1813-1820, 2014.

2. 学会発表

1. 岸本裕歩,小原知之,秦 淳,野藤 悠,熊谷秋三,清原 裕：地域高齢住民における運動習慣が認知症発症に及ぼす影響：久山町研究. 第56回日本老年医学会,福岡市,2014.6
2. 熊谷秋三（シンポジスト）：アンチエイジングの運動疫学. 第14回日本抗加齢医学会総会シンポジウム，あの人は，どうしてあんなに元気なのか！？～三浦雄一郎氏，マスターズアスリート，久山町スタディからひも解くエクササイズ・サイエンス～，大阪市,2014.6
3. 熊谷秋三（シンポジスト）：アルツハイマー病および認知機能低下に関する身体活動，身体不活動および体力の影響. スイス-日本 高齢化時代へのダイアローグ，在日スイス大使館主催. 東京都,2014.6
4. Quan F, Nofuji Y, Narazaki K, Honda T, Chen T, and Kumagai S: Association between objectively measured physical activity and serum brain-derived neurotrophic factor among Japanese workers. 19th Annual Conference of the East Asia, Sport and Exercise Science Society, Busan, South Korea,2014.8
5. Haeuchi Y, Narazaki K, Honda T, Chen S, Chen T, and Kumagai S.: Relationship between participation in social activity and physical activity in Japanese community-dwelling older adults. 19th Annual Conference of the East Asia Sport and Exercise Science Society Busan, South Korea, 2014.8
6. 熊谷秋三（基調講演）：運動疫学研究の成果と課題および今後の展望 -生活習慣病・認知症発症予防の観点から-. 第17回日本運動疫学会学術総会長崎市,2014.9
7. 西地令子，野藤 悠，鷲尾昌一，熊谷秋三：勤労者における睡眠障害と血清脳由来神経栄養因子（BDNF）との関連性. 第73回日本公衆衛生学会総会，宇都宮市，2014.11
8. 高柳茂美，松下智子，熊谷秋三：大学生のセルフケア能力向上のためのABCプログラムの開発. 第63回九州地区大学一般教育研究協議会. 福岡市,2014.9
9. 西地令子，熊谷秋三：男性勤労者における職業性ストレス要因および首尾一貫性と抑うつ状態との関連性. 日本産業看護学会 第3回学術集会,北九州市,2014.9
10. 生内由佳，野藤 悠，松尾恵理，楢崎兼司，陳 涛，陳三妹，本田貴紀，熊谷秋三：地域在住高齢者を対象とした前向きコホート研究：篠栗元気もん研究. 第17回日本運動疫学会，長崎市,2014.9
11. Nadzirah Ahmad Basri, Zhang Yan Ping, Atsushi Ichimiya, Hideaki Fukumori, Tomoko Matsushita, and Shuzo Kumagai : Assessing the unique communication styles of Japanese university students. WPA Section of Epidemiology and Public Health -2014 Meeting, 奈良市,2014.10
12. 齊藤貴文,崎田正博,本田貴紀，熊谷秋三.歩行活動と座位行動の腰痛に対する組み合わせリスクについて－地域在住自立高齢者を対象として－. 第7回日本運動器疼痛学会，宇部市,2014.10
13. Cai J, Chen T, Supartini A, T Honda, H Nagano, Matsuo E, and Kumagai S: Association between Physical Activity and Sleep Onset Latency among Community-Dwelling Older People in Japan: A Cross-sectional Study. GSA's 67th Annual Scientific Meeting, Washington DC, USA,2014.12

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．また認知症患者に併発する種々の疾患の病態は未解明のままである．本研究では，認知症発症リスクの高い脳卒中症例や糖尿病症例の集団を用いて認知症発症の関連因子を明らかにするとともに，認知症を有する脳卒中症例また糖尿病症例の病態をも明らかにする．

A. 研究目的

(1)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(福岡脳卒中データベース研究，FSR；福岡県糖尿病データベース研究，FDR)の解析により，認知症発症の危険因子と防御因子を明らかにする．

(2)上記の大規模コホートに登録された症例を対象に，認知症の有無による脳卒中や糖尿病の病態の差異を明らかにする．また脳卒中や糖尿病患者で認知症を有する症例を対象に，治療内容による病状や経過の差異を明らかにする．

B. 研究方法

(1)血管性認知症ハイリスク群の脳卒中患者の追跡調査であるFSRと，アルツハイマー病ハイリスク群の糖尿病患者の追跡調査であるFDRのデータベース情報を用いて，認知症新規発症の有無に関連する因子を明らかにする．

(2)上記のFSRやFDRに登録された脳卒中や糖尿病患者を対象に，認知症の有無が脳卒中や糖尿病の病態に及ぼす影響を検討する．また登録時に認知症を有する症例を対象に，認知症に対する治療の有無，また脳卒中や糖尿病に対する治療内容の相違による病状や経過の差異を検討する．

(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

(1) データベースの整備

FSRは発症7日以内の急性期脳卒中患者で福岡県内の7つの施設(九州大学病院，九州医療センター，福岡東医療センター，福岡赤十字病院，白十字病院，聖マリア病院，製鉄記念八幡病院，九州労災病院)に入院した症例を対象に，臨床情報，血漿，ゲノムを収集するとともに退院後の予後調査を行うコホート研究である．FSRは平成19年6月に症例登録を開始し，平成26年12月までに同意を取得しえた入院患者10,092例（同意取得率89%）を前向きデータベースに登録した．現在も新規症例の登録を継続している．そして追跡調査は発症3ヶ月後，6ヶ月後，1年，その後1年毎に行っている．平成26年度も引き続き登録症例の追跡調査を継続し，現在の追跡率は95%を越える高い値を維持している．

FDRは福岡県内の糖尿病学会認定の7つ研修病院（九州大学病院，福岡赤十字病院，聖マリア病院，九州中央病院，福岡東医療センター，白十字病院，製鉄記念八幡病院）と学会認定専門医の診療所（9カ所）の計16施設で，外来通院中の糖尿病患者を対象に，臨床情報，血液・尿，ゲノムを収集することで，糖尿病患者の実態を明らかにし，合併症を減少させる効果的治療法を検討するコホート研究である．FDRは平成20年4月に症例登録を開始し，平成22年10月までに計5,131例を登録した．平成26年度は引き続きこれらの糖尿病患者の追跡調査を継続した（追跡率98.0%）．

(2) 認知症新規発症の追跡調査

FSR既登録患者で退院時に認知症や高次脳機能障害を認めなかった者を対象に，脳梗塞発症1年後の追跡調査時に研究内容説明書，同意文書，認知機能を評価するアンケート用紙（IQCODEを用いる）を郵送し，アンケート調査による認知機能評価を行った．IQCODEは家族・介護者からの情報に基づき患者の認知機能を評価する尺度であり，脳卒中患者に対する認知機能評価法としての報告が多く，認知機能評価法として一般的に用いられているMMSEと高い相関を有する．個人情報を削除した後にアンケート結果をFSRデータと連結し，認知症発症の有無や認知症発症に関連する因子の検討を開始した．しかしパイロット研究として九州大学病院外来に通院中のFSR既登録症例に対してIQCODEによる認知機能評価を行ったが，同一患者に対して家族間でIQCODEの結果に相違がある例を多く認めた．FDRにても登録時に認知機能評価（HDS-R, MMSE）を施行した65歳以上の症例を対象に登録5年後の追跡調査時に認知機能評価（HDS-R, MMSE）を開始した．しかしFSRと同様に追跡調査において正確な認知機能評価を行うことは困難であった．そのため現状のFSR・FDRでの追跡調査方法では，登録の一定期間後の時点で認知症の新規発症の有無を精度高く評価するのは困難と判断された．

