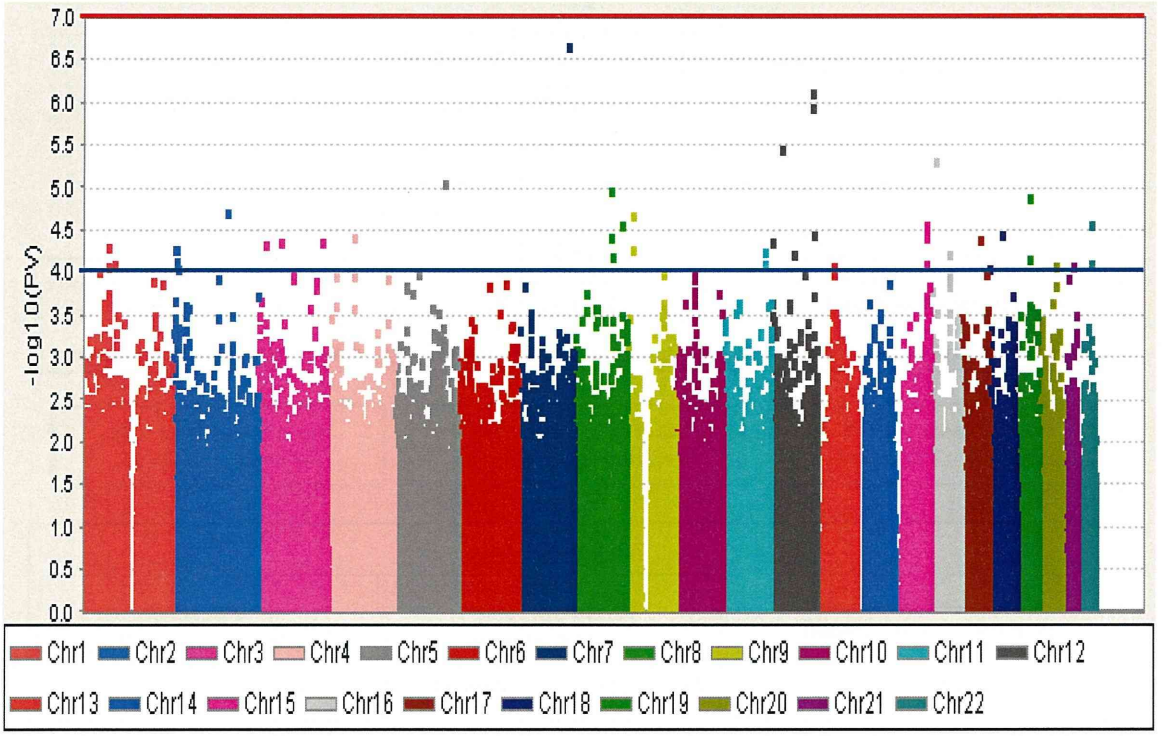

Figure 5. Manhattan plot for GWAS
(All sample, APOE & Age & Sex adjusted)

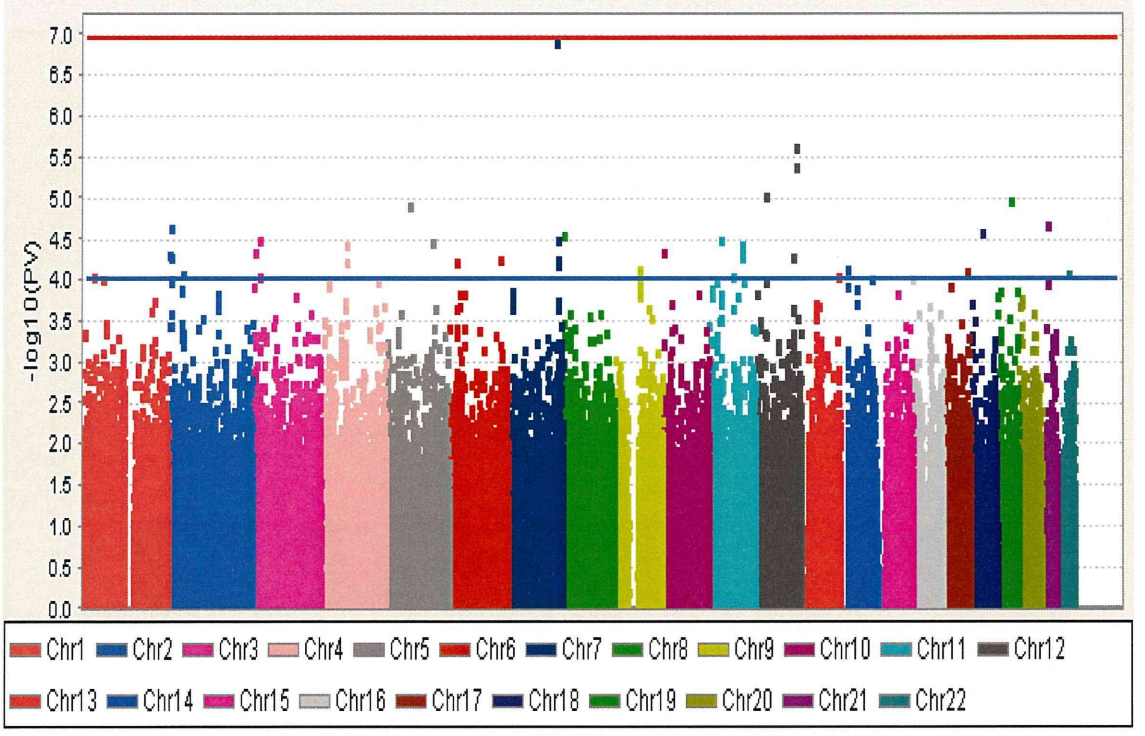

Figure 5. Manhattan plot for GWAS
(Only E4 non-carrier, Age & Sex adjusted)

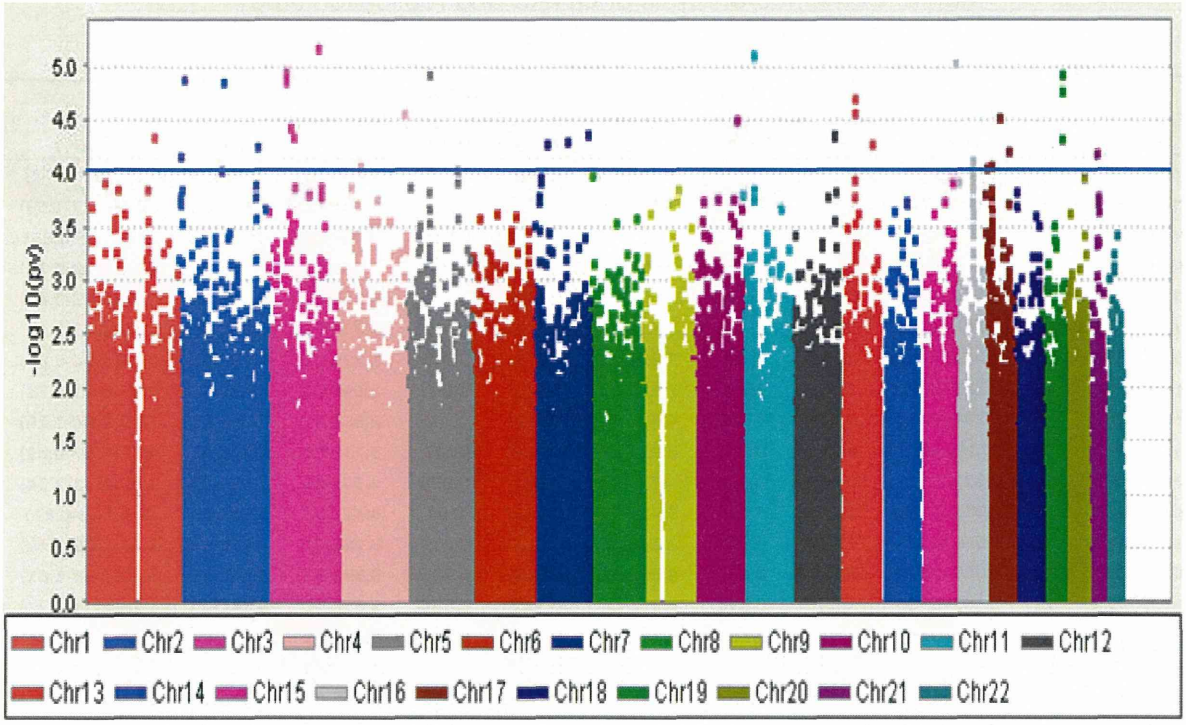

Figure 6. Manhattan plot for GWAS
(Only E4 carrier, Age & Sex adjusted)

