藤　悠，西内久人，永吉　翔，熊谷秋三：：地域在住高齢者において加速度計で実測した座位活動とbody mass indexの関連．第68回日本体力医学会，東京都，2013.9

9. Sakita M, Murakami S, Saito T, Fujino H, Kumagai S: Effects of the short and and medium latency reflex responses during souleus stretching with the difference between thehalleolus and achilles' tendon vibrations in human standing. WCPT-AWP & ACPT Congress 2013, Taichung, Taiwan, 2013.9
10. 熊谷秋三：運動疫学からみた身体活動・不活動．九州大学P&P Aタイプ研究チーム，リサーチコアチーム共同第5回公開講演会招待講演．福岡市，2013.10
11. 熊谷秋三:高齢者の健康実態と科学的証拠に基づいた健康支援．2013健康運動指導者研究大会岡山大会招待講演，岡山市，2013.11
12. 熊谷秋三，大曲めぐみ，Atin Supartini，高柳茂美，眞崎義憲，松下智子，福盛英明，淵田吉男，一宮　厚：大学生における希死念慮の有無とその背景要因に関する報告 - EQUSITE Study - ．第51回全国大学保健管理研究集会，岐阜市，2013.11
13. 齊藤貴文，崎田正博，森山善彦，西内久人，熊谷秋三：歩行活動量と広範囲運動器疼痛との関連性について－地域在住自立高齢者を対象として－．第6回日本運動器疼痛学会，神戸市，2013.12

H. 知的所有権の取得状況

1. 特許取得　なし
2. 実用新案登録　なし

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大規模ゲノム疫学共同研究による認知症の危険因子および防御因子の解明
分担研究報告書

大規模疾患コホート研究における認知症の疫学調査

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研究要旨　認知症患者が増加し大きな社会・医療問題となっている．しかし認知症発症の詳細な危険因子と防御因子は未だ確立していない．本研究では認知症発症リスクの高い症例と健常者を対比することで，認知症発症の危険因子と防御因子を明らかにする．

A. 研究目的

血管性認知症リスクが高い脳卒中患者とアルツハイマー病のリスクが高い糖尿病患者を対象とした大規模疾患コホートの解析と久山町の一般住民の追跡データを合わせた解析により，認知症の危険因子と防御因子を明らかにする．

B. 研究方法

血管性認知症のハイリスク群の脳卒中患者の追跡調査である福岡脳卒中データベース研究(Fukuoka Stroke Registry: FSR)と，アルツハイマー病のハイリスク群の糖尿病患者の追跡調査である福岡県糖尿病データベース研究(Fukuoka Diabetes Registry: FDR)において，新規に認知症を発症した症例に対して，久山町一般住民健常者をコントロールとして，認知症発症の危険因子と防御因子を明らかにする．

（倫理面への配慮）研究対象者の人権の擁護のため，FSR・FDRそれぞれの登録研究において，事前に研究の内容，目的および利益とともに不利益を蒙る可能性についても文書を用いて十分に説明を行い，同意書に署名または記名・押印を取得した上で研究対象者を登録する．また個人情報の流出は不利益となるため，診療情報，予後調査結果，採決結果等を連結可能匿名化されたデータとして，それぞれの共通データベースにて管理する．

C. 研究結果

認知症新規発症情報の収集を可能とするために，FSR・FDRのデータベースの整備を行った．FSRの新規対象者のうち，脳梗塞発症前に認知症がなく，退院時に高次脳機能障害を認めなかった者を対象にMMSEと相関があると報告されているIQCODEを用いて認知症の新規発症情報の収集を開始した．またFDRでは，九州大学病院で登録した65歳以上の対象者69名に対して，登録時に認知機能評価(HDS-R, MSE)を施行しており，この69名の追跡調査を開始し認知症の新規発症情報などを収集中である．

D. 考察

認知機能評価に対する同意取得が本研究遂行の上で重要であると思われる．

E. 結論

FSR・FDRに登録された認知症を有さない症例を前向きに追跡することで，認知症の発症を同定する．また診療情報や採血データ等を用いて，認知症の危険因子と防御因子の解明に努める．

G. 研究発表

1. 論文発表　なし
2. 学会発表　なし

H. 知的所有権の取得状況

1. 特許取得　なし
2. 実用新案登録　なし

厚生労働科学研究（認知症対策総合研究事業）
大規模ゲノム疫学共同研究による認知症の危険因子および防御因子の解明
分担研究報告書

地域高齢住民を対象とした認知症データバンクの形成

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研究要旨　わが国における認知症の危険因子を明らかにするために認知症地域疫学研究に実績のある5チーム（九州大学：久山町，鳥取大学：海士町，金沢大学：中島町，筑波大学：利根町，東北大学：大崎市）を組織化した．次にチームごとに内容の異なる既存のデータを，統一された方法で再整理したデータに編集する．その上でこれらの統合化された既存データを用いて日本人の認知症危険因子を解明することを目的にする．まず各組織の既存データを経時的に整理した．次に組織ごとに対象や標記の異なる従来のデータを整理してコード化しつつ，組織を問わず共通して利用できる情報項目を抽出した．概要として1）調査期間・回数のばらつき大：3年から27年，2回から7回　2）調査項目，用いた評価尺度はかなり類似している　3）ライフスタイル：運動，喫煙，飲酒は全組織で調査実施しているが，生活習慣病関連（DM, HT, HL, CKD, BMIなど）のデータにはばらつきがある　4）介入した組織もあるが，観察研究のみの組織もある，ことが明らかになった．一方，筑波大学では2001年から悉皆調査3回，新規調査1回，部分調査1回と合計5回の調査を実施している．それらをレビューして調査内容をチェックした．その結果，同一施設であっても内容は微妙に異なることが明らかになった．

今後は各施設における調査内容を経時的に調査し，全体のデータ構成を調査年表のなかで経時的に明示してもらう．その上で個々の調査項目について，共通尺度をピックアップする．次に同じカテゴリーの調査内容でも用いられた尺度にばらつきのあるものは，別に整理しておく．さらに今後の総合解析に備えて，組織毎に異なる評価内容と方法をどう統一するかのルールを作成してゆく．

A. 研究目的

わが国における認知症の危険因子を明らかにする．そのために認知症地域疫学研究に実績のある5チーム（九州大学：久山町，鳥取大学：海士町，金沢大学：中島町，筑波大学：利根町，東北大学：大崎市）を組織化する．次にチームごとに内容の異なる既存のデータを，統一された方法で再整理したデータベース（データベース 1）を作

成する．この既存データからまず危険因子を解明する．これを基礎として，新規項目に注目しつつ新たに標準化データベース（データベース 2）を作成する．そして 5 チームは今後新たに得られる疫学データを，データベース 2 を用いて蓄積してゆき将来に備える．

B. 研究方法

本研究グループは，大規模調査に実績のある 5 組織から構成されるが，各組織の既存データを経時的に整理して並べる．次に組織ごとに対象や標記の異なる従来のデータを整理してコード化しつつ，組織を問わず共通して利用できる情報項目を抽出する．このような方法で既存データを整理して，これを用いて全国規模の解析の準備状態を完成させる（データベース 1）である．

データベース1を基盤として，新規項目に注目しつつ新たに標準化データベース（データベース2）を作成する．今後5組織はこれを用いて新たな調査を実施してゆく．このデータベース構築におけるポイントは，まずデータの統合・整理，次に新データ用のシステム作成，さらに必要とされるデータをアーカイブとしてデータベースから取り出してくる仕組みを作ることである．

C. 研究結果

1．5 組織の従来の調査内容

概要として 1)調査期間・回数のばらつき大：3 年から 27 年，2 回から 7 回　2)調査項目，用いた評価尺度はかなり類似している　3)ライフスタイル：運動，喫煙，飲酒は全組織で調査実施しているが，生活習慣病関連（DM，HT，HL，CKD，BMI など）のデータにはばらつきがある 4)介入した組織もあるが，観察研究のみの組織もある．