そこで認知症の有無をシステマティックに評価するために，レセプト情報（保険診療名・抗認知症薬使用有無）の活用を検討している．FSRならびにFDR登録症例を対象に，臨床情報とレセプト情報の突合を行い，慢性期の認知症発症を追跡する方法を検討していきたいと考えている．これらのデータを活用してハイリスク症例に発症する認知症の頻度とその危険因子・防御因子を解明していきたいと考えている．

(3) 認知症を有する脳卒中患者に対する治療の有無による病状・経過の差異

FSRでは2007年～2014年の7年間に登録された症例のうち，発症24時間以内に来院した脳梗塞患者で，発症前ADLが自立（mRS≤2：自分の身の回りのことは介助なしに行える）している症例が4,999例存在する．このうち発症前に認知症があると判断された症例が579例（11.6%）存在した．この脳梗塞発症前より認知症を有する症例を対象に，基礎研究で脳梗塞縮小効果が報告されているコリンエステラーゼ阻害薬（ChE-I）の脳梗塞発症前投与の有無と入院時神経学的重症度の関連を検討した．

発症前認知症を有する579例のうち119例（20.6%）にChE-Iが投与されていた．ChE-I投与群は非投与群と比較して入院時の神経症状軽症（NIHSS≤4）の頻度が有意に高かった（55% vs 37%, $p<0.01$）．ロジスィック回帰分析を用いて交絡因子を調整しても，脳梗塞発症前のChE-I投与は入院時神経症状軽症と有意に関連していた（多変量調整OR, 2.61; 95%CI 1.68-4.11）．脳梗塞臨床病型別，また脳卒中既往の有無別の層別解析にても同様の結果であり，脳梗塞発症前にChE-I投与が投与されていると入院時神経学的重症度が有意に軽症となる可能性を高める結果であった．今後，退院時や3ヶ月後の機能予後，また生命予後にChE-Iが関連するかをも検討していく．

D. 考察

(1) データベースの整備

FSRでは高い同意取得率のもとで新規症例を継続して登録しつつ，高い追跡率を保っている．FDRは症例の登録は終了しているが，FDRにおいても高い追跡率を保っており，平成26年度もデータベースの整備が順調に行えた．

(2) 認知症新規発症の追跡調査

FSRまたFDRの既存追跡システムでは，登録の一定期間後の時点で認知症新規発症を精度高く評価することは困難であった．そこでレセプト情報

に基づき慢性期に発症する認知症の有無を評価するシステムを構築し，レセプト情報とFSRおよびFDRデータベース情報を結合することでハイリスク症例に発症する認知症の危険因子・防御因子を解明していく．

(3) 認知症を有する脳卒中患者に対する治療内容の有無による病状・経過の差異

ChE-Iは抗認知症薬として既に上市されている．これまでChE-Iは脳梗塞動物モデルや培養細胞を用いた基礎研究で神経保護効果を示すことが報告されてきているが，ヒトの脳梗塞に対する保護効果を示した報告ない．ChE-Iは脳梗塞急性期の神経障害を助長する虚血性脱分極やグルタミン酸毒性を抑制し，また脳血流増加作用・脳血管反応性改善作用等が報告されている．そのため認知機能低下抑制作用以外に，脳梗塞発症後の神経症状軽減化に対しChE-Iは有用である可能性が考えられる．

また認知症症例で脳卒中を発症したり，糖尿病を罹患している症例は今後も増加すると予想される．しかし認知症を有する場合の脳卒中や糖尿病の病態は解明されておらず，治療指針も確立していない．次年度では，FSRとFDR登録症例の解析を通じて，認知症を有する際の病態を明らかにするとともに，将来的に認知症患者での治療指針のエビデンスを構築していくように努める．

E. 結論

脳梗塞急性期に発症する認知症の危険因子・防御因子を解明する．また認知症を有する脳卒中患者また糖尿病患者の病態を引き続き検討していく．

G. 研究発表

1. 論文発表

1. Matsuo R, Kamouchi M, Fukuda H, Hata J, Wakisaka Y, Kuroda J, Ago T, Kitazono T; FSR Investigators. Intravenous thrombolysis with recombinant tissue plasminogen activator for ischemic stroke patients over 80 years old: the Fukuoka Stroke Registry. PLoS One 9:e110444, 2014
2. Murao K, Leys D, Jacquin A, Kitazono T, Bordet R, Béjot Y, Kimura K, Godefroy O, Wakisaka Y, Moulin S, Ago T, Sibon I, Bombois S, Mas JL, Hénon H, Pasquier F, Giroud M, Cordonnier C, Okada Y; OPHELIE-COG investigators. Thrombolytic therapy for stroke in patients with preexisting cognitive impairment. Neurology 82:2048-2054, 2014
3. Wakisaka Y, Ago T, Kamouchi M, Kuroda J, Matsuo R, Hata J, Gotoh S, Isomura T, Awano H, Suzuki K, Fukuda K, Okada Y, Kiyohara Y, Ooboshi H, Kitazono T; REBIOS Investigators. Plasma S100A12 is associated with functional outcome after ischemic stroke: Research for Biomarkers in Ischemic Stroke. J Neurol Sci 340:75-79, 2014
4. Ogata T, Kamouchi M, Matsuo R, Hata J, Kuroda J, Ago T, Sugimori H, Inoue T, Kitazono T; Fukuoka Stroke Registry. Gastrointestinal bleeding in acute ischemic stroke: recent trends from the fukuoka stroke registry. Cerebrovasc Dis Extra 4:156-164, 2014
5. Matsuo R, Ago T, Hata J, Kuroda J, Wakisaka Y, Sugimori H, Kitazono T, Kamouchi M; FSR Investigators. Impact of the 1425G/A polymorphism of PRKCH on the recurrence of ischemic stroke: Fukuoka Stroke Registry. J Stroke Cerebrovasc Dis 23:1356-1361, 2014
6. Kiyohara T, Kamouchi M, Kumai Y, Ninomiya T, Hata J, Yoshimura S, Ago T, Okada Y, Kitazono T; Fukuoka Stroke Registry Investigators. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. Stroke 45:418-425, 2014
7. Matsuo R, Kamouchi M, Ago T, Hata J, Shono Y, Kuroda J, Wakisaka Y, Sugimori H, Kitazono T; FSR investigators. Geriatr

Gerontol Int 14:954-959, 2014
8. Kaizu S, Kishimoto H, Iwase M, Fujii H, Ohkuma T, Ide H, Jodai T, Kikuchi Y, Idewaki Y, Hirakawa Y, Nakamura U, Kitazono T. Impact of leisure-time physical activity on glycemic control and cardiovascular risk factors in Japanese patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry. PLoS One 9:e98768, 2014
9. Ohkuma T, Fujii H, Iwase M, Ogata-Kaizu S, Ide H, Kikuchi Y, Idewaki Y, Jodai T, Hirakawa Y, Nakamura U, Kitazono T. U-shaped association of sleep duration with metabolic syndrome and insulin resistance in patients with type 2 diabetes: the Fukuoka Diabetes Registry. Metabolism 63:484-491, 2014