Table1. Combined analysis of GWAS and replication study
(All sample, Age & Sex adjusted, Top 20 SNPs)

rs No	Chr.	Position	GWAS set			Replication set			Combined	
			MAF		Adjusted	MAF		Adjusted		
			Case	Control	P	Case	Control	P	P	OR
rs1992269	18	1862317	0.074	0.076	9.60E-04	0.062	0.08	2.16E-04	6.15E-07	1.66 (1.36-2.04)
rs445925	19	50107479	0.093	0.071	6.48E-05	0.093	0.066	2.11E-02	1.49E-05	0.67 (0.55-0.81)
rs4140576	22	37550854	0.204	0.243	3.43E-04	0.228	0.251	6.49E-03	1.52E-05	1.31 (1.16-1.49)
rs2700893	7	36138210	0.097	0.073	5.47E-04	0.086	0.073	7.71E-03	1.66E-05	0.67 (0.55-0.81)
rs2309394	9	70860935	0.469	0.489	8.47E-04	0.459	0.494	5.80E-03	2.10E-05	1.25 (1.12-1.39)
rs3829062	9	70858017	0.469	0.489	8.48E-04	0.458	0.494	6.06E-03	2.21E-05	1.25 (1.12-1.39)
rs7164548	15	97483852	0.382	0.369	6.26E-05	0.39	0.37	2.82E-02	2.71E-05	1.25 (1.12-1.40)
rs206768	6	33069364	0.266	0.255	8.35E-04	0.281	0.233	7.95E-03	2.85E-05	1.28 (1.14-1.45)
rs2718005	7	36091147	0.095	0.072	6.72E-04	0.086	0.071	1.12E-02	3.11E-05	0.68 (0.56-0.82)
rs1882059	7	36091506	0.097	0.072	5.62E-04	0.086	0.072	1.45E-02	3.68E-05	0.68 (0.56-0.82)
rs2718000	7	36097663	0.095	0.073	7.78E-04	0.085	0.072	1.19E-02	3.73E-05	1.47 (1.22-1.77)
rs5757299	22	37552598	0.218	0.259	1.84E-04	0.245	0.268	1.80E-02	3.83E-05	0.78 (0.68-0.88)
rs1394890	18	1190631	0.022	0.017	8.10E-04	0.025	0.019	1.12E-02	3.96E-05	2.04 (1.45-2.87)
rs206775	6	33062611	0.252	0.242	9.75E-04	0.267	0.219	9.62E-03	4.03E-05	1.28 (1.13-1.45)
rs17641468	4	23843172	0.203	0.225	3.55E-05	0.198	0.225	4.86E-02	4.49E-05	1.30 (1.14-1.48)
rs17757570	8	135240906	0.071	0.085	5.71E-04	0.069	0.091	1.10E-02	4.55E-05	0.68 (0.56-0.82)
rs2239842	6	33369848	0.284	0.262	2.94E-04	0.276	0.245	2.21E-02	4.88E-05	1.28 (1.13-1.44)
rs9655368	7	36115610	0.093	0.073	8.06E-04	0.084	0.072	1.60E-02	5.46E-05	1.46 (1.21-1.76)
rs1478671	13	54224245	0.355	0.381	3.31E-04	0.36	0.391	2.45E-02	7.26E-05	1.24 (1.11-1.38)
rs213220	6	33310617	0.25	0.235	3.41E-04	0.246	0.217	3.34E-02	9.66E-05	1.27 (1.12-1.44)

Table2. Combined analysis of GWAS and replication study
(All sample, APOE & Age & Sex adjusted, Top 20 SNPs)

			GWAS set			Replication set			Combined	
			MAF		Adjusted	MAF		Adjusted		
SNP_ID	chr	chrloc	Case	Control	P_{GC}	Case	Control	P	P_{GC}	OR
rs802571	7	145962186	0.065	0.084	3.14E-05	0.063	0.09	2.08E-03	1.26E-06	0.52(0.4-0.68)
rs2683530	3	24211739	0.421	0.464	3.15E-05	0.431	0.461	1.80E-02	1.99E-05	1.34(1.17-1.53)
rs7939964	11	96675255	0.244	0.19	3.47E-05	0.202	0.194	3.20E-02	2.86E-05	0.71(0.6-0.83)
rs11613092	12	118893248	0.124	0.093	2.31E-06	0.104	0.091	3.56E-02	6.85E-06	0.61(0.49-0.76)
rs1982437	11	96747308	0.286	0.231	3.99E-05	0.239	0.231	5.96E-02	8.33E-05	0.73(0.63-0.86)
rs1207782	6	22059967	0.141	0.116	5.65E-05	0.111	0.121	7.89E-02	3.04E-01	0.9(0.73-1.1)
rs2915236	11	34885510	0.211	0.23	3.09E-05	0.232	0.246	1.26E-01	4.75E-04	0.75(0.64-0.88)
rs227030	14	22986656	0.058	0.04	7.11E-05	0.047	0.042	1.69E-01	4.69E-04	0.57(0.41-0.78)
rs712781	3	7479947	0.279	0.308	4.41E-05	0.326	0.305	2.60E-01	2.35E-01	1.09(0.94-1.26)
rs7022747	9	73435028	0.098	0.078	6.99E-05	0.097	0.085	3.75E-01	3.24E-03	0.71(0.57-0.89)
rs912837	10	3320113	0.049	0.036	4.43E-05	0.041	0.036	4.34E-01	1.83E-03	1.69(1.21-2.34)
rs10900821	5	133049626	0.06	0.034	3.41E-05	0.043	0.04	4.42E-01	1.50E-03	0.6(0.43-0.82)
rs7566447	2	5662812	0.272	0.224	2.26E-05	0.223	0.217	5.18E-01	2.71E-03	1.27(1.09-1.49)
rs12579216	12	108941679	0.113	0.137	4.86E-05	0.13	0.136	5.33E-01	6.54E-03	1.32(1.08-1.61)
rs7299095	12	118896304	0.37	0.395	3.85E-06	0.392	0.394	5.65E-01	3.84E-02	1.16(1.01-1.32)
rs7842534	8	1824066	0.119	0.151	2.72E-05	0.149	0.144	6.60E-01	7.65E-02	1.19(0.98-1.44)
rs12452401	17	71689125	0.404	0.451	7.79E-05	0.439	0.443	7.37E-01	1.19E-02	0.84(0.73-0.96)
rs9690885	7	139366112	0.099	0.058	1.21E-07	0.065	0.064	7.56E-01	3.28E-04	0.63(0.49-0.81)
rs6557548	6	150952769	0.125	0.1	5.21E-05	0.105	0.099	8.48E-01	2.37E-02	0.78(0.63-0.97)
rs11099642	4	76483511	0.191	0.223	3.52E-05	0.25	0.218	9.39E-01	2.72E-02	1.2(1.02-1.41)