個別には，調査期間・回数：東北(栗原)5 年間・4 回，筑波 10 年間・6 回，金沢 6 年間・7 回，鳥取 3 年間・2 回，九大 27 年間・5 回である．調査項目・評価尺度・認知症の診断基準：DSM-ⅢR が多い．一方で東北大学では DSM-IV を用い，金沢大学では認知症の基礎疾患診断基準について記載はない．MCI の診断基準：全サイトで CDR0.5 を用いている．うつの評価：全サイトで GDS を行っている．ADL 評価：Barthel index (ADL)，Lawton (IADL)が主であるが，筑波では NADL を用い，鳥取大学では ADL 評価なし，九大では老研式による IADL 評価がなされている．APOE のタイピング，画像研究は多くでなされているが，APOE については鳥取大学でなされず九大も一部のみである．脳画像検査は九大では一部例のみで実施している．ライフスタイルについては，全サイトで喫煙，飲酒，運動は採用されている．その他に昼寝，睡眠，全般的生活習慣などが調査されている．また生活習慣病データとしては DM(FBS，HbA1c，etc)，血圧，脂質値，Cre 値，BMI が少なくとも部分的には調べてある．最後に介入については，介入有りが東北，筑波，金沢である一方，介入無しは鳥取，九大である．この違いをどう扱うかも大きな課題になる．

2．筑波大学のデータの経時的な精査

筑波大学では 2001 年から悉皆調査 3 回，新規調査 1 回，部分調査 1 回と合計 5 回の調査を実施している．基本属性については，生年月日，性別，修学年数などを調査している．ライフスタイルに関しては，2009 年度の第 3 次悉皆調査では運動習慣を含む詳細な調査項目として採用している．しかし第 1，2 次調査では NSAIDs 服用，飲酒歴と喫煙歴は問うているがその他は調べていない．また医学的な情報（慎重・体重，血液検査，糖尿病，高血圧含む）も第 3 次からは詳細に取れているが，それ以前は血液検査，視力障害・高血圧の有無 BMI などが調べられている．もの忘れの評価をする DECO と，道具的な生活動作をみる IADL 総得点については第 1 次から評価されているが，個々の質問項目を見ているのは第 3 次からである．これに対して基本的生活動作をみる NADL は継続的に実施している．なお糖尿病に関して，HbA1c は第 2 次から継続的に，アディポネクチンは 2008 年に

のみ検査を実施している．認知機能テストとしてはずっと 5Cog で 5 つの認知領域を，MCI は当初から判定しているが 2007 年からはサブタイプ診断もしている．なお認知症の診断とその基礎疾患診断は最初から診断している．以上のように同一施設であっても内容は微妙に異なる．

D. 考察

結果で示したように同一施設であっても従来の調査内容は微妙に異なる．それだけに各施設における調査内容を経時的に調査してもらうことで，全体のデータ構成をその結果を年表のなかで経時的に明示してもらう必要がある．その上で個々の調査項目について，共通尺度をピックアップする．次に同じカテゴリーの調査内容でも用いられた尺度にばらつきのあるものは，別に整理しておく．またある調査項目について，幾つかの大学では調査していなかったなら，その項目をどう扱うかについてのルールを作成する必要がある．その上で各施設で経時的に一貫性あるファイルに連続してデータを入れてもらう．ここでは実施年度の異なるデータを一貫性をもたせるようにつなぎ合わせてゆく作業が必要になる．

いずれにしても総合解析のために，組織毎に異なる評価内容と方法をどう統一するかのルールを作成する必要がある．

E. 結論

わが国における認知症の危険因子を明らかにするために認知症地域疫学研究に実績のある 5 組織(九州大学：久山町，鳥取大学：海士町，金沢大学：中島町，筑波大学：利根町，東北大学：大崎市)からチームを編成した．その上で組織ごとに内容の異なる既存のデータを，統一された方法で再整理したデータベース（データベース 1）を作成すべく基礎的調査を終えた．

G. 研究発表

1. 論文発表

1. K Ito, E Mori, H Fukuyama, K Ishii, Y Washimi, T Asada, S Mori, K Meguro, S Kitamura, H Hanyu, S Nakano, H Matsuda, Y Kuwabara, K Hashikawa, T Momose, Y Uchida, J Hatazawa, S Minoshima, K Kosaka, T Yamada, Y Yonekura, J-COSMIC Study Group: Prediction of outcomes in MCI with 123I-IMP-CBF SPECT:a multicenter prospective cohort study Ann Nucl Med 27: 898-906, 2013
2. Kondo T, Asai M, Tsukita K, Kutoku Y, Ohsawa Y, Sunada Y, Imamura K, Egawa N, Yahata N, Okita K, Takahashi K, Asaka I, Aoi T, Watanabe A, Watanabe K, Kadoya C, Nakano R, Watanabe D, Maruyama K, Hori O, Hibino S, Choshi T, Nakahata T, Hioki H, Kaneko T, Naitoh M, Yoshikawa K, Yamawaki S, Suzuki S, Hata R, Ueno S, Seki T, Kobayashi K, Toda T, Murakami K, Irie K, Klein WL, Mori H, Asada T, Takahashi R, Iwata N, Yamanaka S, Inoue H: Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Aβ and differential drug responsiveness. Cell Stem Cell 12: 487-496, 2013
3. Mizukami K, Abrahamson EE, Mi Z, Ishikawa M, Watanabe K, Kinoshita S, Asada T, Ikonomovic MD: Immunohistochemical analysis of ubiquilin-1 in the human hippocampus: Association with neurofibrillary tangle pathology. Neuropathology 34: 11-18, 2014
4. Musha T, Matsuzaki H, Kobayashi Y, Okamoto Y, Tanaka M, Asada T: EEG Markers for Characterizing Anomalous Activities of Cerebral Neurons in NAT (Neuronal Activity Topography) Method. IEEE Trans Biomed Eng 60: 2232-2238, 2013
5. Miyashita A, Koike A, Jun G, Wang LS, Takahashi S, Matsubara E, Kawarabayashi T, Shoji M, Tomita N, Arai H, Asada T, Harigaya

Y, Ikeda M, Amari M, Hanyu H, Higuchi S, Ikeuchi T, Nishizawa M, Suga M, Kawase Y, Akatsu H, Kosaka K, Yamamoto T, Imagawa M, Hamaguchi T, Yamada M, Moriaha T, Takeda M, Takao T, Nakata K, Fujisawa Y, Sasaki K, Watanabe K, Nakashima K, Urakami K, Ooya T, Takahashi M, Yuzuriha T, Serikawa K, Yoshimoto S, Nakagawa R, Kim JW, Ki CS, Won HH, Na DL, Seo SW, Mook-Jung I; Alzheimer Disease Genetics Consortium, St George-Hyslop P, Mayeux R, Haines JL, Pericak-Vance MA, Yoshida M, Nishida N, Tokunaga K, Yamamoto K, Tsuji S, Kanazawa I, Ihara Y, Schellenberg GD, Farrer LA, Kuwano R: SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians. PLoS One 8: e58618, 2013

6. Endo G, Tachikawa H, Fukuoka Y, Aiba M, Nemoto K, Shiratori Y, Matsui Y, Doi N, Asada T: How perceived social support relates to suicidal ideation: A Japanese social resident survey. Int J Soc Psychiatry 2013, (in press)
7. Yasuno F, Asada T: Effect of plasma lipids and APOE genotype on cognitive decline. Dialogues Clin Neurosci 15: 120-126, 2013
8. Yamane T, Ikari Y, Nishio T, Ishii K, Ishii K, Kato T, Ito K, Silverman DH, Senda M, Asada T, Arai H, Sugishita M, Iwatsubo T; the J-ADNI Study Group: Visual-Statistical Interpretation of 18F-FDG-PET Images for Characteristic Alzheimer Patterns in a Multicenter Study: Inter-Rater Concordance and Relationship to Automated Quantitative Evaluation. AJNR Am J Neuroradiol 2013, (in press)
9. Nose M, Kodama C, Ikejima C, Mizukami K, Matsuzaki A, Tanaka S, Yoshimura A, Yasuno F, Asada T: ApoE4 is not associated with depression when mild cognitive impairment is considered. Int J Geriatr Psychiatry 28: 155-163, 2013
10. Wang J, Zhao Z, Lin E, Zhao W, Qian X, Freire D, Bilski AE, Cheng A, Vempati P, Ho L, Ono K, Yamada M, Pasinetti GM: Unintended effects of cardiovascular drugs on the pathogenesis of Alzheimer's disease. PLoS One 8: e65232, 2013
11. Noguchi-Shinohara M, Yuki S, Dohmoto C, Ikeda Y, Samuraki M, Iwasa K, Yokogawa M, Asai K, Komai K, Nakamura H, Yamada M: Differences in the prevalence of dementia and mild cognitive impairment and cognitive functions between early and delayed responders in a community-based study of the elderly. J Alzheimers Dis 37: 691-698, 2013
12. Ono K, Takasaki J-I, Takahashi R, Ikeda T, Yamada M: Effects of Anti-parkinsonian agents on β-amyloid and α-synuclein oligomer formation. J Neurosci Res 91: 1371-1381, 2013
13. Miyoshi I, Fujimoto Y, Yamada M, Abe, S, Zhao Q, Cronenberger C, Togo K, Ishibashi T, Bednar MM, Kupiec JW, Binneman B: Safety and pharmacokinetics of PF-04360365 following a single-dose intravenous infusion in Japanese subjects with mild-to-moderate Alzheimer's disease: A multicenter, randomized, double-blind, placebo-controlled, dose-escalation study. Int J Clin Pharmacol Ther 51: 911-923, 2013
14. Uemura Y, Wada-Isoe K, Nakashita S, Nakashima K: Depression and cognitive impairment in patients with mild parkinsonian signs. Acta Neurol Scand 128: 153-159, 2013
15. Tanaka K, Wada-Isoe K, Nakashita S, Yamamoto