2. 学会発表

1. 脇坂義信，吾郷哲朗，松尾龍，秦淳，鴨打正浩，北園孝成．認知症患者における脳梗塞発症前のドネペジル塩酸塩内服と入院時神経学的重症度に関する検討：福岡脳卒中データベース研究．第56回日本老年医学会学術集会 福岡市，2014.6

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
研究分担報告書

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　日本人固有の認知症危険因子の解明を目的として，これまで認知症疫学研究を地域で長期間継続している5つのチームの既存のデータを，統一した方法で再整理したデータベースを作成する．方法としては，疫学コンソーシアムは大規模調査に実績のある5チームから構成される．各チームの既存データを用いて従来のデータを経時的に整理し，チームごとに対象や標記の異なる従来のデータを整理しコード化する．チームを問わず共通して利用できる情報項目を抽出して既存データを整理し，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）．次にデータベース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．

5サイトの従来の調査内容を検討したところ，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回であった．2)調査項目について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，酒は全サイトで調査実施していたが，生活習慣病関連（DM, HT, HL, CKD, BMIなどのデータは）についてはあまり統一されていなかった．4)介入したサイト，観察研究のみのサイトと分かれることがわかった．同一施設であっても調査年度により調査内容が異なる可能性を考え，筑波大の内容を経時的にチェックした．その結果，内容は微妙に異なるとわかった．次の実務作業として九大以外の4サイトから既存データを筑波に届けてもらって，そこで評価項目とその尺度や単位に関する具体的情報を得た．また調査年度ごとに100名程度の匿名化した実データの登録をしてもらうことで生データの実態をチェックした．

これからの課題として，個々の調査項目について共通尺度をピックアップする．尺度にばらつきのあるものは，別に整理しておく．ある調査項目について，ある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は継続的に検討する．さらに調査内容の名称や単位統一をアメリカの先行例に倣って推進する必要がある．

A. 研究目的

500万人に達したとも言われる認知症疾患への対

応において，その危険因子の特定は不可欠である．そこで日本人固有の危険因子の解明を目的とする．これまで認知症疫学研究を地域で長期間継続している5つのチームごとに内容の異なる既存のデータを，統一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について，データベース2を用いて蓄積してゆく．

B. 研究方法

疫学コンソーシアムは大規模調査に実績のある 5 チームから構成される．各チームの既存データを用いて従来のデータを経時的に整理して並べ，チームごとに対象や標記の異なる従来のデータを整理しコード化する．チームを問わず共通して利用できる情報項目を抽出する．以上から，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）．次にデータベース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チームはこれを用いて新たな調査を実施してゆく．なおデータベース構築におけるポイントとして，まずデータの統合・整理，次いで新データ用のシステムを構築し，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．

（倫理面への配慮）

本研究は，「疫学研究に関する倫理指針」に基づき研究計画書を作成し，筑波大学，鳥取大学，金沢大学，東北大学，および九州大学医学部倫理委員会および理化学研究所倫理委員会の承認を得て行われた．認知症の有無にかかわらず，対象となる地域住民当事者における人権・プラバシーはもとより，その家族介護者等に求められる権利擁護をはじめとする倫理・価値観も含めて十分に配慮する．

C. 研究結果

5 サイトの従来の調査内容を検討したところ，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 回であった．2)調査項目について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，酒は全サイトで調査実施していたが，生活習慣病関連（DM, HT, HL, CKD, BMI などのデータは）についてはあまり統一されていなかった．4)介入したサイト，観察研究のみのサイトと分かれることがわかった．認知症の診断基準では DSM-IIIR が多かった．認知症の基礎疾患診断基準はほぼ明記されていた．MCI の診断基準として全サイトで CDR0.5 を用いていた．うつの評価:全サイトで GDS を用いていた．ADL 評価の尺度は Barthel index(ADL), Lawton(IADL)が主であったが，筑波は NADL であった．なお鳥取大学の ADL 評価なく，九大は老研式による IADL 評価であった．遺伝子 APOE，画像研究は多くで実施していたが，APOE については，鳥取大学は実施せず，九大は一部のみ，画像も九大は一部のみであった．

同一施設であっても調査年度により調査内容が異なる．そこで筑波大における内容を経時的にチェックした．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た．注目されるライフスタイル系に関しては，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．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，それ以前は視力障害・高血圧の有無 BMI などが問われている．DECO と IADL 総得点については第 1 次から，個々に見ているのは第 3 次から．これに対して NADL は継続的に実施している．HbA1c は第 2 次から，アディポネクチンは 2008 年に実施，認知機

能テストはずっと 5Cog, 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. 次の実務作業として九大以外の 4 サイトから既存データを筑波に届けてもらった. そこで評価項目とその尺度や単位に関する具体的情報を得た. また調査年度ごとに 100 名程度の匿名化した実データの登録をしてもらうことで生データの実態をチェックした

D. 考察

これからの課題として, 個々の調査項目について共通尺度をピックアップする. 尺度にばらつきのあるものは, 別に整理しておく. ある調査項目について, ある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は継続的に検討する. さらに調査内容の名称や単位統一をアメリカの先行例に倣って推進する必要がある.

E. 結論

日本人固有の認知症危険因子の解明を目的として, これまで認知症疫学研究を地域で長期間継続している 5 チームの既存データを統一した方法で再整理して, データベースを作成しつつある. これらを基に将来的には前向き縦断研究調査に使用される全国共通の新規データベースの作成を目指す. .

G. 研究発表

1. 論文発表

1. Ikejima C, Ikeda M, Hashimoto M, Ogawa Y, Tanimukai S, Kashibayashi T, Miyanaga K, Yonemura K, Kakuma T, Murotani K, Asada T. Multicenter population-based study on the prevalence of early onset dementia in Japan: vascular dementia as its prominent cause. Psychiatry Clin Neurosci 68:216-24, 2014
2. Yamawaki M, Wada-Isoe K, Yamamoto M, Nakashita S, Uemura Y, Takahashi Y, Nakayama T, Nakashima K. Association of cerebral white matter lesions with cognitive function and mood in Japanese elderly people: a population-based study. Brain Behav 2015, in press
3. Adachi T, Kitayama M, Nakano T, Adachi Y, Kato S, Nakashima K. Autopsy case of spinocerebellar ataxia type 31 with severe dementia at the terminal stage. Neuropathology 2014, in press
4. Tanaka K, Wada-Isoe K, Yamamoto M, Tagashira S, Tajiri Y, Nakashita S, Nakashima K. Clinical evaluation of fatigue in Japanese patients with Parkinson's disease. Brain Behav 4:643-649, 2014
5. Kurashiki-Osaka T, Adachi T, Nakayasu H, Nakashima K. Alpha-synuclein accumulation in a patient with Auerbach's plexus of pure autonomic failure. Intern Med 53:2261, 2014
6. Miyashita A, Wen Y, Kitamura N, Matsubara E, Kawarabayashi T, Shoji M, Tomita N, Furukawa K, Arai H, Asada T, Harigaya Y, Ikeda M, Amari M, Hanyu H, Higuchi S, Nishizawa M, Suga M, Kawase Y, Akatsu H, Imagawa M, Hamaguchi T, Yamada M, Morihara T, Takeda M, Takao T, Nakata K, Sasaki K, Watanabe K, Nakashima K, Urakami K, Ooya T, Takahashi M, Yuzuriha T, Serikawa K, Yoshimoto S, Nakagawa R, Saito Y, Hatsuta H, Murayama S, Kakita A, Takahashi H, Yamaguchi H, Akazawa K, Kanazawa I, Ihara Y, Ikeuchi T, Kuwano R. Lack of genetic association between TREM2 and late-onset Alzheimer's disease in a Japanese population. J Alzheimers Dis 41:1031-1038, 2014
7. Yasui K, Yabe I, Yoshida K, Kanai K, Arai K, Ito M, Onodera O, Koyano S, Isozaki E, Sawai S, Adachi Y, Sasaki H, Kuwabara S, Hattori T, Sobue G, Mizusawa H, Tsuji S, Nishizawa