Table3. Combined analysis of GWAS and replication study
(Only E4 non-carrier, Age & Sex adjusted, Top 20 SNPs)

			GWAS set			Replication set			combined	
			MAF		Adjusted	MAF		Adjusted		
SNP_ID	chr	chrloc	Case	Control	P_{GC}	Case	Control	P	P_{GC}	OR
rs5757299	22	39222652	0.216	0.26	2.64E-05	0.245	0.268	1.77E-02	2.12E-05	0.76(0.67-0.86)
rs11613092	12	118893248	0.118	0.093	1.11E-06	0.094	0.093	5.54E-02	1.02E-05	0.67(0.56-0.8)
rs10418830	19	29724513	0.48	0.496	1.23E-05	0.493	0.487	1.39E-01	2.21E-01	1.07(0.96-1.19)
rs3930233	3	184216196	0.13	0.108	4.22E-05	0.11	0.111	1.48E-01	2.70E-01	1.1(0.93-1.31)
rs916815	17	55222196	0.487	0.431	3.88E-05	0.438	0.439	1.66E-01	2.61E-01	1.06(0.95-1.19)
rs4977448	9	18807071	0.455	0.476	2.05E-05	0.48	0.473	2.98E-01	1.30E-03	1.19(1.07-1.33)
rs7566447	2	5662812	0.257	0.221	5.02E-05	0.228	0.219	4.04E-01	2.70E-03	1.22(1.07-1.38)
rs1435397	15	88454826	0.179	0.145	3.14E-05	0.129	0.154	4.15E-01	6.07E-02	1.16(0.99-1.35)
rs7299095	12	118896304	0.37	0.394	7.56E-07	0.401	0.394	5.82E-01	2.33E-02	1.14(1.02-1.27)
rs983034	1	68603586	0.121	0.146	4.71E-05	0.143	0.14	6.60E-01	7.79E-02	1.15(0.98-1.35)
rs9690885	7	139366112	0.087	0.059	2.11E-07	0.061	0.063	6.90E-01	4.40E-04	0.68(0.55-0.84)
rs16869497	8	103541717	0.401	0.433	1.05E-05	0.417	0.429	6.92E-01	3.84E-02	1.12(1.01-1.25)
rs7652337	3	24220643	0.445	0.497	4.40E-05	0.498	0.487	7.45E-01	1.10E-02	0.87(0.78-0.97)
rs1435400	15	88480751	0.173	0.139	2.61E-05	0.129	0.143	7.64E-01	2.23E-02	1.2(1.03-1.4)
rs10520672	15	88566617	0.215	0.188	2.84E-05	0.176	0.187	7.91E-01	2.79E-02	0.86(0.75-0.98)
rs10846773	12	125412478	0.073	0.06	3.51E-05	0.066	0.06	7.98E-01	1.02E-02	1.33(1.07-1.66)
rs7723229	5	142337083	0.083	0.067	8.41E-06	0.072	0.067	8.48E-01	1.13E-02	0.76(0.62-0.94)
rs2903404	16	13857840	0.232	0.285	4.78E-06	0.284	0.287	9.23E-01	1.79E-02	0.86(0.77-0.98)
rs11131036	3	65726434	0.419	0.468	4.09E-05	0.461	0.463	9.66E-01	2.27E-02	1.13(1.02-1.26)
rs11099642	4	76483511	0.198	0.226	3.74E-05	0.24	0.221	9.82E-01	2.79E-02	1.16(1.02-1.32)

Table4. Combined analysis of GWAS and replication study
(Only E4 carrier, Age & Sex adjusted, Top 20 SNPs)

			GWAS set			Replication set			Combined	
			MAF			MAF				
SNP_ID	chr	chrloc	Case	Control	Adjusted P	Case	Control	Adjusted P	P	OR
rs7968513	12	125414416	0.056	0.034	4.45E-05	0.038	0.028	1.80E-01	7.93E-02	0.7(0.47-1.05)
rs269951	19	55441995	0.286	0.26	1.16E-05	0.265	0.264	2.61E-01	7.56E-03	0.61(0.41-0.88)
rs346410	5	62537479	0.142	0.107	1.17E-05	0.108	0.116	3.25E-01	1.84E-03	12.74(2.56-63.15)
rs11921930	3	50897386	0.237	0.177	1.23E-05	0.189	0.186	3.33E-01	1.07E-01	1.18(0.96-1.45)
rs7317235	13	46295113	0.164	0.208	1.91E-05	0.228	0.204	4.42E-01	3.82E-02	1.29(1.01-1.64)
rs10190431	2	215048212	0.368	0.33	5.46E-05	0.322	0.317	4.61E-01	1.31E-01	1.19(0.94-1.51)
rs7680411	4	183771387	0.028	0.015	2.66E-05	0.009	0.014	4.66E-01	5.35E-02	0.83(0.69-1.01)
rs12637997	3	51434215	0.24	0.175	1.10E-05	0.181	0.18	5.39E-01	3.50E-02	1.22(1.01-1.48)
rs1647791	7	37473071	0.308	0.347	5.15E-05	0.339	0.331	5.45E-01	4.11E-04	0.41(0.24-0.68)
rs7946109	11	33841739	0.449	0.5	7.47E-06	0.488	0.493	5.60E-01	3.09E-02	0.81(0.66-0.99)
rs10846773	12	125412478	0.08	0.06	4.16E-05	0.075	0.059	5.77E-01	3.60E-01	0.91(0.73-1.12)
rs17098973	10	121288501	0.418	0.481	2.98E-05	0.469	0.472	5.98E-01	1.19E-02	1.53(1.09-2.12)
rs634742	19	55434818	0.211	0.193	4.69E-05	0.187	0.195	6.49E-01	7.24E-03	0.77(0.64-0.94)
rs17705339	7	95616309	0.046	0.071	4.75E-05	0.068	0.069	7.39E-01	6.09E-02	0.83(0.68-1.01)
rs7626892	3	63655742	0.485	0.463	3.51E-05	0.47	0.489	7.47E-01	1.71E-02	0.41(0.19-0.86)
rs9561536	13	94975788	0.42	0.358	5.11E-05	0.35	0.36	8.04E-01	6.43E-03	1.66(1.15-2.4)
rs4968876	17	66127358	0.107	0.088	5.90E-05	0.1	0.09	8.23E-01	4.05E-02	0.81(0.66-1)
rs11719545	3	72582977	0.08	0.075	4.47E-05	0.074	0.072	8.50E-01	2.86E-02	0.79(0.63-0.98)
rs2024365	7	154019581	0.223	0.244	4.13E-05	0.245	0.247	9.58E-01	1.09E-01	0.79(0.58-1.06)
rs10798713	1	179680642	0.351	0.327	4.40E-05	0.348	0.347	9.96E-01	8.51E-02	1.19(0.97-1.46)