M, Nakashima K: Impulsive compulsive behaviors in Japanese Parkinson's disease patients and utility of the Japanese version of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. J Neurol Sci 331: 76-80, 2013

16. Adachi T, Kitayama M, Wada-Isoe K, Nakano T, Nakashima K: Autopsy-confirmed progressive supranuclear palsy with decreased uptake of metaiodobenzylguanidine. Clin Neurol Neurosurg 115: 1555-1557, 2013
17. Multiple-System Atrophy Research Collaboration: Mutations in COQ2 in familial and sporadic multiple-system atrophy. N Engl J Med 369: 233-244, 2013
18. Meguro K, Akanuma K, Ouchi Y, Meguro M, Nakamura K, Yamaguchi S: Vascular dementia with left thalamic infarction: Neuropsychological and behavioral implications suggested by involvement of the thalamic nucleus and the remote effect on cerebral cortex: the Osaki-Tajiri Project. Psychiatry Res 213: 56-62, 2013
19. Meguro K, Akanuma K, Meguro M: Patient-reported outcome is important in psychosocial intervention for dementia: A secondary analysis on RCT of group reminiscence approach data. Dementia Geriatr Cogn Dis Extra 3: 37-38, 2013
20. Honda Y, Meguro K, Meguro M, Akanuma K: Social withdrawal of vascular dementia associated with disturbance of basic daily activities, apathy and impaired social judgment. Care Manag J 14: 108-113, 2013
21. Nakatsuka M, Meguro K, Tsuboi H, Nakamura K, Akanuma K, Yamaguchi S: Contents of delusional thoughts in Alzheimer's disease and content-specific brain dysfunction assessed with BEHAVE-AD-FW and SPECT. Int Psychogeriatr 25: 939-948, 2013
22. Tanaka N, Nakatsuka M, Ishii H, Meguro K: Clinical utility of the Functional Independence Measure for assessment of patients with Alzheimer's disease and vascular dementia. Psychogeriatrics 13: 199-205, 2013
23. Tanaka N, Meguro K, Ishikawa H, Yamaguchi S: Improved functional status by comprehensive physical and psychosocial approach through right insula activation in poststroke vascular dementia. Int J Neurosci 123: 698-704, 2013
24. Takeda K, Meguro K, Tanaka N, Nakatsuka M: Difficulty with learning of exercise instructions associated with "working memory" dysfunction and frontal glucose hypometabolism in a patient with very mild subcortical vascular dementia with knee osteoarthritis. BMJ Case Rep Jul: 25, 2013
25. Takahashi Y, Meguro K, Nakatsuka M, Kasai M, Akanuma K, Yamaguchi S: Semantic dementia shows both storage and access disorders of semantic memory. Behav Neurol 2013, (in press)
26. Nakamura K, Kasai M, Ouchi Y, Nakatsuka M, Tanaka N, Kato Y, Nakai M, Meguro K: Apathy is more severe in vascular than amnesitc mild cognitive impairment in a community: the Kurihara Project. Psychiatry Clin Neurosci 67: 517-525, 2013
27. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Rockwood K, Xiao S, Li J, Li X, Brayne C, Matthews FE, Stephan BC, Lipton RB, Katz MJ, Ritchie K, Carrière I, Ancelin ML, Seshadri S, Au R, Beiser AS, Lam LC, Wong CH, Fung AW, Kim KW, Han JW, Kim TH, Petersen RC, Roberts RO, Mielke MM, Ganguli M, Dodge H,

Hughes T, Anstey KJ, Cherbuin N, Butterworth P, Ng TP, Gao Q, Reppermund S, Brodaty H, Meguro K, Schupf N, Manly J, Stern Y, Lobo A, Lopez-Anton R, Santabárbara J: COSMIC (Cohort Studies of Memory in an International Consortium): An international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. BMC Neurol 13: 165, 2013

28. Ito K, Mori E, Fukuyama H, Ishii K, Washimi Y, Asada T, Mori S, Meguro K, Kitamura S, Hanyu H, Nakano S, Matsuda H, Kuwabara Y, Hashikawa K, Momose T, Uchida Y, Hatazawa J, Minoshima S, Kosaka K, Yamada T, Yonekura Y; J-COSMIC Study Group: Prediction of outcomes in MCI with (123)I-IMP-CBF SPECT: a multicenter prospective cohort study. Ann Nucl Med 27: 898-906, 2013

2. 学会発表　なし

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2. 実用新案登録　なし

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Ozawa M, Ninomiya T, Ohara T, Doi Y, Uchida K, Shirota T, Yonemoto K, Kitazono T, Kiyohara Y	Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama Study.	Am J Clin Nutr	97	1076-1082	2013
Hokama M, Oka S, Leon J, Ninomiya T, Honda H, Sasaki K, Iwaki T, Ohara T, Sasaki T, Laferla FM, Kiyohara Y, Nakabeppu Y	Altered expression of diabetes-related genes in Alzheimer's disease brains: The Hisayama study.	Cereb Cortex		In press	2013
Hata J, Ninomiya T, Hirakawa Y, Nagata M, Mukai N, Gotoh S, Fukuhara M, Ikeda F, Shikata K, Yoshida D, Yonemoto K, Kamouchi M, Kitazono T, Kiyohara Y	Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961-2009).	Circulation	128	1198-1205	2013
Ninomiya T, Nagata M, Hata J, Hirakawa Y, Ozawa M, Yoshida D, Ohara T, Kishimoto H, Mukai N, Fukuhara M, Kitazono T, Kiyohara Y	Association between ratio of serum eicosapentaenoic acid to arachidonic acid and risk of cardiovascular disease: the Hisayama Study.	Atherosclerosis	231	261-267	2013
Hata A, Doi Y, Ninomiya T, Mukai N, Hirakawa Y, Hata J, Ozawa M, Uchida K, Shirota T, Kitazono T, Kiyohara Y	Magnesium intake decreases Type 2 diabetes risk through the improvement of insulin resistance and inflammation: the Hisayama Study.	Diabet Med	30	1487-1494	2013
Hamasaki H, Honda H, Suzuki SO, Hokama M, Kiyohara Y, Nakabeppu Y, Iwaki T	Down-regulation of MET in hippocampal neurons of Alzheimer's disease brains.	Neuropathology		In press	2014
本田裕之，岩城徹	病理学から見た認知症の原因疾患と疫学．久山町研究から．	最新医学	68	754-760	2013
Murakami N, Ohtsubo T, Kansui Y, Goto K, Noguchi H, Haga Y, Nakabeppu Y, Matsumura K, Kitazono T	Mice heterozygous for the xanthine oxidoreductase gene facilitate lipid accumulation in adipocytes.	Arterioscler Thromb Vasc Biol	34	44-51	2014