M, Nakashima K. A 3-year cohort study of the natural history of spinocerebellar ataxia type 6 in Japan. Orphanet J Rare Dis 9:118, 2014

8. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, Arnold SE, Attems J, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Gearing M, Grinberg LT, Hof PR, Hyman BT, Jellinger K, Jicha GA, Kovacs GG, Knopman DS, Kofler J, Kukull WA, Mackenzie IR, Masliah E, McKee A, Montine TJ, Murray ME, Neltner JH, Santa-Maria I, Seeley WE, Serrano-Pozo A, Shelanski ML, Stein T, Takao M, Thal DR, Toledo JB, Troncoso JC, Vonsattel JP, White 3rd CL, Wisniewski T, Woltjer RL, Yamada M, Nelson PT. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 128:755-766, 2014
9. Wang J, Land D, Ono K, Galvez J, Zhao W, Vempati P, Steele JW, Cheng A, Yamada M, Levine S, Mazzola P, Pasinetti GM. Molecular topology as novel strategy for discovery of drugs with Aβ lowering and anti-aggregation dual activities for Alzheimer's disease. PLoS One 9:e92750, 2014
10. Wang J, Varghese M, Ono K, Yamada M, Levine S, Tzavaras N, Gong B, Hurst WJ, Blitzer RD, Pasinetti GM. Cocoa extracts reduce oligomerization of amyloid-β: implications for cognitive improvement in Alzheimer's disease. J Alzheimers Dis 41: 643-650, 2014
11. Noguchi-Shinohara M, Yuki S, Dohmoto C, Ikeda Y, Samuraki M, Iwasa K, Yokogawa M, Asai K, Komai K, Nakamura H, Yamada M. Consumption of green tea, but not black tea or coffee, is associated with reduced risk of cognitive decline. PLoS One 9:e96013, 2014
12. Miyashita A, Wen Y, Kitamura N, Matsubara E, Kawarabayashi T, Shoji M, Tomita N, Furukawa K, Arai H, Asada T, Harigaya Y, Ikeda M, Amari M, Hanyu H, Higuchi S, Nishizawa M, Suga M, Kawase Y, Akatsu H, Imagawa M, Hamaguchi T, Yamada M, Moirhara T, Takeda M, Takao T, Nakata K, Sasaki K, Watanabe K, Nakashima K, Urakami K, Ooya T, Takahashi M, Yzuriha T, Serikawa K, Yoshimoto S, Nakagawa R, Saito Y, Hatsuta H, Murayama S, Kakita A, Takahashi H, Yamaguchi H, Akazawa K, Kanazawa I, Ihara Y, Ikeuchi T, Kuwano R. Lack of genetic association between TREM2 and late-onset Alzheimer's disease in a Japanese population. J Alzheimers Dis 41:1031-1038, 2014
13. Ono K, Takahasi R, Ikeda T, Mizuguchi M, Hamaguchi T, Yamada M. Exogenous amyloidogenic proteins function as seeds in amyloid β-protein aggregation. Biochim Biophys Acta- Molecular Basis of Disease 1842:646-653, 2014
14. Takamura Y, Ono K, Matsumoto J, Yamada M, Nishijo H. Effects of the neurotrophic agent T-817MA on oligomeric amyloid-β-induced deficits in long-term potentiation in the hippocampal CA1 subfield. Neurobiol Aging 35:532-536, 2014
15. Meguro K, Kasai M, Akanuma K, Meguro M, Ishii H, Yamaguchi S. Donepezil and life expectancy in Alzheimer's disease: A retrospective analysis in the Tajiri Project. BMC Neurology 14:83, 2014
16. Nakatsuka M, Meguro K, Nakamura K, Akanuma K, Yamaguchi S. "Residence is not home" is a particular type of delusion that associates with cognitive declines of

Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 38:46-54, 2014

17. Meguro K, Ouchi Y, Akanuma K, Meguro M, Kasai M. Donepezil can improve daily activities and promote rehabilitation for severe Alzheimer's patients in Long-Term Care Health Facilities. BMC Neurology 14:243, 2014
18. Kasai M, Meguro K, Akanuma K, Yamaguchi S. Alzheimer's disease patients institutionalized in Group Homes run by Long-Term Care Insurance exhibit fewer symptoms of behavioral problems as evaluated by the BEHAVE-AD. Psychogeriatrics 2014, in press
19. Takada J, Meguro K, Sato Y, Chiba Y; Kurihara Project Members. Life concerns of elderly people living at home determined by Community General Support Center staff: Implications for organizing more effective integrated community care system. The Kurihara Project. Psychogeriatrics 14:188-195, 2014

2. 学会発表

1. Yoshita M, Tsuji S, Yokoyama K, Sakamoto H. The Utility of Amyloid Imaging with PET in Alzheimer Disease Diagnosis. 14st Asian & Oceanian Congress of Neurology, Macau, 2014. 3
2. 小野賢二郎，髙橋良一，池田篤平，山田正仁：Cross-seeding effects of amyloid β-protein and α-synuclein. 第55回日本神経学会学術大会，福岡市，2014.5
3. 佐村木美晴，松成一朗，島　啓介，山田正仁：機械学習プログラムを用いた将来の認知機能予測. 第55回日本神経学会学術大会，福岡市，2014.5
4. 篠原もえ子，柚木颯偲，堂本千晶，池田芳久，佐村木美晴，岩佐和夫，横川正美，淺井貴美子，駒井清暢，中村裕之，山田正仁：緑茶摂取と認知症および軽度認知障害の罹患リスク：前方視的縦断研究. 第55回日本神経学会学術大会，福岡市，2014.5
5. 山田正仁：認知症の神経病理を臨床診断する，治療・予防する. 第55回日本神経病理学会総会学術研究会，東京都，2014.6
6. 山田正仁：地域における認知症の現状と課題. 市民健康講座 第7回生き活きハッピーライフ～ようこそ食と健康の世界へ～，七尾市，2014.6
7. 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 between early and delayed responders in a community-based study. Alzheimer's Association International Conference 2014, Copenhagen, 2014. 7
8. Ono K, Takahashi R, Ikeda T, Yamada M. Cross-seeding effects of amyloid β-protein and α-synuclein. Alzheimer's Association International Conference on Alzheimer's Disease 2014, Denmark, 2014. 7
9. 山田正仁：神経原線維変形型老年期認知症（SD-NFT）. 第19回認知神経科学会学術集会，東京都，2014.7
10. 小野賢二郎，髙橋良一，池田篤平，山田正仁：アミロイドβ蛋白とα-シヌクレイン蛋白のクロス・シーディング効果. 第2回日本アミロイドーシス研究会学術集会，東京都，2014.8
11. 小野賢二郎，髙橋良一，池田篤平，山田正仁：Cross-seeding effects of amyloid β-protein and α-synuclei. 第37回日本神経科学大会 Neuroscience 2014，横浜市，2014.9