厚生労働科学研究（認知症対策総合研究事業）
アルツハイマー病の危険因子の解明と予防に関する大規模ゲノム疫学研究
分担研究報告書

久山町研究の証拠の基づくCPAスマートライススタイル（60－70歳からはじめる認知症予防編）の開発

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研究要旨　本年度は、当初の研究計画に基づき、認知症予防のための介入研究の方法論を検討した。まず4年間の久山町疫学研究の証拠に基づいた介入プログラム開発とその実施マニュアルを作成することを目的とした。さらに、地域在住高齢者への「久山町方式：食・運動お勧めメニュー」の実行性について検証した。その結果、認知症（特に、アルツハイマー病（AD））予防に向けた「久山町方式：食・運動お勧めメニュー」とその実施に向けたツールを開発・作成した（CPA スマートライフスタイル：60－70 歳からはじめる認知症予防編）。また介入実施にあたっての実行性検証については、対象者に対し良好な反応が得られ、今後の久山町住民に向けた介入にあたっての実行可能性が示唆された。

A. 研究目的

わが国では、高齢者人口の増加に伴い認知症患者が急速に増えており、その対策が急務となっている。これまで我々は、認知機能の低下や認知症発症における運動要因や食事要因の予防効果について横断的または縦断的に検討してきた。

福岡県久山町において，1988 年から 60 歳以上の認知症のない 1191 名を 17 年間前向きに追跡し，運動習慣とアルツハイマー病（AD）および脳血管性認知症（VD）発症との関係を検討した．調査開始時の運動習慣の有無により対象者を 2 群に分類し，運動なし群を基準として，運動あり群の AD，および VD 発症の相対危険を算出した．調整後の AD 発症の相対危険は，運動あり群で 0.69 と有意に低かった．一方，VD 発症の相対危険は両群で有意な差異を認めなかった。以上の成績より，運動習慣を有することは AD 発症の有意な予防因子であることが示唆された．

認知機能と食事性因子との関係については、改訂長谷川式簡易知能評価スケール（HDS-R）と Mini-Mental State Examination（MMSE）を用い検討した結果、HDS-R、MMSE の両方において有意なリスクの低下がみられた食事性因子は、カリウム、マグネシウム、総食物繊維、不溶性食物繊維で、さらに食事パタンとの関連では副菜型の食事パタンが認知機能低下のリスクを減少させることが示唆された。また、認知症発症と食事性因子との関係については、大豆製品、野菜類、海藻類、乳製品の高摂取と、米の低摂取が認知症発症のリスクを低下させることが示唆されている。

そこで本年度は、当初の研究計画に基づき、介入試験の実施するための方法論の検討を行うことを第一の目的とした。さらに、認知機能水準でカテゴリー化された対象者への介入実施にあたっての実行性について検証することを第二の目的とした。

B. 研究方法

1．介入試験実施の方法論について

これまでの運動要因、食事要因の、これまでの解析結果に基づいて、介入プログラム開発を目的とした行動科学的アプローチ法による「久山町方式：食・運動お勧めメニュー」の作成を行った。さらにメニュー実施にあたっての手順や説明書のマニュアルの作成を行った。

2．介入実施にあたっての実行性検証について

認知機能水準でカテゴリー化された対象者への「久山方式：食・運動お勧めメニュー」の実行性の検証として、太宰府市在住の高齢者男女 16 名（男性：７名、女性：９名；平均年齢：　75.1 歳）を対象とし、1 週間の短期介入を実施した。

特に、運動面ではＣＰＡの運動知識に表示している、三角の握る用具（にぎってごらん：資料参

照）を持ち帰っていただいた。握り方、構え方、動かし方の簡単な紹介を実施した。さらに、身体活動量の改善を目的として歩数計を全員に配布した。

C. 研究結果

1. 介入試験実施の方法論について

図 1、2 に示すような久山町方式：食・運動お勧めメニュー「CPA スマートライフスタイル：60－70 歳からはじめる認知症予防編」を作成した。教材名の『CPA』とは『チェック（Check）→プラン（Plan）→アクション（Action)』の頭文字をとったもので、行動療法の治療構造を表す我々が新しく作った用語である。CPA スマートライフスタイルは、研究協力者である山津が研究代表者となって展開した厚生労働科学研究費補助金循環器疾患・糖尿病等生活習慣病対策総合研究事業の中で開発してきたコンセプトである。

今回作成した「CPA スマートライフスタイル：60－70 歳からはじめる認知症予防編」は、前述のとおり久山町研究のこれまでの研究成果からの知見を利用した。チェックの欄では、久山研究から得られた AD の危険因子を参考とし、記入者本人が自分の AD 罹患の危険度を知ることができるようにした。また、プランの欄で選択される目標設定の項目も、久山町研究や国内外の研究知見から報告されている生活習慣改善目標を網羅するよう工夫した。

また、認知症予防を主対象とする場合の教材利用者は高齢者が中心となることを想定し、A3 用紙で可能な限り大きな文字サイズとした。教材利用に際しては、介入指導者がいなくても高齢者が自ら書き込みながら読み進めることができるようにした。

2. 介入実施にあたっての実行性検証について

太宰府市在住の高齢者男女１６名を対象とした 1 週間の短期介入を実施した結果、教材を利用した初回介入において、アクション：ライフスタイルの改善目標を記入して実行した結果、アクションプランの記入数は男性で平均 2.4 個、女性は 2.7 個であった。そのプランの実行達成率は、全体で、80.1%となり男性で 85.7%、女性は 75.9%と高い達成率であった。

選択されたアクションプランで一番多く記入された項目は、「筋肉を鍛える運動」（7 人：男性 1 人、女性 6 人）であった。次に「普通より早く歩く」（４人：女性４人)、「日記を書く」（４人：男性１人、女性３人）となり、３人が「1 日 8000 歩く」「肉か魚を毎日食べる」を記入した。改善目標に選ばれたすべての項目の、運動、食事、生活での比率は、54：19：27 と運動部門からの項目の選択が半数以上であった。

目標の達成率が 100%の項目は、「１日１万歩を歩く」「１日 3000 歩く」「畑や庭仕事」「毎日赤ワインを飲む」「食事のバランス」「地域や自治会などで社会的役割をもつ」となり、運動部門から３項目、食事部門から２項目、生活習慣部門から１項目であった。

部門別の平均達成率を比較すると、食事部門が 90.4%と高く、ついで生活習慣部門が 82.8%,運動部門の 79.1%となった。

このように１６名全員が,それぞれの改善目標を確認し、達成度合いは項目により違いはあるが、全体の平均達成率が 80.1%と高い数値であることを確認した。

また、１週間の介入後の事後アンケートでの問いの「教材を読んだ後に、あなたが変えたことは？」の問いの選択結果では、食事など日ごろの食べ方･運動などの日頃の動き方が 10 点であり、次いで、昼寝などの眠り方が９点、その他３点、特に変えたことはないが１点という結果であり、食事と運動、生活面において行動変容が確認された。

D. 考察

1. 介入試験実施の方法論について

久山町研究のこれまでの成果を活用し、かつ介入対象となる高齢者に配慮した介入教材を作成することができた。

2. 介入実施にあたっての実行性検証について

今回開発した教材を用いた介入試行の結果、初回介入を含めた介入初期の脱落は少なかった。

今回の介入試行の結果を反映し、さらに利用しやすい教材に改良余地があると考えられた。

E. 結論

4 年間の久山町疫学研究の証拠に基づいた介入プログラム開発とその実施マニュアルを作成することを目的とした。さらに、地域在住高齢者への「久山町方式：食・運動お勧めメニュー」の実行性について検証した。その結果、認知症（特に、AD 予防に向けた「久山町方式：食・運動お勧めメニュー」とその実施に向けたツールを開発・作成した（CPA スマートライフスタイル：60－70 歳からはじめる認知症予防編)。また介入実施にあたっての実行性検証については、対象者に対し良好な反応が得られ、今後の久山町住民に向けた介入にあたっての実行可能性が示唆された。