Perera MA, Cavallari LH, Limdi NA, Gamazon ER, Konkashbaev A, Daneshjou R, Pluzhnikov A, Crawford DC, Wang J, Liu N, Tatonetti N, Bourgeois S, Takahashi H, Bradford Y, Burkley BM, Desnick RJ, Halperin JL, Khalifa SI, Langaee TY, Lubitz SA, Nutescu EA, Oetjens M, Shahin MH, Patel SR, Sagreiya H, Tector M, Weck KE, Rieder MJ, Scott SA, Wu AH, Burmester JK, Wadelius M, Deloukas P, Wagner MJ, Mushiroda T, Kubo M, Roden DM, Cox NJ, Altman RB, Klein TE, Nakamura Y, Johnson JA.	Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study.	Lancet	382	790-796	2013
Hara K, Fujita H, Johnson TA, Yamauchi T, Yasuda K, Horikoshi M, Peng C, Hu C, Ma RC, Imamura M, Iwata M, Tsunoda T, Morizono T, Shojima N, So WY, Leung TF, Kwan P, Zhang R, Wang J, Yu W, Maegawa H, Hirose H; DIAGRAM consortium, Kaku K, Ito C, Watada H, Tanaka Y, Tobe K, Kashiwagi A, Kawamori R, Jia W, Chan JC, Teo YY, Shyong TE, Kamatani N, Kubo M, Maeda S, Kadowaki T.	Genome-wide association study identifies three novel loci for type 2 diabetes.	Hum Mol Genet	23	239-246	2014
Kou I, Takahashi Y, Johnson TA, Takahashi A, Guo L, Dai J, Qiu X, Sharma S, Takimoto A, Ogura Y, Jiang H, Yan H, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yanagida H, Taneichi H, Hosono N, Tsuji T, Suzuki T, Sudo H, Kotani T, Yonezawa I, Londono D, Gordon D, Herring JA, Watanabe K, Chiba K, Kamatani N, Jiang Q, Hiraki Y, Kubo M, Toyama Y, Tsunoda T, Wise CA, Qiu Y, Shukunami C, Matsumoto M, Ikegawa S.	Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis.	Nat Genet	45	676-679	2013

Fujii H, Iwase M, Ohkuma T, Ogata-Kaizu S, Ide H, Kikuchi Y, Idewaki Y, Joudai T, Hirakawa Y, Uchida K, Sasaki S, Nakamura U, Kitazono T	Impact of dietary fiber intake on glycemic control, cardiovascular risk factors and chronic kidney disease in Japanese patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry.	Nutr J	12	159	2013
Narazaki K, Nofuji Y, Honda T, Matsuo E, Yonemoto K, Kumagai S	Normative data for the Montreal Cognitive Assessment (MoCA) in a Japanese community-dwelling older population.	Neuroepidemiology	40	23-29	2013
Yasuno F, Asada T	Effect of plasma lipids and APOE genotype on cognitive decline.	Dialogues Clin Neurosci	15	120-126	2013
Miyashita A, Koike A, Jun G, Wang LS, Takahashi S, Matsubara E, Kawarabayashi T, Shoji M, Tomita N, Arai H, Asada T, Harigaya Y, Ikeda M, Amari M, Hanyu H, Higuchi S, Ikeuchi T, Nishizawa M, Suga M, Kawase Y, Akatsu H, Kosaka K, Yamamoto T, Imagawa M, Hamaguchi T, Yamada M, Moriaha T, Takeda M, Takao T, Nakata K, Fujisawa Y, Sasaki K, Watanabe K, Nakashima K, Urakami K, Ooya T, Takahashi M, Yuzuriha T, Serikawa K, Yoshimoto S, Nakagawa R, Kim JW, Ki CS, Won HH, Na DL, Seo SW, Mook-Jung I; Alzheimer Disease Genetics Consortium, St George-Hyslop P, Mayeux R, Haines JL, Pericak-Vance MA, Yoshida M, Nishida N, Tokunaga K, Yamamoto K, Tsuji S, Kanazawa I, Ihara Y, Schellenberg GD, Farrer LA, Kuwano R	SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians.	PLoS One	8	e58618	2013
Wang J, Zhao Z, Lin E, Zhao W, Qian X, Freire D, Bilski AE, Cheng A, Vempati P, Ho L, Ono K, Yamada M, Pasinetti GM	Unintended effects of cardiovascular drugs on the pathogenesis of Alzheimer's disease.	PLoS One	8	e65232	2013

Adachi T, Kitayama M, Wada-Isoe K, Nakano T, Nakashima K	Autopsy-confirmed progressive supranuclear palsy with decreased uptake of metaiodobenzylguanidine.	Clin Neurol Neurosurg	115	1555-1557	2013
Noguchi-Shinohara M, Yuki S, Dohmoto C, Ikeda Y, Samuraki M, Iwasa K, Yokogawa M, Asai K, Komai K, Nakamura H, Yamada M	Differences in the prevalence of dementia and mild cognitive impairment and cognitive functions between early and delayed responders in a community-based study of the elderly.	J Alzheimers Dis	37	691-698	2013
Tanaka N, Nakatsuka M, Ishii H, Meguro K	Clinical utility of the Functional Independence Measure for assessment of patients with Alzheimer's disease and vascular dementia.	Psychogeriatrics	13	199-205	2013
Nakamura K, Kasai M, Ouchi Y, Nakatsuka M, Tanaka N, Kato Y, Nakai M, Meguro K	Apathy is more severe in vascular than amnesitc mild cognitive impairment in a community: the Kurihara Project.	Psychiatry Clin Neurosci	67	517-525	2013

Dietary patterns and risk of dementia in an elderly Japanese population: the Hisayama Study[1–3]

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ABSTRACT

Background: To our knowledge, there are no previous reports that assessed the association between dietary patterns and risk of dementia in Asian populations.

Objective: We investigated dietary patterns and their potential association with risk of incident dementia in a general Japanese population.

Design: A total of 1006 community-dwelling Japanese subjects without dementia, aged 60–79 y, were followed up for a median of 15 y. The reduced rank regression procedure was used to efficiently determine their dietary patterns. Estimated risk conferred by a particular dietary pattern on the development of dementia was computed by using a Cox proportional hazards model.

Results: Seven dietary patterns were extracted; of these, dietary pattern 1 was correlated with high intakes of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice. During the follow-up, 271 subjects developed all-cause dementia. Of these individuals, 144 subjects had Alzheimer disease (AD), and 88 subjects had vascular dementia (VaD). After adjustment for potential confounders, risks of development of all-cause dementia, AD, and VaD were reduced by 0.66 (95% CI: 0.46, 0.95), 0.65 (95% CI: 0.40, 1.06), and 0.45 (95% CI: 0.22, 0.91), respectively, in subjects in the highest quartile of score for dietary pattern 1 compared with subjects in the lowest quartile.

Conclusion: Our findings suggest that a higher adherence to a dietary pattern characterized by a high intake of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice is associated with reduced risk of dementia in the general Japanese population. *Am J Clin Nutr* 2013;97:1076–82.

INTRODUCTION

The number of patients with dementia is growing rapidly in conjunction with the aging of the world population (1). However, the cause of most types of dementia has not been fully clarified. Consequently, those factors that are known to affect dementia and can be modified, such as dietary factors, have been widely discussed in terms of their potential to prevent the development of the disease (2). Some epidemiologic studies have reported that the intake of certain types of foods, such as fish and vegetables, may protect against all-cause dementia and Alzheimer disease (AD)[4], but these results are still inconsistent (3, 4). In any case, we do not consume foods or nutrients in isolation but, rather, combined as meals. Therefore, a key part of the solution may be to identify the dietary patterns that make the greatest contribution to dementia prevention. In Western countries, there have been several epidemiologic reports that suggested that a Mediterranean dietary pattern is protective against dementia (5–7). However, a Mediterranean diet is very different from a traditional Asian diet, and it is possible that there is another dietary pattern that would be equally or more effective for Asian people. Thus, it is important to determine whether there is a dietary pattern specific to Asian customs that would help to reduce risk of dementia. To clarify this issue, we performed a prospective cohort study to evaluate dietary factors associated with the development of dementia in a general Japanese elderly population. The ultimate goal of this study was to identify a dietary pattern that could contribute to risk of dementia and its subtypes in elderly Japanese.

SUBJECTS AND METHODS

Study populations

The Hisayama Study is a population-based prospective cohort study ongoing in the town of Hisayama, which is located in

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[4] Abbreviations used: AD, Alzheimer disease; DP1, dietary pattern 1; RRR, reduced rank regression; VaD, vascular dementia.

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a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan (8). The study began in 1961 to elucidate the actual conditions of cerebrocardiovascular diseases and their risk factors in Japanese. Data from the national census and nutrition survey has shown that the age and occupational distributions and nutrient intake of the population of Hisayama have been mostly the same as those of Japan as a whole for each year from 1961 until now (9). Comprehensive surveys of cognitive impairment and dementia in the elderly, including neuropsychological tests, have been conducted since 1985 (8). In 1988, a screening examination, including a dietary survey, was performed in 1073 residents aged 60–79 y (participation rate: 89.6%) for the current study. After the exclusion of 15 subjects who already suffered from dementia, one subject with no blood sample, and 51 subjects who did not complete dietary questionnaires at baseline, the remaining 1006 subjects (433 men and 573 women) were enrolled in this study.

