRP>1.0 mg/l was 2.10 (95% CI: 1.13–3.88) compared to lower CRP values. Thus, a high level of CRP is related to a low ankle brachial index among Japanese elderly as well as Western subjects. This is the first study to report the relationship between CRP and low ankle brachial index among Japanese elderly. (*Hypertens Res* 2004; 27: 955–961)

***Key Words*: C-reactive protein, cardiovascular risk factors, ankle brachial index, Japanese, elderly**

Introduction

In recent years, C-reactive protein (CRP) has become established as a risk factor for cardiovascular diseases (*1–14*). Higher levels of CRP predict future myocardial infarction and stroke independently of other cardiovascular disease risk factors, and it has been suggested that the measurement of CRP, in addition to cardiovascular disease risk factors, may improve our ability to predict cardiovascular diseases (*10, 13*).

Peripheral artery disease (PAD) is a severe atherosclerotic condition causing intermittent claudication and is associated with higher incidence of future cardiovascular and cerebrovascular diseases (*15–19*). The low ankle brachial systolic blood pressure index (ABI) has been used as a measure of lower limb PAD (*20*). In Western countries, some prospective studies have demonstrated a positive relationship between CRP and low ABI (*21, 22*) as well as a relationship

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This study was supported by a Grant-in-Aid for Scientific Research (13557031), by a grant for JSPS Research (14010301) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, by a Research Grant (2002, 2003) from the Japan Atherosclerosis Prevention Fund, by a Health Science Grant on Health Services (H13-kenko-008), and by grants for Comprehensive Research on Aging and Health (H13-choju-007, H13-choju-023) from the Ministry of Health, Labour and Welfare of Japan.

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Received June 28, 2004; Accepted in revised form August 25, 2004.

between CRP and cardiovascular diseases (*1–14*).

In Japan, however, epidemiological data about risk factors for low ABI among Japanese have been limited (*23, 24*). Furthermore, no studies have investigated the relationship between CRP and low ABI. Therefore, in the present study, we investigated the relationship between ABI and cardiovascular disease risk factors, including CRP, among Japanese elderly.

Methods

Study Participants

Our study population comprised subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. At the time of the study, there were 2,730 people aged 70 years and older living in Tsurugaya (*25, 26*). We invited all of these individuals to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status, and 1,178 of these people agreed to participate and give their informed consent for analysis of the data. The protocol for this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine. We excluded subjects whose CRP had not been measured ($n=29$) and subjects whose ABI had not been measured ($n=21$). We assessed hypertension using home blood pressure (BP) data, and subjects who did not measure their BP on at least 3 days during the 4-week study period were excluded ($n=176$). This criterion was based on our previous observation that the average BP values for the first 3 days did not differ significantly from those obtained during the entire study period (*27*). Furthermore, we excluded subjects who did not complete the questionnaire about alcohol consumption ($n=6$). Therefore, the study population comprised 946 subjects (mean age 75.2± 4.6 years, men: 45%).

CRP Measurement

We collected the blood sample under non-fasting conditions. Serum CRP levels were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high sensitivity assay utilizes a monoclonal antibody coated on polystyrene particles and fixed-time kinetic nephelometric measurements (*28*). The BN II nephelometer makes a 1:400 dilution to measure CRP concentrations between 3.5 and 210 mg/l. The assay has been approved by the US Food and Drug Administration for use in assessing the risk of cardiovascular and peripheral vascular disease.

ABI Measurement

Bilateral ABI was measured in all subjects using a new device, the FORM ABI/PWV (Colin Co., Komaki, Japan), which incorporates an automatic oscillometer (*29*). The FORM ABI/PWV is a device with four cuffs that can measure BP levels simultaneously in both arms and both legs, and automatically calculates the ABI. This device is useful for mass medical examinations and population-based studies because it enables measurements of ABI and brachial ankle pulse wave velocity in a short time and is not affected by the operator's technique. This device has been used in other Japanese epidemiological studies (*24, 30, 31*).

Classification of Subjects

We treated the lowest ABI in either leg as the ABI value. We defined the subjects with an ABI<0.90 as the "low ABI" subjects, and we classified serum CRP levels into three groups, <1 mg/l, 1 to 2.9 mg/l and 3 mg/l and over, according to the previous reports (*10, 13*).

Data Analysis

Variables were compared by the χ^2 test, *t*-test or analysis of variance, as appropriate. The odds ratio (OR) of PAD was calculated using multiple logistic regression analysis.

We used the following variables as confounding factors: age, sex, smoking habit, drinking habit, hypertension, hypercholesterolemia, a low level of high density lipoprotein (HDL) cholesterol, body mass index (BMI), diabetes, prior cardiovascular diseases and use of statin drugs.