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H. 知的財産権の出願・登録状況

1. 特許取得 なし
2. 実用新案登録 なし

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分担研究報告書

認知症予防のための運動介入研究：
神経新生や認知機能の改善に効果的な運動様式に関する動物研究

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研究要旨　老化促進・アルツハイマー病発症モデルマウスであるSAMP8マウスを用いた動物研究を通して、認知機能の改善に効果的な運動様式の検討を実施した。その結果、低強度運動に対して認知機能の改善効果が認められ、効果的運動様式である可能性が示された。

A. 研究目的

本動物研究では、認知症予防のための運動介入実現に向け、認知機能の改善に効果的な運動様式を検討することを目的とした。

B. 研究方法

SAMP8マウス（オス21週齢）を、低強度運動群（Low:12m/min）、中強度運動群（Mid:17m/min）、高強度運動群（High：22m/min）の各運動群（各n=10）と、対照群（Con：n=9）の4群に割り当てた。各運動群に対しては、トレッドミルを用いた5週間（週5日間）の運動介入を実施し、その際、運動強度毎に走行時間を調節して、各群で走行距離が同一になるよう制御した。運動介入後、モリス水迷路検査およびオープンフィールド検査を実施した。各検査成績の群間比較には、一元配置分散およびTukey多重比較法、もしくは、対応なしt検定を用いた。

（倫理面への配慮）
本研究は中村学園大学実験動物委員会の倫理審査にて承認を得た上で、同大学アニマルセンターにおいて実施した。

C. 研究結果

モリス水迷路検査における記憶保持試験の成績（ターゲット区間内の滞在時間）については、一元配置分散分析では主効果が認められなかったが（$p=0.174$）、ConとLow間のt検定では有意差が認められた（$p=0.029$：図1）。また、オープンフィールド検査の成績（中央区間内の滞在時間）については、群間の主効果が認められ、多重比較の結果、ConとLow間に有意差が認められた（$p=0.032$：図2）。

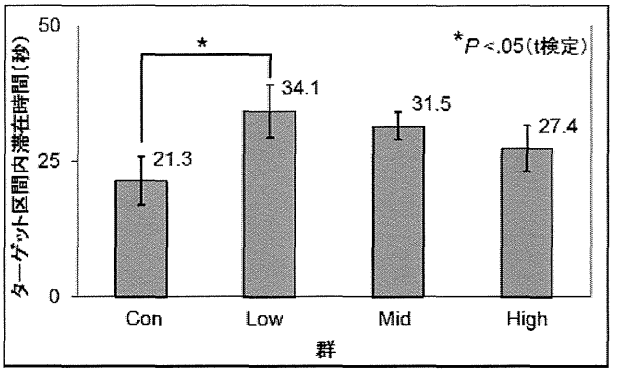

図1：モリス水迷路検査の結果

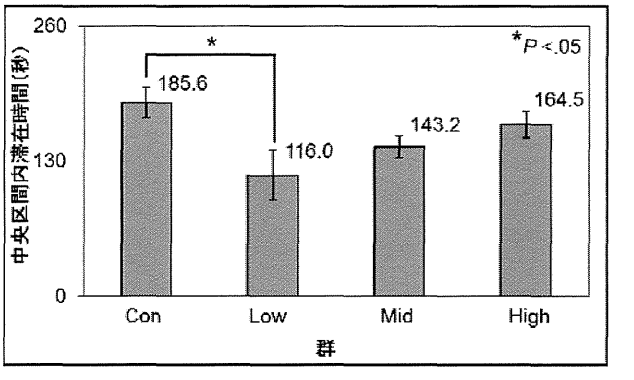

図2：オープンフィールド検査の結果

D. 考察

モリス水迷路検査の成績は、空間記憶能力の指標であることから、本研究では、Lowの空間記憶能力がConと比べ改善されていることが示唆された。また、オープンフィールド検査の成績は、

SAMP8 マウスで認められる老化性情動障害に伴う低不安状態の指標であることから、本研究では、Low の低不安状態が Con と比べ改善されていることが示唆された。今後は、生化学検体の解析等を通して、認められた効果の機序解明を図るとともに、認知機能の改善に効果的な運動様式に関して、より深い考察を進める予定である。

E. 結論

本研究では、低強度運動に対して認知機能の改善効果が認められ、効果的運動様式である可能性が示された。

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H. 知的財産権の出願・登録状況

1. 特許取得 なし
2. 実用新案登録　なし

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研究成果の刊行に関する一覧表

書籍

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Original Article

Prevalence and Causes of Functional Disability in an Elderly General Population of Japanese: The Hisayama Study

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ABSTRACT

Background: There are limited data on the prevalence and causes of disability in the elderly general population in Japan.

Methods: In a population-based cross-sectional study of 1550 Japanese aged 65 years or older, we examined the prevalence of functional disability (defined as a Barthel Index score of ≤95) and its causes.

Results: A total of 311 of the participants had a disability (prevalence 20.1%). The prevalence of disability increased with age and doubled with every 5-year increment in age. Prevalence was higher in women than in men, especially among those aged 85 years or older. With respect to the cause of functional disability, dementia accounted for 23.5%, stroke for 24.7%, orthopedic disease for 12.9%, and other disease for 38.9% of cases in men; in women, the respective values were 35.8%, 9.3%, 31.0%, and 23.9%. Regarding age, dementia was the most frequent cause of disability in subjects aged 75 years or older, whereas stroke was most common in subjects aged 65 to 74 years. Approximately two-thirds of cases of total dependence were attributed to dementia in both sexes, whereas the main cause of slight or moderate/severe dependence was stroke in men and orthopedic disease in women. Among participants with total dependence, 94.8% resided in a hospital or health care facility.

Conclusions: Our findings indicate that functional disability is common among Japanese elderly adults and that its major cause is stroke in men and dementia in women.

Key words: functional disability; dementia; stroke; prevalence; Japanese elderly

INTRODUCTION

The elderly population has been rapidly increasing worldwide, especially in developed countries. In Japan, the proportion of adults aged 65 years or older among the whole population has been the highest in the world since 2004, and it reached 23.0% in 2010.[1] Along with this aging population, an increase in functional disability, which causes dependency and institutionalization, is a serious social, medical, and economic concern.[2,3] Studies of the prevalence, causes, and effects of functional disability among the elderly population are therefore needed for appropriate public health policy and planning. Several community-based studies have reported the prevalence of functional disability and its causes in the elderly in Western countries[4–9] and Japan.[10–14] However, participants staying in hospitals or health care facilities were not surveyed in those studies, which likely led to underestimation of the prevalence of disability. Furthermore, information from questionnaires was used to determine causes of disability in those studies. Therefore, it might be valuable to use less-biased community surveys and detailed clinical information to determine the status of functional disability and its causes in Japan. We examined the prevalence and underlying causes of functional disability in an elderly general population of Japanese.

METHODS

Study population

The Hisayama Study is a prospective cohort study of cerebrocardiovascular diseases in the town of Hisayama, a subrural community adjacent to the metropolitan area

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of Fukuoka, Japan.[15] The population of the town has distributions of age, occupational status, and nutrient intake that are almost identical to those for the whole of Japan.[15] Full community surveys of the health status and neurological conditions of residents aged 40 years or older have been repeated since 1961.[15] One characteristic of this study is that all event data on cerebrocardiovascular diseases have been verified by detailed neurological and morphological examinations, including neuroimaging.[15] Additionally, comprehensive surveys of functional disability and dementia in elderly adults have been carried out since 1985.[16] Between October 2005 and August 2006, a total of 1566 residents aged 65 or older (91.5% of the total population in this age group) participated in the examination for the present study. The examination was performed in the public hall of the town or at home. In addition, we visited hospitals and health care facilities to examine institutionalized individuals. After excluding 16 subjects for whom activity of daily living (ADL) status was not available, data from 1550 subjects (601 men and 949 women) were included in the present analysis.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. All participants gave written informed consent, which included the purpose and procedures of the research, potential risks and benefits associated with participation, voluntary participation in the study, the right of withdrawal from the research without prejudice or penalty, and the confidentiality and security of personal data.