Follow-up survey

Subjects were followed up from December 1988 to November 2005. The median follow-up time was 15 y. During this time, health examinations were performed every 1–2 y (10). For subjects who did not have examinations or who had moved out of town, the postal service or telephone was used to collect their health information (11). We also established a daily monitoring system in the study team and local physicians or members of the Health and Welfare Office of the town to identify new events, including stroke, cognitive impairment, and dementia. Follow-up screening surveys of cognitive function, including neuropsychological tests, the Hasegawa Dementia Scale (12), the Hasegawa Dementia Scale-Revised (13), or the Mini-Mental State Examination (14), were conducted in 1992, 1998, and 2005. When a subject was suspected to have new neurologic symptoms, including cognitive impairment, the subject was carefully evaluated by the study physician and psychiatrist, who conducted comprehensive investigations including interviews of the family or attending physician, physical and neurologic examinations, and a review of the clinical records. Furthermore, when a subject died, we reviewed all available clinical information, interviewed the attending physician and the family of the deceased subject, and tried to obtain permission for an autopsy from the family. During follow-up, 446 subjects died; of those, 326 (73.1%) underwent a brain examination at autopsy. No subjects were lost to follow-up.

Diagnosis of dementia

The guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, were used for defining the diagnosis of dementia (15). The criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association were used to define subjects with AD (16), and the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences were used to determine the diagnoses of vascular dementia (VaD) (17). Clinical information, including neuroimaging, was used to diagnose possible and probable dementia subtypes. Definite dementia subtypes were also determined on the basis of clinical and neuropathologic information in dementia subjects who underwent autopsy. The diagnostic procedure for autopsy cases has been reported previously (18). Definite VaD cases were confirmed with a causative stroke or cerebrovascular change and no neuropathologic evidence of other forms of dementia. Each case of dementia was adjudicated by expert stroke physicians and psychiatrists.

During the follow-up period, 271 incident cases of dementia were shown. Of these cases, 128 subjects (47.2%) underwent an autopsy, and 114 subjects were examined by using brain imaging, such as computed tomography and MRI. Therefore, 242 subjects in all (89.3%) underwent some kind of morphologic examination. The remaining 29 subjects were examined by using clinical features. In all dementia cases, 19 AD cases and 15 VaD cases had other subtypes of dementia; of those, 11 cases were a mixed type of AD and VaD. These cases were counted as events in the analyses for each subtype. Finally, 144 subjects experienced AD, 88 subjects experienced VaD, and 50 subjects experienced other subtypes of dementia.

Nutritional survey

At the baseline screening examination in 1988, a dietary survey was conducted by using a 70-item semiquantitative food-frequency questionnaire concerning food intake (19). The validity of this questionnaire has been reported previously (20). The questionnaire was completed by each participant in advance and was checked by a trained dietitian or a nutritionist in the screening examination. The average food intake per day was calculated from the weekly frequency of intake of various foods and the amount (quantity) of each food portion. The nutritional intake was calculated by using the fourth revision of the Standard Tables of Food Composition in Japan (21). Each nutritional element was adjusted for energy intake by using the nutrient density method (22).

Risk-factor measurements

At baseline, each subject completed a self-administered questionnaire that covered medical history, antidiabetic and antihypertensive treatments, educational status, smoking habits, and physical activity. A history of stroke was defined as a preexisting sudden onset of nonconvulsive and focal neurologic deficit that persisted >24 h on the basis of all available clinical data. Educational levels were divided into 3 categories as follows: low (<7 y of education), intermediate (7–12 y of education), and high (≥13 y of education). Smoking habits were categorized as either current use or no current use. Physical activity during leisure time was defined as 4 categories as follows: always sedentary, walking, exercise or sports 1–2 d/wk, and exercise or sports ≥3 d/wk. Blood pressure was measured 3 times by using a standard mercury sphygmomanometer in the sitting position after rest for ≥5 min. The mean of 3 measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg or current use of antihypertensive drugs. Body height and weight were measured in light clothing without shoes, and BMI (in kg/m^2) was calculated. Diabetes was defined as a fasting plasma glucose concentration ≥7.0 mmol/L, 2-h postload glucose concentrations or postprandial

glucose concentrations ≥11.1 mmol/L, or the current use of insulin or oral medication for diabetes.

Statistical analysis

Dietary patterns associated with risk of dementia were assessed by using a reduced rank regression (RRR) analysis (23). Usually, a dietary pattern analysis is conducted by using either a hypothesis-oriented approach that requires a known ideal dietary pattern (eg, the Mediterranean diet) or a principal components analysis that determines dietary patterns specific to the target population. In contrast with these analyses, RRR does not require any known dietary pattern and can allow for previous information about the pathway from the diet to relevant disease. RRR identifies linear functions of food groups (ie, the dietary pattern) that explain as much of the variation of nutrients selected as risk or preventive factors for the relevant disease as possible. Consequently, the score for dietary pattern computed by this method is likely to be associated with risk of the relevant disease. RRR could be the most appropriate method to estimate the ideal dietary pattern for the prevention of dementia. We selected the following 7 nutrients as risk or preventive factors for dementia: SFA (24, 25), MUFA (25), PUFA (25, 26), vitamin C (27), potassium (28), calcium (28), and magnesium (28). These nutrients were known or suspected to confer risk of or protection against dementia and were variables with $P < 0.2$ in the univariate analyses regarding their intakes and risk of the development for dementia. Dietary patterns related to the intakes of these 7 nutrients were derived on the basis of 19 food groups. Pearson's correlation coefficients in nutrients, food groups, and scores for the extracted dietary pattern were calculated. Scores for the dietary pattern were categorized in quartiles. Trends in mean values or frequencies of risk factors across scores for the dietary pattern were tested by using the general linear model or logistic regression analysis, respectively. The age- and sex-adjusted or multivariate-adjusted HRs and 95% CIs were estimated by using the Cox proportional hazards model. The heterogeneity of HRs in subgroups was tested by adding interaction terms to the relevant Cox model. Two-sided $P < 0.05$ was considered statistically significant in all analyses. The SAS software package (version 9.2; SAS Institute) was used to perform all statistical analyses.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from participants.

RESULTS

The mean age of the overall study population was 68 y, and the proportion of women was 57%. The prevalence of diabetes and hypertension was 15.0% and 51.7%, respectively. In total subjects, 23.7% of subjects had smoking habits, and 70.5% of subjects were sedentary during leisure time.

In our subjects, 7 dietary patterns were extracted by using RRR. These dietary patterns explained 87.1% of the total variation of intakes of the following 7 nutrients selected as responsible variables: SFA, MUFA, PUFA, vitamin C, potassium, calcium, and magnesium. Scores for dietary pattern 1 (DP1) accounted for 54.3% of the total variation of all responsible variables, and scores for dietary patterns 2–7 explained very few variations (*see* Table 1 under "Supplemental data" in the online issue). Therefore, we selected scores for DP1 as a target dietary pattern in this study. Scores for DP1 were highly correlated with intakes of each nutrient (all Pearson's correlation coefficients >0.50) (**Table 1**).

Factor loadings of the 19 food groups associated with scores for DP1 and correlation coefficients between food groups and 7 response variables are shown in **Table 2**. Factor loadings represent the magnitude and direction of each food group's contribution to scores for DP1. A positive value of a factor loading indicated that a higher score for DP1 was associated with an increased intake for that food group. Food groups with a factor loading ≥0.2 were soybeans and soybean products, green vegetables, other vegetables, algae, and milk and dairy products, whereas the food with a factor loading less than −0.2 was rice.

Clinical characteristics of study subjects according to the quartile of scores for DP1 at baseline are shown in **Table 3**. Subjects with higher scores for DP1 were likely to be women and more likely to have diabetes and smoking habits. Mean values of serum total cholesterol and BMI increased with higher scores for DP1.

We estimated HRs and 95% CIs for the development of dementia and its subtypes according to the quartile of scores for DP1 (**Table 4**). Risk of all-cause dementia decreased by two-thirds in subjects with the highest quartile of scores for DP1 compared with subject with the lowest quartile; the age- and sex-adjusted HR (95% CI) was 0.66 (0.47, 0.94). This relation remained unchanged even after adjustment for education, diabetes, hypertension, total cholesterol, history of stroke, BMI, smoking habits, and the intake of energy. With regard to subtypes of dementia, subjects with the highest quartile of scores for DP1 had a significant lower risk of either AD or VaD after adjustment for the aforementioned confounding factors; the HR (95% CI) was 0.65 (0.40, 1.06) for AD and 0.45 (0.22, 0.91) for VaD (**Table 5**). There was a significant linear relation between scores for DP1 levels and risk of VaD (P-trend = 0.02) but not for AD (P-trend = 0.17). As a reference, there was no evidence of a significant relation between dietary patterns 2–7 and dementia.