12. 山田正仁：非アルツハイマー型変性認知症：アルツハイマー病との鑑別．認知症治療学術講演会 － アルツハイマー型認知症の新しい治療戦略 －，神戸市，2014.9
13. Samuraki M, Matsunari I, Yoshita M, Shima K, Noguchi-Shinohara M, Hamaguchi T, Ono K, Yamada M. Regional glucose metabolism and gray-matter volume in Alzheimer's disease with cerebral amyloid angiopathy-related microbleeds. 4th International CAA (Cerebral Amyloid Angiopathy) Conference. London, 2014. 9
14. Yoshita M, Yamada M. Myocardial Sympathetic Nerve Imaging, Symposium 8: Recent advances in neuroimaging for geriatric psychoneurological disorders. 14th The International College of Geriatric Psychoneurophalmacology. Tsukuba, 2014. 10
15. 小野賢二郎，山田正仁：病態に基づいた Alzheimer 病の予防・治療薬の開発．第 32 回日本神経治療学会総会，東京都，2014.11
16. 篠原もえ子，柚木颯偲，堂本千晶，池田芳久，佐村木美晴，岩佐和夫，横川正美，駒井清暢，中村裕之，山田正仁：緑茶摂取と認知症・軽度認知障害の罹患リスク：なかじまプロジェクト．第 33 回日本認知症学会学術集会，横浜市，2014.11
17. 柚木颯偲，篠原もえ子，堂本千晶，横川正美，淺井貴美子，岩佐和夫，駒井清暢，中村裕之，山田正仁：脳検診を受診しない地域住民の心理的態度に関する検討．第33回日本認知症学会学術集会，横浜市，2014.11

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

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
特になし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ozawa M, Ohara T, Ninomiya T, Hata J, Yoshida D, Mukai N, Nagata M, Uchida K, Shirota T, Kitazono T, Kiyohara Y	Milk and dairy consumption and risk of dementia in an elderly Japanese population: the Hisayama Study.	J Am Geriatr Soc	62	1224-1230	2014
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	24	2476-2488	2014
Mukai N, Doi Y, Ninomiya T, Hirakawa Y, Nagata M, Yoshida D, Hata J, Fukuhara M, Nakamura U, Kitazono T, Kiyohara Y	Trends in the prevalence of type 2 diabetes and prediabetes in community-dwelling Japanese subjects: the Hisayama Study.	J Diabetes Invest	5	162-169	2014
Kishimoto H, Hata J, Ninomiya T, Nemeth H, Hirakawa Y, Yoshida D, Kumagai S, Kitazono T, Kiyohara Y	Midlife and late-life handgrip strength and risk of cause-specific death in a general Japanese population: the Hisayama Study.	J Epidemiol Community Health	68	663-668	2014
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	34	284-290	2014
Wakamiya T, Suzuki SO, Hamasaki H, Honda H, Mizoguchi M, Yoshimoto K, Iwaki T	Elevated expression of fatty acid synthase and nuclear localization of carnitine palmitoyltransferase 1C are common among human gliomas.	Neuropathology	34	465-474	2014
Honda H, Hamasaki H, Wakamiya T, Koyama S, Suzuki SO, Fujii N, Iwaki T	Loss of hnRNPA1 in ALS spinal cord motor neurons with TDP-43-positive inclusions.	Neuropathology	35	37-43	2015
Monji A, Motomura K, Mizoguchi Y, Ohara T, Baba S, Yoshiura T, Kanba S	A case of late-onset bipolar disorder with severely abnormal behavior and neuroimaging observations very similar to those of frontotemporal dementia.	J Neuropsychiatry Clin Neurosci	26	E35	2014

Nakajima M, Takahashi A, Tsuji T, Karasugi T, Baba H, Uchida K, Kawabata S, Okawa A, Shindo S, Takeuchi K, Taniguchi Y, Maeda S, Kashii M, Seichi A, Nakajima H, Kawaguchi Y, Fujibayashi S, Takahata M, Tanaka T, Watanabe K, Kida K, Kanchiku T, Ito Z, Mori K, Kaito T, Kobayashi S, Yamada K, Takahashi M, Chiba K, Matsumoto M, Furukawa K, Kubo M, Toyama Y Genetic Study Group of Investigation Committee on Ossification of the Spinal Ligaments, Ikegawa S.	A genome-wide association study identifies susceptibility loci for ossification of the posterior longitudinal ligament of thespine.	Nat Genet	46	1012-1016	2014
Hara M, Nakamura K, Nanri H, Nishida Y, Hishida A, Kawai S, Hamajima N, Kita Y, Suzuki S, Mantjoro EM, Ohnaka K, Uemura H, Matsui D, Oze I, Mikami H, Kubo M, Tanaka H	Associations Between hOGG1 Ser326Cys Polymorphism and Increased Body Mass Index and Fasting Glucose Level in the Japanese General Population.	J Epidemiol	24	379-384	2014
Tsuruya K, Fukuma S, Wakita T, Ninomiya T, Nagata M, Yoshida H, Fujimi S, Kiyohara Y, Kitazono T, Uchida K, Shirota T, Akizawa T, Akiba T, Saito A, Fukuhara S	Dietary patterns and clinical outcomes in hemodialysis patients in Japan: a cohort study	PLoS One	10	e0116677	2014
Narazaki K, Matuo E, Honda T, Nofuji Y, Yonemoto K, Kumagai S	Physical fitness measures as potential markers of low cognitive function in Japanese community-dwelling older adults without apparent cognitive problems	J Sports Sci Med	14	1307	2014
Murao K, Leys D, Jacquin A, Kitazono T, Bordet R, Béjot Y, Kimura K, Godefroy O, Wakisaka Y, Moulin S, Ago T, Sibon I, Bombois S, Mas JL, Hénon H, Pasquier F, Giroud M, Cordonnier C, Okada Y; OPHELIE-COG investigators	Thrombolytic therapy for stroke in patients with preexisting cognitive impairment.	Neurology	82	2048-2054	2014
Ikejima C, Ikeda M, Hashimoto M, Ogawa Y, Tanimukai S, Kashibayashi T, Miyanaga K, Yonemura K, Kakuma T, Murotani K, Asada T	Multicenter population-based study on the prevalence of early onset dementia in Japan: vascular dementia as its prominent cause.	Psychiatry Clin Neurosci	68	216-224	2014