Questionnaire

In the examination, each participant completed a self-administered questionnaire that inquired about socio-demographic data (including age, sex, marital status, employment status, and place of residence [domicile, hospital, long-term care facility, or nursing home]), Barthel Index items,[17] and past history of diseases (including stroke, coronary heart disease, fracture, head injury, hypertension, diabetes, hyperlipidemia, depression, and other conditions). The completed questionnaires were reviewed by trained nurses or physicians to identify inconsistent answers and unanswered items. To diagnose dementia, all participants took neuropsychological tests (revised version of Hasegawa's Dementia Scale [HDS-R][18] and Mini-Mental State Examination [MMSE][19]), which were performed by trained nurses and physicians. Among the participants, 395 (25.2%) with test scores below the cutoff values (21/30 for the HDS-R and MMSE) underwent an additional comprehensive investigation.

Definition of functional disability

ADL status was determined using the Barthel Index,[17] which estimates the degree of independence in ADL of subjects by using 10 items: feeding (0, 5, or 10 points), bathing (0, 5), dressing (0, 5, 10), grooming (0, 5), bladder control (0, 5, 10), bowel control (0, 5, 10), toileting (0, 5, 10), transferring from bed to a wheelchair (0, 5, 10, 15), walking on a level surface (0, 5, 10, 15), and ascending and descending stairs (0, 5, 10). Functional disability was defined as a Barthel Index score of 95 or lower, in accordance with the definition previously reported in epidemiologic studies.[17,20–22] In addition, the severity of disability was categorized into 3 levels as follows: slight dependence (a Barthel Index score of 95, which corresponds to 1 decrease in an item on the Barthel Index), moderate/severe dependence (a score of 25–90), and total dependence (a score of 0–20, which corresponds approximately to a bedridden state, with at least 8 decreased items).[17]

Cause of disability

To determine the cause of functional disability, all available past clinical information, including medical records and findings from neurologic examination and brain imaging studies, which was gathered by using the follow-up system of the Hisayama Study,[15,23] was reviewed independently by 2 of the authors (D.Y. and T.N.). Any disagreement in cause attribution was resolved by a consensus of a panel of the authors (D.Y., T.N., and Y.K). If a subject had 2 or more conditions that impaired ADL, the disease that contributed to the deterioration of at least 1 category of ADL level (eg, from moderate/severe dependence to total dependence) was defined as the major cause. For instance, if a subject had mild gait disturbance caused by stroke but gradually became bedridden due to subsequent dementia, dementia would be considered the major cause, whereas stroke would be selected if the subject became bedridden soon after a severe stroke event, even if the participant later developed dementia. Among the 311 disability cases, the 2 researchers completely agreed on the cause of functional disability in 242 (77.8%) cases. In the remaining 68 (22.1%) cases, a consensus on the cause was reached after discussion.

Causes of disability were categorized into 4 groups: dementia (vascular dementia, Alzheimer disease, and other dementia), stroke (ischemic stroke and hemorrhagic stroke), orthopedic disease (fracture, arthritis, rheumatoid arthritis, and other orthopedic disease), and other disease. Dementia and its subtypes were diagnosed according to the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R),[24] the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association,[25] and the criteria of the National Institute of Neurological Disorders and Stroke–Association International pour la Recherche et l'Enseignement en Neurosciences.[26] Stroke was defined as the sudden onset of nonconvulsive and focal neurologic deficits persisting at least 24 hours. A diagnosis of stroke and its subtypes

Table 1. Characteristics of study population by functional disability (Hisayama Study, 2005)

	All subjects (n = 1550)	Subjects without disability (n = 1239)	Subjects with disability (n = 311)	P-value[a]
Age, mean ± SD	75.8 ± 7.3	74.2 ± 6.3	82.1 ± 7.7	<0.001
Women, %	61.1	58.2	72.7	<0.001
Current working status, %				<0.001
Unemployed/retired/housewife	73.1	68.9	90.4	
Working	26.9	31.1	9.6	
Marital status, %				<0.001
Never married	2.5	2.2	3.5	
Married	63.4	68.6	42.8	
Divorced/widowed/separated	34.1	29.2	53.7	
Living arrangement, %				0.04
Living alone	10.9	10.1	14.2	
Living with others	89.1	89.9	85.8	
Place of residence, %				<0.001
Home	91.6	99.3	60.5	
Hospital	5.2	0.6	23.8	
Health care facility	3.2	0.1	15.7	
ADL disability level, %				
Slight dependence	5.0	—	25.4	
Moderate/severe dependence	10.0	—	49.8	
Total dependence	5.1	—	24.8	

[a]P value, comparison between subjects with and without disability.

Table 2. Prevalence of disability by age category (Hisayama Study, 2005)

Age category	Total (n = 1550)		Men (n = 603)		Women (n = 947)		P value between sexes
	No. with disability/ participants	Prevalence, % (95% CI)	No. with disability/ participants	Prevalence, % (95% CI)	No. with disability/ participants	Prevalence, % (95% CI)	
65–69	18/366	4.9 (2.9–7.7)	9/161	5.6 (2.6–10.4)	9/205	4.4 (2.0–8.2)	0.60
70–74	38/393	9.7 (6.9–13.0)	14/171	8.2 (4.6–13.4)	24/222	10.8 (7.1–15.7)	0.38
75–79	53/331	16.0 (12.2–20.4)	18/129	14.0 (8.5–21.2)	35/202	17.3 (12.4–23.3)	0.41
80–84	75/256	29.3 (23.8–35.3)	20/91	22.0 (14.0–31.9)	55/165	33.3 (26.2–41.1)	0.06
85+	127/204	62.3 (55.2–68.9)	24/51	47.1 (32.9–61.5)	103/153	67.3 (59.3–74.7)	0.01
All ages	311/1550	20.1 (18.1–22.2)	85/603	14.1 (11.4–17.1)	226/947	23.9 (21.1–26.7)	<0.001
P for trend		<0.001		<0.001		<0.001	

was determined on the basis of medical records and brain imaging studies.[27] Hemorrhagic stroke included brain hemorrhage and subarachnoid hemorrhage. The diagnosis and classification of orthopedic disease were determined with clinical information available from the questionnaire, medical records, and annual health examinations.

Statistical analysis

The software package SAS (version 9.2; SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. The Student t-test was used to compare continuous variables, and the chi-square test was used to evaluate proportions. We calculated the prevalences of disability with 95% confidence intervals (CIs) by using a binary distribution. Trends in the prevalence of disability across 5-year age categories were tested by means of logistic regression analysis. A 2-sided P value less than 0.05 was considered statistically significant in all analyses.

RESULTS

The characteristics of study subjects according to functional disability status are shown in Table 1. The mean overall age was 76 years, and the proportion of women was 61.1%. A total of 311 subjects (85 men and 226 women) had some type of functional disability, resulting in a prevalence of 20.1%. As compared with those without disability, subjects with disability were more likely to be older, female, unemployed, living alone, and institutionalized. Among those with disability, the proportions of subjects with slight, moderate/severe, and total dependence were 25.4%, 49.8%, and 24.8%, respectively.