Subjects were considered hypertensive if their home systolic BP (SBP) was at least 135 mmHg and/or home diastolic BP (DBP) was at least 85 mmHg, or if they were using antihypertensive agents (*32, 33*). Subjects were considered diabetic if their non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Subjects were considered hypercholesterolemic if their level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol was defined as a level of HDL cholesterol below 40 mg/dl. The information on smoking status, drinking status and history of prior cardiovascular diseases was obtained using questionnaire surveys. Current drinkers were also asked about drinking frequency, beverage types usually consumed, and amount consumed on a single occasion. From these responses we calculated the average daily alcohol consumption in grams. Since statins have been reported to lower CRP levels (*34, 35*), we treated them as independent confounding factors. When we analyzed the relationship between low ABI and CRP as a continuous variable, we used the log-transformed value (CRP value+1), because the CRP distribution was skewed to the right among Japanese (*36*); we added 1 before transformation because the log-transformation expands the scale for values below 1. Since the CRP level has been reported to be related to risk clustering (*37*), we analyzed the relationship between low ABI and a combi-

Table 1. Association between Lower Ankle Brachial Index and Cardiovascular Disease Risk Factors, for 946 Subjects, the Tsurugaya Project, Sendai, Japan, 2002

	Ankle brachial index		
	<0.9	≧0.9	*p*
Number of subjects	54	892	
Age (years)	77	76	0.049*
Sex (male %)	67	43	<0.01**
Current smoker (%)	26	12	<0.01**
Ex-smoker (%)	43	30	
Never smoker (%)	31	58	
Mean alcohol consumption (g)	14	10	0.37*
Body mass index (kg/m^2)	24	24	0.46*
Hypertension (%)	91	69	<0.01**
Diabetes (%)	26	9	<0.01**
Hypercholesterolemia (%)	31	36	0.49**
Low HDL cholesterol (%)	33	11	<0.01**
Use of statin drugs (%)	30	16	0.01**
History of cardiovascular diseases (%)	31	15	<0.01**

* *t*-test, ** χ^2-test. Hypertension: home systolic blood pressure (BP) was at least 135 mmHg and/or home diastolic BP was at least 85 mmHg, or they were using antihypertensive agents. Diabetes: non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Hypercholesterolemia: level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol: level of high density lipoprotein cholesterol below 40 mg/dl.

Table 2. Association between C Reactive Protein (CRP) and Cardiovascular Disease Risk Factors

	CRP (mg/l)			*p*
	−0.9	1.0−2.9	3.0−	
Number of subjects	637	201	108	
Age (years)	76	76	76	0.70*
Sex (male %)	43	47	47	0.44**
Current smoker (%)	11	17	12	0.02*
Ex-smoker (%)	29	32	40	
Never smoker (%)	60	51	47	
Alcohol consumption (g)	11	13	7	0.22*
Body mass index (kg/m^2)	24	25	25	<0.01*
Hypertension (%)	68	74	81	0.01**
Diabetes (%)	8	11	16	0.03**
Hypercholesterolemia (%)	33	42	40	0.047**
Low HDL cholesterol (%)	11	14	16	0.20**
Use of statin drugs (%)	18	13	19	0.27**
History of cardiovascular diseases (%)	15	17	24	0.051**

* ANOVA, ** χ^2-test. Hypertension: home systolic blood pressure (BP) was at least 135 mmHg and/or home diastolic BP was at least 85 mmHg, or they were using antihypertensive agents. Diabetes: non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Hypercholesterolemia: level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol: level of high density lipoprotein cholesterol below 40 mg/dl.

nation of cardiovascular disease risk factors and CRP level. In this analysis, we treated hypertension, diabetes, current smoking or low HDL cholesterol as cardiovascular disease risk factors.

The drug information was confirmed by an experienced pharmacist. The level of statistical significance was set at $p<0.05$. All statistical analyses were performed with SAS software, version 8.2 (SAS Institute, Cary, USA).

Results

Association between ABI and Atherosclerosis Risk Factors

Table 1 shows the association between low ABI and cardiovascular disease risk factors. The mean age was significantly higher in subjects with low ABI than those without low ABI. The proportions of never smokers and females were lower in low ABI subjects. Similarly, the proportions of subjects with hypertension, diabetes, and low HDL cholesterol, and the proportions of statin users or subjects with a history of prior cardiovascular diseases, were higher in low ABI subjects. The proportions of subjects with hypercholesterolemia did not differ between subjects who had a low ABI and subjects who did not. Neither alcohol consumption nor BMI differed between subjects with or without a low ABI.

Association between CRP and Other Cardiovascular Disease Risk Factors

The median (interquartile range) of CRP was 0.61 (0.17–1.37) mg/l. Table 2 shows the association between CRP value and cardiovascular disease risk factors. The proportion of never smokers was lower in subjects with high CRP, and the proportions of ex-smokers or subjects with hypertension, hypercholesterolemia, diabetes or prior cardiovascular diseases were higher in subjects with the highest CRP level. The proportions of each gender, subjects with low HDL cholesterol or statin users did not differ among the CRP groups. Mean age or alcohol consumption also did not differ among the CRP groups. BMI was lower in the subjects of the lowest CRP group.

OR of Low ABI Was Associated with CRP and Cardiovascular Disease Risk Factors

Table 3 shows the results of the multiple logistic regression analysis. Compared with the lowest CRP group, the moder-