Noguchi-Shinohara M, Yuki S, Dohmoto C, Ikeda Y, Samuraki M, Iwasa K, Yokogawa M, Asai K, Komai K, Nakamura H, Yamada M	Consumption of green tea, but not black tea or coffee is associated with reduced risk of cognitive decline	PLoS One	9	e96013	2014
Yamawaki M, Wada-Isoe K, Yamamoto M, Nakashita S, Uemura Y, Takahashi Y, Nakayama T, Nakashima K	Association of cerebral white matter lesions with cognitive function and mood in Japanese elderly people: a population-based study	Brain Behav	In press		2015
Meguro K, Kasai M, Akanuma K, Meguro M, Ishii H, Yamaguchi S	Donepezil and life expectancy in Alzheimer's disease: A retrospective analysis in the Tajiri Project.	BMC Neurology	14	83	2014
Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, Arnold SE, Attems J, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Gearing M, Grinberg LT, Hof PR, Hyman BT, Jellinger K, Jicha GA, Kovacs GG, Knopman DS, Kofler J, Kukull WA, Mackenzie IR, Masliah E, McKee A, Montine TJ, Murray ME, Neltner JH, Santa-Maria I, Seeley WE, Serrano-Pozo A, Shelanski ML, Stein T, Takao M, Thal DR, Toledo JB, Troncoso JC, Vonsattel JP, White 3rd CL, Wisniewski T, Woltjer RL, Yamada M, Nelson PT	Primary age-related tauopathy (PART): a common pathology associated with human aging.	Acta Neuropathol	128	755-766	2014
Miyashita A, Wen Y, Kitamura N, Matsubara E, Kawarabayashi T, Shoji M, Tomita N, Furukawa K, Arai H, Asada T, Harigaya Y, Ikeda M, Amari M, Hanyu H, Higuchi S, Nishizawa M, Suga M, Kawase Y, Akatsu H, Imagawa M, Hamaguchi T, Yamada M, Morihara T, Takeda M, Takao T, Nakata K, Sasaki K, Watanabe K, Nakashima K, Urakami K, Ooya T, Takahashi M, Yuzuriha T, Serikawa K, Yoshimoto S, Nakagawa R, Saito Y, Hatsuta H, Murayama S, Kakita A, Takahashi H, Yamaguchi H, Akazawa K, Kanazawa I, Ihara Y, Ikeuchi T, Kuwano R.	Lack of Genetic Association Between TREM2 and Late-Onset Alzheimer's Disease in a Japanese Population.	J Alzheimers Dis	41	1031-1038	2014

Milk and Dairy Consumption and Risk of Dementia in an Elderly Japanese Population: The Hisayama Study

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OBJECTIVES: To determine the effect of milk and dairy intake on the development of all-cause dementia and its subtypes in an elderly Japanese population.

DESIGN: Prospective cohort study.

SETTING: The Hisayama Study, Japan.

PARTICIPANTS: Individuals aged 60 and older without dementia (N = 1,081).

MEASUREMENTS: Milk and dairy intake was estimated using a 70-item semiquantitative food frequency questionnaire grouped into quartiles. The risk estimates of milk and dairy intake on the development of all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD) were computed using a Cox proportional hazards model.

RESULTS: Over 17 years of follow-up, 303 subjects developed all-cause dementia; 166 had AD, and 98 had VaD. The age- and sex-adjusted incidence of all-cause dementia, AD, and VaD significantly decreased as milk and dairy intake level increased (P for trend = .03 for all-cause dementia, .04 for AD, .01 for VaD). After adjusting for potential confounders, the linear relationship between milk and dairy intake and development of AD remained significant (P for trend = .03), whereas the relationships with all-cause dementia and VaD were not significant. The risk of AD was significantly lower in the second, third, and fourth quartiles of milk and dairy intake than in the first quartile.

CONCLUSION: Greater milk and dairy intake reduced the risk of dementia, especially AD, in the general Japanese population. **J Am Geriatr Soc 62:1224–1230, 2014.**

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The increasing prevalence of dementia worldwide is a major public health concern. According to the World Health Organization and Alzheimer's Disease International, the number of people living with dementia will double by 2030 and more than triple by 2050,[1] but the causes of dementia, especially Alzheimer's disease (AD), remain unclear, and there are no disease-modifying therapies. Thus, there is an urgent need to identify factors that can prevent development of dementia to decrease the burden of this disease. Diet is one of the factors that can be modified, and it may have a protective influence against dementia. Milk and dairy intake has been reported to decrease cerebrovascular risk factors, such as hypertension,[2] diabetes mellitus,[3] and obesity,[4] which are associated with the development of dementia,[5] but a limited number of epidemiological studies have assessed the relationship between milk and dairy intake and cognitive impairment or dementia.[6–12] To this end, a community-based prospective cohort study was established to evaluate risk factors for or protective factors against dementia in the Japanese population. A feature of this study is that the subtypes of dementia have been verified using detailed neurological and morphological examination, including neuroimaging and autopsy. The purpose of this study was to elucidate the relationship between milk and dairy intake and the development of dementia and its subtypes in an elderly Japanese population.

METHODS

Study Populations

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

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of the Fukuoka metropolitan area in the southern part of Japan.[13] This study was begun in 1961 to determine the prevalence and incidence of cerebro- and cardiovascular diseases and their risk factors in Japanese. Data from the national census and nutrition survey indicate that the age and occupational distributions and nutrient intake of the population of Hisayama are similar to those of Japan as a whole for each year from 1961 to the present.[14] Full community surveys of the health status and neurological condition of residents aged 40 and older have been repeated every 1 to 2 years since 1961. Comprehensive surveys of cognitive impairment have also been performed every 6 or 7 years in the elderly adults of the town since 1985.[15,16] In 1988, 1,228 residents aged 60 and older (participation rate 91.1%) underwent a screening examination for the present study. After excluding 35 subjects who already had dementia at baseline, 111 subjects whose dietary questionnaires were not available, and one subject with no blood sample, 1,081 subjects (457 men, 624 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed prospectively for 17 years, from December 1988 to November 2005, during which time health examinations were repeated every 1 to 2 years.[13] Letters or telephone calls were used to collect the health information of subjects who did not have examinations or who had moved out of town. A daily monitoring system was also established with the study team and local physicians or members of the town's Health and Welfare Office to collect information about new events, including stroke, cognitive impairment, and dementia. Follow-up screening surveys of cognitive function, including neuropsychological tests (the Hasegawa Dementia Scale,[17] the Hasegawa Dementia Scale—Revised,[18] or the Mini-Mental State Examination[19]), were conducted in 1992, 1998, and 2005. The study physician and psychiatrist carefully evaluated any subject suspected of having new neurological symptoms, including cognitive impairment, by conducting a comprehensive investigation including interviews of the family or attending physician, physical and neurological examinations, and a review of the clinical records. Furthermore, when a subject died, all the available clinical information was reviewed, the attending physician and family of the deceased were interviewed, and an attempt was made to obtain permission for an autopsy from the family. During follow-up, 518 subjects died, 387 (74.7%) of whom underwent 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 to define the diagnosis of dementia,[20] 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,[21] 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).[22] 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 neuropathological information in subjects with dementia who underwent autopsy. The diagnostic procedure for autopsy cases has been previously reported.[23] A neuropathological diagnosis of AD was made following the National Institute on Aging—Reagan Institute criteria;[24] the frequency of neuritic plaques and neurofibrillary tangles was evaluated using the Consortium to Establish a Registry for Alzheimer's Disease criteria[25] and Braak stage.[26] Definite VaD cases were confirmed with causative stroke or cerebrovascular change and no neuropathological evidence of other forms of dementia. Expert stroke physicians and psychiatrists adjudicated each case of dementia.

During the 17 years of follow-up, 303 subjects (103 men, 200 women) developed dementia; 261 (86.1%) were evaluated using brain imaging, 155 (51.2%) underwent autopsy, and both were performed in 143. Thus, 273 subjects (90.0%) had some kind of morphological examination. Of subjects with dementia cases, 25 with AD and 18 with VaD had other, coexisting subtypes of dementia, 14 of which were a mixed type of AD and VaD. These cases were counted as events in the analyses for each subtype. Finally, 166 subjects had AD (77 definite AD, 68 probable AD, 21 possible AD), and 98 had VaD (63 definite VaD, 35 probable VaD).