As shown in Table 2, the prevalence of functional disability increased with age, with a doubling in prevalence for every 5-year increment. The prevalence of disability was significantly higher in women than in men ($P < 0.001$), especially among participants aged 85 or older ($P = 0.01$). A comparable relationship was observed in subjects with total dependence,

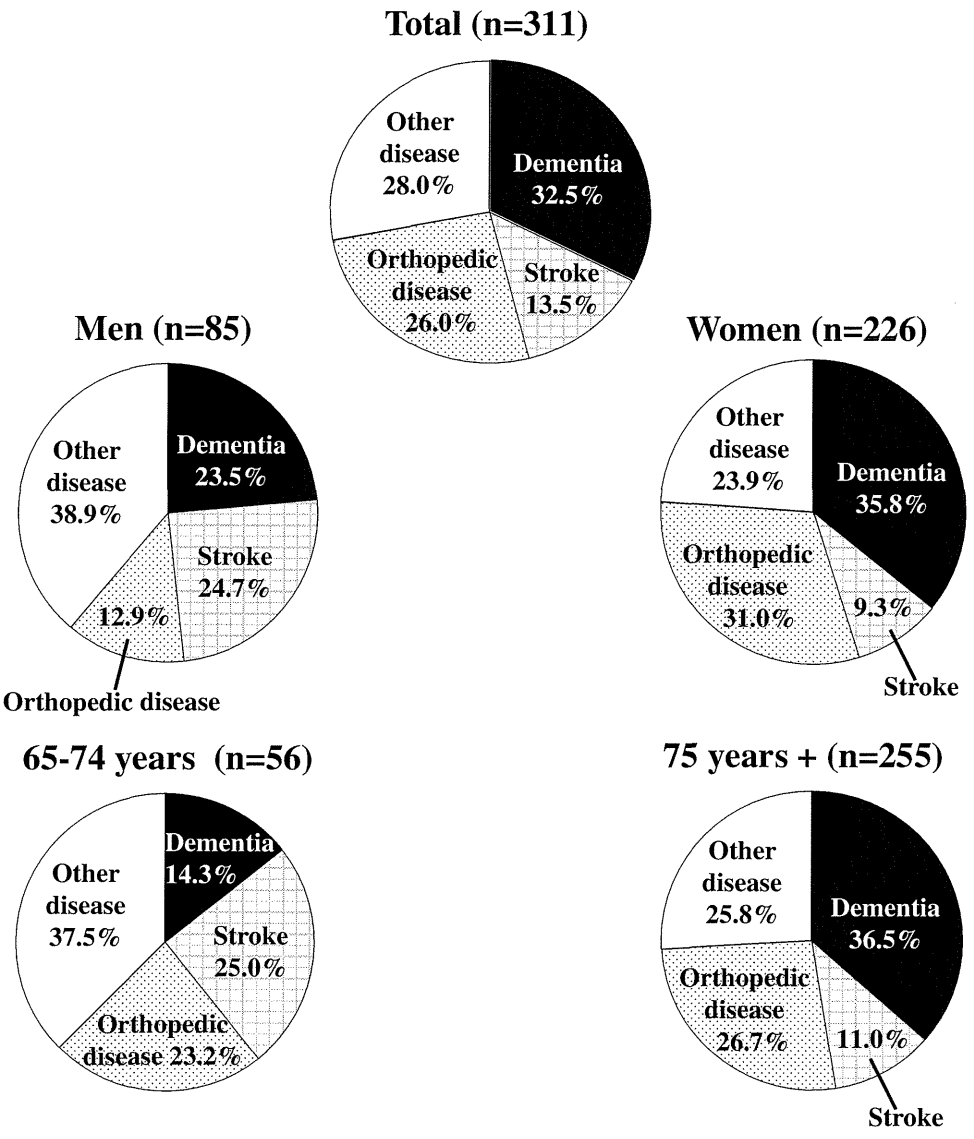

Figure 1. Causes of functional disability by sex and age (Hisayama Study, 2005).

whereas the prevalence of slight and moderate/severe dependence was not significantly different between sexes in any age category (data not shown).

Next, we investigated the causes of functional disability (Figure 1). Among the 311 disability cases, dementia accounted for 32.5%, stroke for 13.5%, orthopedic disease for 26.0%, and other disease for 28.0% of cases. Among the 101 subjects with dementia-related disability, 22 (21.8%) had a history of a stroke events that resulted in slight or moderate/severe dependence. When the results were categorized by sex, dementia accounted for 23.5%, stroke for 24.7%, orthopedic disease for 12.9%, and other disease for 38.9% of cases of functional disability in the 85 disabled men; the respective values were 35.8%, 9.3%, 31.0%, and 23.9% in the 226 disabled women. Stroke was the most common cause of disability in men, whereas dementia and orthopedic disease were more frequent in women. When the findings were analyzed by age category, dementia accounted for 14.3%, stroke for 25.0%, orthopedic disease for 23.2%, and other disease for 37.5% of disability cases in subjects aged 65 to 74 years; the respective proportions were 36.5%, 11.0%, 26.7%, and 25.8% for subjects aged 75 or older; that is, dementia was the most frequent cause of disability in subjects aged 75 or older, whereas stroke was the most common cause in subjects aged 65 to 74 years.

The subtypes of causes of functional disability by sex are shown in Table 3. Among cases of dementia, vascular dementia was most frequent in men (12.9%), whereas Alzheimer disease was most common in women (15.0%). With regard to stroke subtype, ischemic stroke was more frequent in men than in women (17.6% vs 6.2%). With regard to orthopedic disease, the proportions of fracture and arthritis were higher, especially in women (15.0% and 10.2%, respectively).

Figure 2 shows the causes of functional disability among the 311 subjects according to disability severity by sex. In subjects with total dependence, dementia was the most

Table 3. Subtypes of causes of disability by sex (Hisayama Study, 2005)

Disease/condition	Total (n = 311)		Men (n = 85)		Women (n = 226)		P-value[a]
	Number	%	Number	%	Number	%	
Dementia	101	32.5	20	23.5	81	35.8	0.04
Vascular dementia	30	9.6	11	12.9	19	8.4	0.23
Alzheimer disease	40	12.9	6	7.1	34	15.0	0.06
Other dementia	31	10.0	3	3.5	28	12.4	0.02
Stroke	42	13.5	21	24.7	21	9.3	<0.001
Ischemic stroke	29	9.3	15	17.6	14	6.2	0.002
Hemorrhagic stroke	13	4.2	6	7.1	7	3.1	0.20
Orthopedic disease	81	26.0	11	12.9	70	31.0	0.001
Fracture	38	12.2	4	4.7	34	15.0	0.01
Arthritis	25	8.0	2	2.4	23	10.2	0.03
Rheumatoid arthritis	11	3.5	2	2.4	9	4.0	0.73
Other orthopedic disease	7	2.3	3	3.5	4	1.8	0.40
Other disease	87	28.0	33	38.8	54	23.9	0.009

[a]*P* value for comparison between sexes.