Finally, we conducted sensitivity analyses stratified by diabetic status because subjects with diabetes were likely to modify their

TABLE 1
Pearson's correlation coefficients between nutrients (response variables) and extracted dietary patterns[1]

	Dietary patterns						
Nutrients	1	2	3	4	5	6	7
SFA	0.50[2]	0.49[2]	0.51[2]	0.02	0.06	0.11[2]	0.04
MUFA	0.57[2]	0.58[2]	0.08[2]	0.34[2]	−0.06	−0.13[2]	−0.07
PUFA	0.59[2]	0.45[2]	−0.50[2]	0.16[2]	0.08	0.07	0.05
Vitamin C	0.51[2]	−0.70[2]	0.1	0.35[2]	−0.02	−0.06	0.1
Potassium	0.84[2]	−0.44[2]	−0.04	0.07	−0.1	0.14[2]	−0.09
Calcium	0.84[2]	0.16[2]	−0.05	−0.42[2]	−0.15[2]	−0.06	0.06
Magnesium	0.84[2]	−0.30[2]	0.03	−0.21[2]	0.21[2]	−0.07	−0.05

[1] Dietary patterns were derived by reduced rank regression analysis.
[2] $P < 0.001$.

TABLE 2
Factor loadings of food groups associated with dietary pattern 1 and correlation coefficients between food groups and nutrients (response variable)[1]

Food groups	Factor loadings (dietary pattern 1)	Correlations between food groups and 7 response variables						
		SFA	MUFA	PUFA	Vitamin C	Potassium	Calcium	Magnesium
Rice	−0.45	−0.48[2]	−0.49[2]	−0.53[2]	−0.07	−0.37[2]	−0.57[2]	−0.40[2]
Breads	0.10	0.29[2]	0.12	0.13[2]	−0.04	0.01	0.16[2]	0.06
Noodles and other cereals	0.01	−0.03	−0.03	0.02	−0.03	−0.001	0.02	0.09
Potatoes	0.16	0.01	0.1	0.05	0.22[2]	0.33[2]	0.08	0.23[2]
Soybeans and soybean products	0.37	0.07	0.28[2]	0.72[2]	0.02	0.34[2]	0.46[2]	0.42
Miso	0.01	−0.006	0.09	0.02	0.03	0.03	−0.02	−0.21
Pickles	0.04	−0.08	−0.09	−0.11	0.30[2]	0.31[2]	−0.02	−0.07
Green vegetables	0.40	−0.004	0.06	0.1	0.72[2]	0.70[2]	0.28[2]	0.63[2]
Other vegetables	0.36	−0.009	0.03	0.04	0.74[2]	0.67[2]	0.22[2]	0.57[2]
Fruits and fruit juices	0.19	−0.007	−0.01	−0.03	0.56[2]	0.32[2]	0.07	0.30[2]
Algae	0.24	0.04	0.17[2]	0.21[2]	0.22[2]	0.37[2]	0.22[2]	0.28[2]
Fish	0.17	−0.07	0.16[2]	0.21[2]	−0.05	0.12[2]	0.46[2]	0.13[2]
Meat	0	0.34[2]	0.1	−0.14[2]	0.02	−0.01	−0.11	−0.05
Egg	0.15	0.29[2]	0.36[2]	0.07	0.03	0.1	0.14	0.08
Milk and dairy products	0.37	0.63[2]	0.27[2]	0.06	−0.03	0.26[2]	0.64[2]	0.50[2]
Fats and oils	0.12	0.41[2]	0.61[2]	0.23[2]	0.07	−0.04	−0.07	−0.1
Sugar and confectioneries	−0.1	0.01	−0.06	−0.12[2]	−0.006	−0.11	−0.12	−0.19[2]
Alcoholic drinks	−0.17	−0.14[2]	−0.23[2]	−0.17[2]	−0.19[2]	−0.19[2]	−0.09	−0.14[2]
Salt	−0.008	−0.05	−0.008	−0.13[2]	0.24[2]	0.15[2]	−0.08	−0.14[2]

[1] Factor loadings represent the magnitude and direction of the contribution of each food group to a dietary pattern 1 score. A positive value of factor loading indicated an increased intake of the food group. A negative value of loading indicated less intake of the food group. Patterns were derived by using a reduced rank regression with 7 nutrients (ie, SFA, MUFA, PUFA, vitamin C, potassium, calcium, and magnesium) as response variables and 19 foods and food groups as independent variables.

[2] $P < 0.001$.

dietary customs because of the medical treatment. As a consequence, multivariable-adjusted HRs of all-cause dementia and its subtypes increased linearly with higher scores for DP1 in subjects without diabetes (all P-trend < 0.01) but not in subjects with diabetes.

DISCUSSION

The current study identified a dietary pattern that was associated with lower risk of dementia in a general Japanese elderly population. This dietary pattern was characterized by high intakes of soybeans and soybean products, green vegetables, other vegetables, algae, and milk and dairy products and a low intake of rice, which roughly correspondent to a customary Japanese diet. The findings from this study are expected to provide valuable information for the establishment of preventive strategies against dementia through lifestyle modification in the general Japanese population.

Several studies have assessed the relation between a dietary pattern and risk of dementia (29). Most studies addressed effects of the Mediterranean dietary pattern on risk of dementia and showed that higher intakes of vegetables, fruits, and fish were linked to lower risk of dementia. However, it would not be desirable to apply a Mediterranean dietary pattern to Asian populations because it is not a common dietary pattern for Asian people. For a similar reason, Gu et al (30) have assessed the relation between the dietary pattern and risk of dementia by using RRR in a US population. Gu et al (30) used 7 nutrients as response variables: SFA, MUFA, ω-3 PUFA, ω-6 PUFA, vitamin E, vitamin B-12, and folate. As a consequence, the extracted dietary pattern was positively correlated with the high intake of salad dressing, nuts, tomatoes, poultry, cruciferous vegetables, fruits, and dark-green leafy vegetables and highly negatively correlated with high-fat dairy, red meat, organ meat, and butter, and subjects with a greater adherence to this dietary pattern had lower risk of dementia. Similar findings were also observed in our analysis. This consistency was observed despite the clear difference in dietary customs between the 2 study populations, which underscores the reliability of our results.

In the current study, intakes of potassium, calcium, and magnesium were included in the RRR analysis as preventive factors for dementia on the basis of our previous findings (28). These minerals are abundantly present in milk and dairy products. As a consequence, a greater milk and dairy intake was positively correlated with higher scores for DP1, which linked to lower risk of dementia. Some cross-sectional studies have shown that the lower intake of dairy products was related to poor cognitive function (31, 32). These findings may support our results. We also showed that scores for DP1 were positively correlated with the intake of SFA. Even though the favorable effects of ω-3 PUFA on dementia have been well established in several epidemiologic studies (33, 26), effects of SFA remain inconclusive (34). The Chicago Health and Aging Project showed a positive association between SFA intake and risk of AD (24), whereas the Rotterdam study indicated no association between saturated fat and risk of dementia (35). Despite this fact, DP1, which suggested a protective effect on dementia, showed a positive correlation with SFA. Our findings could be attributable to the abundance of SFA in milk and dairy products, which also contain a lot of favorable minerals such as calcium and magnesium.