Nutritional Survey

The dietary survey was conducted using a 70-item semiquantitative food frequency questionnaire (SFFQ) concerning food intake.[27] Average food intake per day was calculated from the weekly frequency of various foods and the amount (quantity) of each food portion. The validity of this questionnaire has been reported previously.[28] Briefly, 65 subjects were randomly selected from 981 individuals aged 40 and older who underwent a health examination in 1987. Information regarding food intake was collected for 7 successive days using a weighted food record. Similarly, information regarding food intake was collected from the same subjects using the SFFQ. As a result, the 1-day average intake of milk and dairy products based on SFFQ was 84.6 g, and that based on the weighted food record was 103.9 g. The correlation coefficient in the amount of milk and dairy intake between the SFFQ and weighted food record was 0.53 ($P < .001$); this correlation was considered moderate.

The questionnaire was administered before initiation of this study; a trained dietician or nutritionist questioned each participant in the screening examination. Nutritional intake was calculated using the *Standard Tables of Food Composition in Japan, Fourth Revision*.[29] Each food group was adjusted for energy intake using the residual method.[30]

Risk Factor Measurements

At the baseline survey, each subject was asked to complete a self-administered questionnaire covering medical history, antidiabetes and antihypertensive treatments, educational status, smoking habits, alcohol consumption, and physical

activity. History of stroke was defined as a preexisting sudden onset of nonconvulsive and focal neurological deficit persisting for longer than 24 hours on the basis of all available clinical data. Low educational level was defined as less than 7 years of formal education. Smoking habits and alcohol consumption were categorized as current use or no current use. Regular exercise was defined as engaging in sports more than three times a week during leisure time. Blood pressure was measured three times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes rest. The mean of three measurements was used for the analysis. Hypertension was defined as blood pressure of 140/90 mmHg or greater or current use of antihypertensive drugs. Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. Diabetes mellitus was defined as fasting plasma glucose of 7.0 mmol/L or more, 2-hour postload glucose concentrations or postprandial glucose concentrations of 11.1 mmol/L or more, or current use of insulin or oral medication for diabetes mellitus. Serum total cholesterol levels were measured enzymatically.

Statistical Analysis

Subjects were grouped into quartiles based on amount of milk and dairy intake per day, according to sex. The quartiles for milk and dairy intake were less than 45, 45 to 96, 97 to 197, and 198 g/d or more for women and less than 20, 20 to 75, 76 to 173, and 174 g/d or more for men. The trends in the mean values of risk factors for the milk and dairy intake levels were tested using linear regression and the frequencies using logistic regression analysis. Participants were censored at date of death or end of follow-up for survival analyses. The incidence of dementia was calculated using a person-year method and adjusted for age and sex using the direct method using 10-year age groups of the overall study population. The age- and sex-adjusted or multivariable-adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. The assumption of proportional hazards was checked graphically using log cumulative hazard plots for outcomes according to milk and dairy intake levels. In the multivariable-adjusted model, 15 covariates known to be potential risk or protective factors for dementia were selected: age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking habits; regular exercise; and energy, vegetable, fruit, fish, and meat intake.[31] Heterogeneity in the relationship between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. Two-sided $P < .05$ was considered statistically significant in all analyses. SAS version 9.3 (SAS Institute, Inc., Cary, NC) 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 baseline characteristics of subjects according to milk and dairy intake levels are summarized in Table 1. Mean age and total cholesterol levels and frequencies of diabetes mellitus and regular exercise were higher with higher milk and dairy intake levels, whereas mean systolic blood pressure and frequencies of hypertension, smoking habits, and alcohol consumption were lower with higher milk and dairy intake levels. In relation to dietary factors, subjects in the fourth quartile of milk and dairy intake ate more fruit and had lower intake of fish and meat than those in the first quartile.

Figure 1 shows the age- and sex-adjusted incidence of all-cause dementia, AD, and VaD according to quartiles of milk and dairy intake levels. The age- and sex-adjusted incidence of all-cause dementia, AD, and VaD was significantly lower with higher milk and dairy intake levels (P for trend = .03 for all-cause dementia, = .04 for AD, and = .01 for VaD).

Table 2 shows the estimated HRs and 95% CIs for the development of dementia and its subtypes according to milk and dairy intake level. There was a significant inverse relationship between milk and dairy intake level and age- and sex-adjusted HR of all-cause dementia (P for trend = .03). This linear relationship did not remain significant after adjustment for age; sex; low education; diabetes mellitus; hypertension; total cholesterol; history of stroke; body mass index; smoking habits; regular exercise; and total energy, vegetable, fruit, fish, and meat intake (P for trend = .09), but the risk of all-cause dementia remained significantly lower in the third quartile than in the first quartile (adjusted HR = 0.69, 95% CI = 0.50–0.96).

With regard to dementia subtypes, multivariable-adjusted HRs of AD were significantly lower with higher milk and dairy intake, but no such relationship was observed for VaD (P for trend = .03 for AD; P for trend = .14 for VaD). The multivariable-adjusted HR of AD was significantly lower in subjects in the second, third, and fourth quartile of milk and dairy intake than in those in the first quartile (adjusted HR = 0.64, 95% CI = 0.41–0.99 for the second quartile; adjusted HR = 0.57, 95% CI = 0.37–0.87 for the third quartile; adjusted HR = 0.63, 95% CI = 0.41–0.98 for the fourth quartile). Although the age- and sex-adjusted HR of VaD was significantly lower in subjects in the fourth quartile of milk and dairy intake than in those in the first quartile, this relationship was not significant after multivariable adjustment (adjusted HR = 0.69, 95% CI = 0.37–1.29 for the fourth quartile). There was no evidence of heterogeneity between men and women in the risk of dementia and its subtypes.

DISCUSSION

This long-term prospective study of an elderly Japanese population demonstrated a significant inverse relationship between milk and dairy intake and risk of development of all-cause dementia, AD, and probably VaD. This is, to the best of the authors' knowledge, the first prospective cohort study to investigate the protective relationship between milk and dairy intake and risk of dementia and its subtypes.

Table 1. Baseline Characteristics of Subjects According to Quartile of Milk and Dairy Consumption: The Hisayama Study, 1988

Characteristic	Q1 (Low), n = 270	Q2, n = 270	Q3, n = 271	Q4 (High), n = 270	*P* for Trend
Female, %	57.8	57.8	57.6	57.8	.99
Age, mean ± SD	68.6 ± 6.4	69.8 ± 6.4	68.9 ± 6.1	70.4 ± 6.8	.008
Education ≤6 years, %	12.0	16.8	11.2	12.0	.56
History of stroke, %	4.1	4.4	4.4	4.4	.84
Systolic blood pressure, mmHg, mean ± SD	142 ± 24	138 ± 23	139 ± 21	137 ± 21	.02
Diastolic blood pressure, mmHg, mean ± SD	77 ± 11	76 ± 11	77 ± 10	75 ± 10	.10
Hypertension, %	57.8	53.7	53.5	48.5	.04
Diabetes mellitus, %	11.5	13.7	14.4	20.0	.007
Total cholesterol, mg/dL, mean ± SD	200 ± 42	204 ± 45	213 ± 43	220 ± 43	<.001
Body mass index, kg/m^2, mean ± SD	22.3 ± 3.1	22.1 ± 3.2	22.5 ± 3.2	22.4 ± 2.7	.40
Smoking habits, %	27.4	23.7	22.9	19.3	.03
Alcohol consumption, %	30.0	26.7	27.7	20.4	.02
Regular exercise, %	13.7	10.0	13.7	21.5	.005
Dietary intake, mean ± SD					
Energy, kcal/d[a]	1,703 ± 402	1,509 ± 395	1,721 ± 400	1,605 ± 372	.44
Vegetable, g/d[a]	251 ± 118	242 ± 102	257 ± 124	256 ± 128	.30
Fruit, g/d[a]	69 ± 69	74 ± 69	91 ± 93	84 ± 64	.002
Fish, g/d[a]	43 ± 43	41 ± 28	36 ± 28	37 ± 22	.006
Meat, g/d[a]	22 ± 24	20 ± 14	19 ± 15	19 ± 15	.03

Quartiles for milk and dairy intake were <45, 45–96, 97–197, ≥198 g/d for women and <20, 20–75, 76–173, ≥174 g/d for men.
SD = standard deviation.
[a]All food groups were adjusted for energy intake using the residual method.