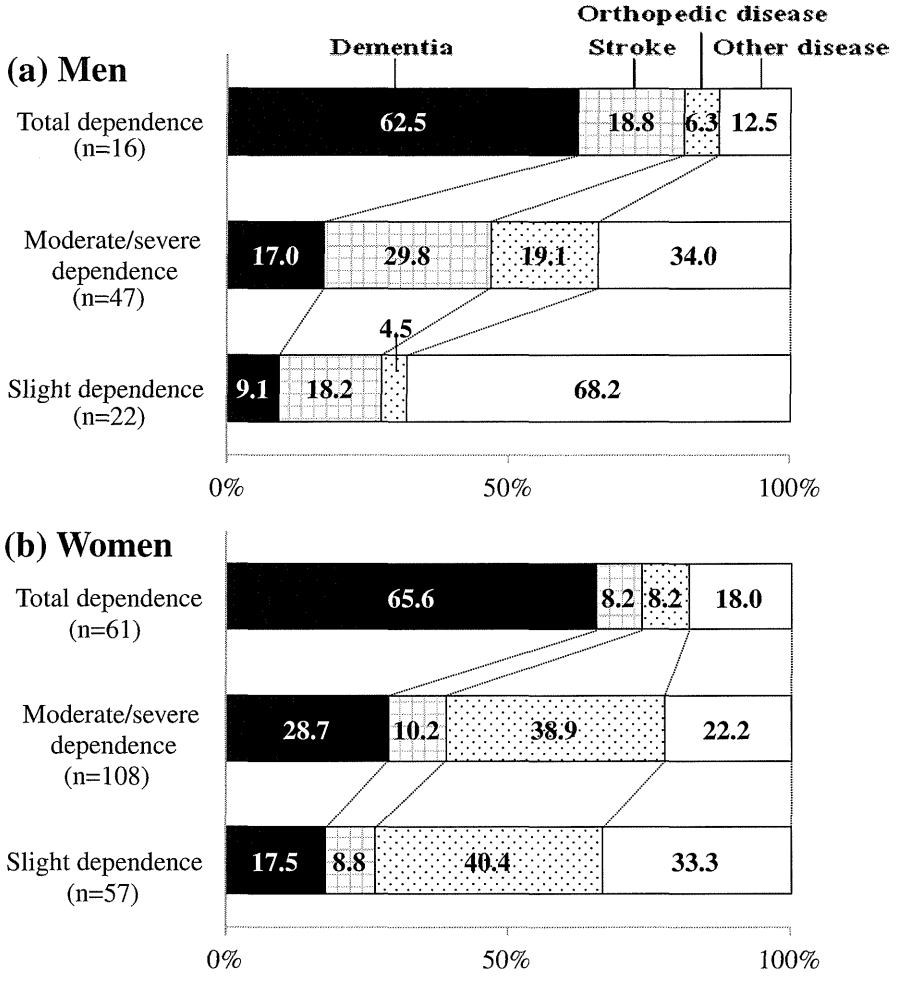

Figure 2. Causes of functional disability by severity of disability in men and women (Hisayama Study, 2005). Total dependence: Berthel Index score = 0–20. Moderate/severe dependence: Berthel Index score = 25–90. Slight dependence: Berthel Index score = 95.

frequent cause in both sexes: the proportion was 62.5% in men and 65.6% in women. In subjects with slight or moderate/severe dependence, stroke was the most common cause of disability in men, whereas orthopedic disease was the most frequent in women.

Finally, we investigated place of residence in the 311 disabled subjects according to functional severity. Among subjects with slight dependence, 91.1% lived at home, 6.3% were hospitalized, and 2.6% stayed in health care facilities; the respective values were 72.3%, 17.4%, and 10.3% for those

with moderate/severe dependence. In contrast, among subjects with total dependence, only 5.2% lived at home, whereas 54.6% and 40.2% stayed in a hospital or health care facility, respectively.

DISCUSSION

The present study demonstrated that the prevalence of functional disability was 20.1% in an elderly general population of Japanese. Additionally, we found that the prevalence of disability increased steeply with age, with a doubling of prevalence for each 5-year increment. Prevalence was higher in women than in men, especially in individuals aged 85 or older. Importantly, in our subjects the major cause of disability was stroke in men and dementia in women. In particular, dementia was the most common cause of disability in subjects with total dependence, most of whom required full-time care in hospitals or health care facilities. These findings highlight the clinical importance of effective strategies for preventing dementia. Such strategies could reduce the social and economic burden of functional disability among elderly Japanese.

Prevalence of disability

There is considerable divergence in the prevalence of disability reported in community-based studies, with values ranging from 6% to 34.5%.[4–13] For aged Japanese populations, these studies have reported a disability prevalence ranging from 8% to 17%,[10–13] which is lower than that obtained in the present study. A possible reason for this discrepancy is the difference in the proportion of old old adults in the studies, as this group is at high risk for functional disability. Among people aged 65 years or older, the proportion of those aged 85 years or older was 4.5% to 8.7% in previous studies, which were conducted from 1977 to 1996,[1,10–13] as compared with 11.4% in the present study, performed in 2005. These findings indicate that the proportion of old old has increased over time in Japan, which has led to a recent increase in the prevalence of functional disability. In addition, some selection bias was likely in previous studies, because subjects staying in hospitals or health care facilities might not have been fully examined. In contrast, the participation rate was high (91%) in our study, and we included institutionalized subjects in the study to minimize selection bias. This bias in previous studies would lead to underestimation of the prevalence of disability. Furthermore, the discrepant findings may have been due to a difference in the definition of disability across studies. The Barthel Index, which was used in our study, has been reported to be more sensitive in detecting disability as compared with other indices with fewer ADL domains (eg, the Katz Index), which were used in other studies.[6,28] Indeed, in a sensitivity analysis using the Katz Index—in which functional disability was defined as need for assistance in 1 or more activities of 6 ADL domains, including feeding, bathing, dressing, toileting, transferring, and continence—the prevalence of disability declined to 18.3% in our study.

Sex differences in disability

In our study, the prevalence of disability was higher in women than in men, especially among persons aged 85 or older. Comparable findings were observed in previous community-based studies in Sweden and Japan.[8,29,30] However, there is no consensus on the interpretation of this sex difference. A possible explanation is that there are sex differences in death rates for underlying diseases; that is, women might survive with some form of disability after developing cardiovascular disease, whereas men might be more likely to die immediately after the incident disease, since the underlying comorbidity may be more severe in men than in women.[31,32] Another possible explanation is that musculoskeletal disease may have a greater influence on functional limitations in women than in men. For example, a population-based study in the United States indicated that musculoskeletal impairments were attributed to disability more frequently in women than in men.[33] In our subjects, disabled women also had a greater incidence than men of orthopedic diseases such as fracture and arthritis.

Cause of disability

In the present study, dementia was the most frequent cause of functional disability in both sexes, especially among those aged 75 or older. In agreement with this finding, the Adult Health Study in Hiroshima, Japan and a community-based study in Stockholm, Sweden showed that dementia had a greater influence on the development of disability and ADL decline than did stroke, orthopedic disease, or other chronic diseases.[34,35] Furthermore, our study found that the proportion of stroke was high in subjects aged 65 to 74 years. Previous community-based prospective studies in Japan and the United States have also shown that stroke was associated with risk of functional disability.[36–38] A systematic review reported that more than one-third of patients with recurrent stroke later developed dementia.[39] We also revealed that 21.8% of subjects with dementia-related disability had a history of stroke events with slight or moderate/severe dependence. These findings indicate that it is important to prevent stroke events to reduce the risk of future dementia and total dependence. Interestingly, orthopedic disease such as fracture and arthritis contributed mainly to slight dependence and moderate/severe dependence in women. Further investigations will be needed to determine the effect of orthopedic disease on subsequent ADL level.

Place of residence and severity of disability

To date, few studies of general populations have classified ADL level according to place of residence. In our study, approximately 95% of subjects with total dependence were institutionalized in hospitals or health care facilities. Most of