We showed a negative correlation between rice intake and DP1. Rice constitutes a large part of the Japanese daily diet. This association may arise from an imbalance in food intake (ie, a high

TABLE 3
Clinical characteristics of the study population by quartiles of score for dietary pattern 1[1]

Variables	Score for dietary pattern 1				
	Quartile 1 (n = 251), less than −0.82	Quartile 2 (n = 252), −0.82 to −0.05	Quartile 3 (n = 252), −0.06 to 0.83	Quartile 4 (n = 251), ≥0.83	P-trend
Scores for dietary pattern 1[2]	−1.5	−0.4	0.4	1.6	<0.001
Age (y)	68 ± 5.5[3]	69 ± 5.6	68 ± 5.4	69 ± 5.6	0.63
Women (%)	42.7	53.2	57.1	74.9	<0.001
Education (%)					
<7 y	11.9	11.9	12.3	7.6	0.15
7–12 y	82.9	80.6	78.6	80.9	0.47
≥13 y	5.2	7.5	9.1	11.5	0.01
Systolic blood pressure (mm Hg)	140 ± 24	136 ± 22	138 ± 23	138 ± 20	0.36
Diastolic blood pressure (mm Hg)	77 ± 11	75 ± 10	76 ± 10	76 ± 11	0.47
Hypertension (%)	55.0	50.0	51.6	50.6	0.46
Diabetes (%)	10.0	13.1	13.5	23.5	<0.001
Serum total cholesterol (mg/dL)	199 ± 43	207 ± 46	214 ± 42	217 ± 40	<0.001
BMI (kg/m^2)	22 ± 3	22.3 ± 3	22.5 ± 3	22.8 ± 3	0.01
History of stroke (%)	4.4	4.8	4.0	4.4	0.89
Smoking habits (%)	33.5	24.6	25.8	10.8	<0.001
Physical activity (%)					
Always sedentary	75.3	71.0	69.9	65.7	0.02
Walking	6.0	9.5	8.7	12.0	0.04
Exercise or sport 1–2 d/wk	5.2	6.0	7.1	5.6	0.72
Exercise or sport ≥3 d/wk	13.5	13.5	14.3	16.7	0.30
Energy intake (kcal/d)	1721 ± 469	1605 ± 392	1620 ± 374	1649 ± 358	0.08

[1] General linear model was used to test trends in mean values of risk factors across scores for the dietary pattern. Logistic regression analysis was used to test trends in frequencies of risk factors across scores for the dietary pattern.
[2] All values are medians.
[3] Mean ± SD (all such values).

intake of rice may result in lower intake of foods favorable for the prevention of dementia) rather than any harmful effects of rice itself. Therefore, these findings cannot be taken to mean that ta cessation of rice consumption per se will have any benefit against dementia; rather, they findings may simply underscore that a well-balanced meal with many nutritional foods is recommended for a reduction in risk of dementia.

In the current study, diabetes was associated with a greater adherence to DP1. This may be because subjects with diabetes tend to adopt a more favorable pattern of diet in response to diet therapy. Because diabetes has been considered a risk factor for dementia (36), this reclassification of the dietary pattern is likely to weaken the relation between the dietary pattern and risk of dementia, especially AD, in subjects with diabetes. In support of this idea, the analysis stratified by diabetic status revealed significant linear relationships between the dietary pattern and risk of all-cause dementia and its subtypes in subjects without diabetes. In contrast, there was no significant relation between DP1 and dementia in

TABLE 4
HRs (95% CIs) of incident dementia associated with the score for dietary pattern 1[1]

	Score for dietary pattern 1				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
All-cause dementia					
Events/population at risk (n)	69/251	72/252	63/252	67/251	—
Age and sex adjusted	1	0.84 (0.60, 1.18)	0.70 (0.50, 0.99)	0.66 (0.47, 0.94)	0.01
Multivariate adjusted[2]	1	0.85 (0.61, 1.19)	0.72 (0.50, 1.02)	0.66 (0.46, 0.95)	0.02
Alzheimer disease					
Events/population at risk (n)	36/251	31/252	37/252	40/251	—
Age and sex adjusted	1	0.64 (0.39, 1.03)	0.70 (0.44, 1.11)	0.62 (0.39, 0.99)	0.096
Multivariate adjusted[2]	1	0.64 (0.39, 1.04)	0.74 (0.46, 1.18)	0.65 (0.40, 1.06)	0.17
Vascular dementia					
Events/population at risk (n)	26/251	27/252	21/252	14/251	—
Age and sex adjusted	1	0.93 (0.54, 1.60)	0.72 (0.40, 1.29)	0.48 (0.24, 0.93)	0.02
Multivariate adjusted[2]	1	0.97 (0.56, 1.68)	0.74 (0.41, 1.34)	0.45 (0.22, 0.91)	0.02

[1] Cox proportional hazards model was used to estimate the age- and sex-adjusted or multivariate-adjusted HRs (95% CIs).
[2] Adjusted for age, sex, education, diabetes, hypertension, total cholesterol, history of stroke, BMI, smoking habits, exercise, and energy intake.

TABLE 5
HRs (95% CIs) of incident dementia associated with the score for dietary pattern 1 by diabetes status[1]

	Score for dietary pattern 1				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-trend
All-cause dementia					
Without diabetes					
Events/population at risk (*n*)	64/226	62/219	55/218	42/192	—
Age and sex adjusted	1.0	0.81 (0.57, 1.16)	0.69 (0.48, 0.99)	0.52 (0.35, 0.78)	<0.001
With diabetes					
Events/population at risk (*n*)	5/25	10/33	8/34	25/59	—
Age and sex adjusted	1.0	0.94 (0.32, 2.81)	0.58 (0.18, 1.86)	0.87 (0.31, 2.50)	0.87
Alzheimer disease					
Without diabetes					
Events/population at risk (*n*)	35/226	28/219	31/218	27/192	—
Age and sex adjusted	1.0	0.60 (0.36, 0.99)	0.62 (0.38, 1.01)	0.49 (0.29, 0.82)	0.01
With diabetes					
Events/population at risk (*n*)	1/25	3/33	6/34	13/59	—
Age and sex adjusted	1.0	1.36 (0.14, 13.36)	2.17 (0.25, 19.02)	2.37 (0.29, 19.64)	0.31
Vascular dementia					
Without diabetes					
Events/population at risk (*n*)	23/226	23/219	20/218	7/192	—
Age and sex adjusted	1.0	0.94 (0.53, 1.69)	0.82 (0.45, 1.50)	0.32 (0.13, 0.76)	0.01
With diabetes					
Events/population at risk (*n*)	3/25	4/33	1/34	7/59	—
Age and sex adjusted	1.0	0.63 (0.14, 2.93)	0.12 (0.01, 1.30)	0.42 (0.09, 2.04)	0.30

[1] Cox proportional hazards model was used to estimate the age- and sex-adjusted HRs (95% CIs).

subjects with diabetes, probably because of the limited sample size and existence of confounders caused by diet therapy. Additional investigations will be needed to elucidate this issue.

Some potential limitations of this study should be noted. Information regarding the intake of dietary nutrients derived from a semiquantitative food-frequency questionnaire may not be fully valid. In addition, the dietary assessment was performed only once at baseline. These limitations were likely to lead to some extent of misclassification of food intake. Such misclassifications would have weakened the association shown in the current study and biased the results toward the null hypothesis. In addition, there is a possibility of reverse causation (ie, our subjects might have already changed their dietary custom because of underlining dementia and other diseases in older age). However, after the sensitivity analysis in which cases who were diagnosed with dementia in the first 3 y after the baseline survey were excluded did not make any material differences in the findings. Finally, we may not have been able to completely exclude the influence of residual confounding on the relation between the identified dietary pattern and dementia risk.

In conclusion, to our knowledge, this is the first report to suggest a dietary pattern that protects against dementia in a general Japanese population. Subjects with this dietary pattern had an inverse relation with risk of all-cause dementia, AD, and VaD. These results could help to motivate changes in the dietary behavior of the general population in Japan and, thereby, lower risk of the development of dementia.

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REFERENCES

1. Suh GH, Shah A. A review of the epidemiological transition in dementia–cross-national comparisons of the indices related to Alzheimer's disease and vascular dementia. Acta Psychiatr Scand 2001;104:4–11.
2. Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. BMJ 2010;341:c3885–93.
3. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alperovitch A. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology 2007;69:1921–30.
4. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet Neurol 2004;3:579–87.
5. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59:912–21.
6. FéartC, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, Scarmeas N, Barberger-Gateau P. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 2009;302:638–48.
7. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302:627–37.
8. Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, Arima H, Sasaki K, Iida M, Iwaki T, et al. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study. Acta Psychiatr Scand 2010;122:319–25.

9. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. Stroke 2003;34:2349–54.
10. Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45:1161–8.
11. Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Nomiyama K, Ohmori S, Yoshitake T, Shinkawu A, et al. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. Diabetologia 1993;36:1198–203.
12. Hasegawa K, Inoue K, Moriya K. [An investigation of dementia rating scale in a general population of Japanese elderly.] Seishin Igaku 1974; 6:965–9 (in Japanese).
13. Katoh S, Simogaki H, Onodera A, Ueda H, Oikawa K, Ikeda K, Kosaka A, Imai Y, Hasegawa K. [Development of the revised version of Hasegawa's Dementia Scale (HDS-R).] Jpn J Geriatr Psychiatry 1991;2: 1339–47 (in Japanese).
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987.
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology1984; 34:939–44.
17. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–60.
18. Fujimi K, Sasaki K, Noda K, Wakisaka Y, Tanizaki Y, Matsui Y, Sekita A, Iida M, Kiyohara Y, Kanba S, et al. Clinicopathological outline of dementia with Lewy bodies applying the revised criteria: the Hisayama Study. Brain Pathol 2008;18:317–25.
19. Kiyohara Y, Shinohara A, Kato I, Shirota T, Kubo M, Tanizaki Y, Fujishima M, Iida M. Dietary factors and development of impaired glucose tolerance and diabetes in a general Japanese population: the hisayama study. J Epidemiol 2003;13:251–8.
20. Shirota T, Yoshizumi E. [A study on convenient dietary assessment.] Nihon Koshu Eisei Zasshi 1990;37:100–8 (in Japanese).
21. Resouces Council of Science and Technology Agency. [Standard tables of food composition for in Japan, 4th ed]. Tokyo, Japan: Ministry of Finance Printing Bureau, 1982 (in Japanese).
22. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
23. Hoffmann K, Schulze MB, Schienkiewitz A, Nothlings U, Boeing H. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. Am J Epidemiol 2004;159:935–44.
24. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Schneider J, Wilson RS. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 2003;60:194–200.
25. Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Torres F, Rizzo C, Capurso A, Panza F. Dietary intake of unsaturated fatty acids and age-related cognitive decline: a 8.5-year follow-up of the Italian Longitudinal Study on Aging. Neurobiol Aging 2006;27:1694–704.
26. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n−3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60:940–6.
27. Harrison FE. A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. J Alzheimers Dis 2012;29:711–26.
28. Ozawa M, Ninomiya T, Ohara T, Hirakawa Y, Doi Y, Hata J, Uchida K, Shirota T, Kitazono T, Kiyohara Y. Self-reported dietary intake of potassium, calcium, and magnesium and risk of dementia in Japanese: the Hisayama Study. J Am Geriatr Soc 2012;60:1515–20.
29. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Effectiveness of the Mediterranean diet: can it help delay or prevent Alzheimer's disease? J Alzheimers Dis 2010;20:795–801.
30. Gu Y, Nieves JW, Stern Y, Luchsinger JA, Scarmeas N. Food combination and Alzheimer disease risk: a protective diet. Arch Neurol 2010; 67:699–706.
31. Lee L, Kang SA, Lee HO, Lee BH, Park JS, Kim JH, Jung IK, Park YJ, Lee JE. Relationships between dietary intake and cognitive function level in Korean elderly people. Public Health 2001;115:133–8.
32. Rahman A, Sawyer Baker P, Allman RM, Zamrini E. Dietary factors and cognitive impairment in community-dwelling elderly. J Nutr Health Aging 2007;11:49–54.
33. Samieri C, Feart C, Letenneur L, Dartigues JF, Peres K, Auriacombe S, Peuchant E, Delcourt C, Barberger-Gateau P. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. Am J Clin Nutr 2008;88:714–21.
34. Solfrizzi V, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Vendemiale G, Capurso A, Panza F. Dietary fatty acids in dementia and predementia syndromes: epidemiological evidence and possible underlying mechanisms. Ageing Res Rev 2010;9:184–99.
35. Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM. Diet and risk of dementia: does fat matter?: The Rotterdam Study. Neurology 2002;59:1915–21.
36. Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, Kanba S, Kiyohara Y. Glucose tolerance status and risk of dementia in the community: the Hisayama study. Neurology 2011;77:1126–34.

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Altered Expression of Diabetes-Related Genes in Alzheimer's Disease Brains: The Hisayama Study

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Diabetes mellitus (DM) is considered to be a risk factor for dementia including Alzheimer's disease (AD). However, the molecular mechanism underlying this risk is not well understood. We examined gene expression profiles in postmortem human brains donated for the Hisayama study. Three-way analysis of variance of microarray data from frontal cortex, temporal cortex, and hippocampus was performed with the presence/absence of AD and vascular dementia, and sex, as factors. Comparative analyses of expression changes in the brains of AD patients and a mouse model of AD were also performed. Relevant changes in gene expression identified by microarray analysis were validated by quantitative real-time reverse-transcription polymerase chain reaction and western blotting. The hippocampi of AD brains showed the most significant alteration in gene expression profile. Genes involved in noninsulin-dependent DM and obesity were significantly altered in both AD brains and the AD mouse model, as were genes related to psychiatric disorders and AD. The alterations in the expression profiles of DM-related genes in AD brains were independent of peripheral DM-related abnormalities. These results indicate that altered expression of genes related to DM in AD brains is a result of AD pathology, which may thereby be exacerbated by peripheral insulin resistance or DM.

Keywords: Animal model, Hippocampus, Insulin, Microarray, Postmortem brains

Introduction

More than 20 million people worldwide suffer from dementia, and this number is expected to exceed 80 million by 2040 because of the rapid increase in the numbers of elderly (Ferri et al. 2005). The prevalences of all-cause dementia and Alzheimer's disease (AD) in the general population of Japanese elderly have increased significantly over the past 20 years, especially among subjects aged ≧75 years (Sekita et al. 2010). Thus, it is important to establish effective prevention strategies for dementia, and particularly for AD. To reach this goal, it is essential to understand the risk factors for developing dementia, including AD, in the elderly population.

Several recent studies have indicated effects of insulin and glucose metabolism on the risk of developing dementia, especially AD (Kuusisto et al. 1997; de la Monte and Wands 2008; Schrijvers et al. 2010). The results of the Hisayama study suggested that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate the formation of neuritic plaques (NPs) in combination with the effect of the *APOE ε4* allele, a major risk factor for AD (Matsuzaki et al. 2010).

To identify molecular pathological alterations in AD brains, we performed interspecies comparative microarray analyses using RNA prepared from postmortem human brain tissues donated for the Hisayama study (Katsuki 1966; Matsuzaki et al. 2010; Sekita et al. 2010), and hippocampal RNAs from the triple-transgenic mouse model of AD (3xTg-AD) (Oddo et al. 2003). We found altered expression profiles of diabetes mellitus (DM)-related genes in AD brains, which were independent of peripheral DM-related abnormalities.

Materials and Methods

Postmortem Brain Tissues

We examined 88 autopsy samples from Hisayama residents obtained between 15 December 2008 and 24 February 2011. Clinical data related to DM or prediabetes were collected as described (Ohara et al. 2011). The study was approved by the Ethics Committee of the Faculty of Medicine, Kyushu University. Written informed consent for all subjects was obtained from their families. Neuropathologic changes were examined as described previously (Matsuzaki et al. 2010). Sections were routinely stained using hematoxylin–eosin, Klüver-Barrera stain, and a modified Bielschowsky method. Specimens from each subject were immunostained using antibodies against phosphorylated microtubule-associated protein tau (MAPT) (AT8, mouse monoclonal, 1:500; Innogenetics, Belgium) and the assessment of AD pathology was conducted according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) guidelines (Mirra et al. 1991) and the Braak stage (Braak and Braak 1991). During autopsy dissection, parts of the frontal cortex, temporal cortex, and hippocampus were cut out from each brain and preserved at −80 °C until RNA preparation.

Animals

3xTg-AD-H mice harboring a homozygous $Psen1_{M146V}$ mutation and homozygous mutant transgenes for APP_{Swe} and $MAPT_{P301L}$, 3xTg-AD-h mice harboring a homozygous $Psen1_{M146V}$ mutation and hemizygous APP_{Swe} and $MAPT_{P301L}$ transgenes, and nontransgenic control mice (non-Tg) (Oddo et al. 2003) were used in this study. At age 14 months, brains were removed ($N=3$ male mice of each type) under pentobarbital anesthesia (i.p.), with perfusion of 40 mL of saline via the left ventricle. Hippocampi were isolated and preserved at −80 °C until RNA preparation. The handling and killing of all animals was performed in accordance with the national prescribed guidelines, and ethical approval for the study was granted by the Animal Experiment Committee of Kyushu University.

Gene Expression Profiling with Microarray Analyses

Total RNA was isolated using a combination of Isogen (Nippon Gene, Tokyo, Japan) and the RNeasy Mini Kit (Qiagen, Tokyo, Japan),