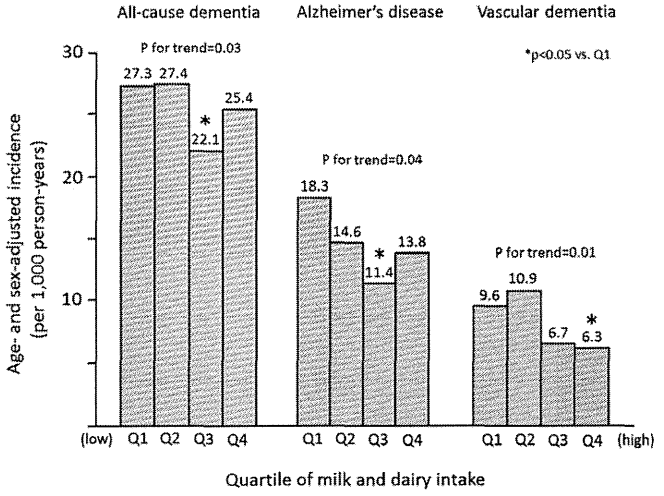

Figure 1. Age- and sex-adjusted incidence of all-cause dementia, Alzheimer's disease, and vascular dementia according to quartile of milk and dairy intake at baseline, 1988–2005.

Several epidemiological studies have investigated the relationship between milk and dairy intake and cognitive impairment or dementia.[6–12] Some cross-sectional studies have evaluated this relationship and found that higher milk and dairy intake is likely to have a protective effect against cognitive impairment.[6–8] A study in Australia demonstrated that low-fat milk and dairy consumption was associated with significantly lower likelihood of poor cognitive function but found the opposite to be true for whole-fat cream and ice cream rich in fat.[9] Similarly, a few prospective studies conducted in Western countries have reported that higher consumption of full-cream milk, milk and dairy desserts, and ice cream increased the risk of cognitive decline.[10,11] These results suggest that low-fat milk and dairy intake might have a more-favorable influence on cognitive function, especially in Western populations, although only one study has evaluated the relationship between milk intake and the risk of dementia longitudinally; the Adult Health Study with atomic bomb survivors in Japan retrospectively evaluated the relationship between milk intake, assessed 25 to 30 years earlier, and the prevalence of AD and VaD. The study concluded that subjects who consumed milk every day had significantly lower prevalence of VaD, but not of AD, than those who consumed milk twice a week or less.[12] This finding is inconsistent with that of the current study, but because the current study and the Adult Health Study had different designs (prospective vs retrospective), the heterogeneity of the methods may explain the discrepancy.

A few cohort studies in Western countries have found that it is possible that the Mediterranean dietary pattern provides protection against dementia, especially AD.[32,33] This diet recommends low to moderate consumption of milk and dairy products. Again, this is a finding that is inconsistent with that of the present study, although in a previous study of the present cohort, the greater adherence to the dietary pattern derived using a reduced rank regression analysis, which was characterized by high intake of milk and dairy products, was associated with a lower risk of dementia.[34] According to data from the Food and Agriculture Organization of the United Nations, there has consistently been a clear difference in the amount of milk and

Table 2. Likelihood of Development of All-Cause Dementia, Alzheimer's Disease, and Vascular Dementia According to Quartile of Milk and Dairy Consumption, 1988–2005

Outcome	Q1 (Low), n = 270	Q2, n = 270	Q3, n = 271	Q4 (High), n = 270	*P* for Trend
All-cause dementia					
Events, n	82	77	67	77	
HR (95% CI)[a]	1.0	0.90 (0.66–1.22)	0.66 (0.48–0.91)	0.76 (0.56–1.04)	.03
HR (95% CI)[b]	1.0	0.85 (0.62–1.18)	0.69 (0.50–0.96)	0.80 (0.57–1.11)	.09
Alzheimer's disease					
Events, n	49	38	37	42	
HR (95% CI)[a]	1.0	0.72 (0.47–1.10)	0.58 (0.38–0.89)	0.68 (0.45–1.03)	.04
HR (95% CI)[b]	1.0	0.64 (0.41–0.99)	0.57 (0.37–0.87)	0.63 (0.41–0.98)	.03
Vascular dementia					
Events, n	28	30	21	19	
HR (95% CI)[a]	1.0	1.04 (0.62–1.74)	0.65 (0.37–1.15)	0.54 (0.30–0.98)	.01
HR (95% CI)[b]	1.0	1.02 (0.59–1.77)	0.74 (0.42–1.33)	0.69 (0.37–1.29)	.14

HR = hazard ratio; CI = confidence interval.

[a]Adjusted for age and sex.

[b]Adjusted for age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking habits; regular exercise; and energy, vegetable, fruit, fish, and meat intake.

dairy consumption in Japan and Western countries; consumption in the Japanese population is historically approximately half that of Western populations.[35] This evidence, together with the findings of the present study, suggest that the difference in the amount of milk and dairy consumed in Japan and in Western countries could be the reason for the discrepancy in the influence of these foods on the risk of dementia between the populations. In populations with low intake of milk and dairy, such as the Japanese, a "high" intake of these foods is considered to reduce the risk of dementia. Further investigation is needed to clarify this in other ethnic populations.

In the present study, the age- and sex-adjusted HR of VaD was significantly lower in subjects in the fourth quartile of milk and dairy intake than in the first quartile, but this relationship was attenuated after adjustment for other covariates. This finding may have been due to the small number of VaD cases. In addition, because the frequencies of other known cerebrovascular risk factors, such as hypertension and smoking habits, were low in the fourth quartile of milk and dairy intake (Table 1), the risk of VaD may have appeared to decrease in this quartile through mediation of these risk factors.

There are presumably mechanisms for the protective influence of dairy intake against the risk of dementia. In several prospective studies, higher intake of milk and dairy was associated with lower risk of developing stroke and its risk factors, such as hypertension,[2] diabetes mellitus,[3] and obesity,[4] and these same factors were also recognized as risk factors for dementia.[5] Therefore, it is possible that milk and dairy intake decreases the risk of dementia, especially VaD, through mediating these risk factors. Another possible mechanism could be the benefits from some of the nutritional components of milk and dairy. It was previously reported that calcium and magnesium, which are components of milk and dairy, reduced the risk of development of dementia.[36] Milk and dairy consumption is also an important source of vitamin B_{12}, which is known to reduce plasma homocysteine levels. Because low serum vitamin B_{12} levels and high plasma homocysteine levels are reported risk factors for the development of dementia, especially AD,[37,38] milk and dairy consumption could decrease risk because of the influence of these nutrients.[39] Whey protein, another component of milk and dairy products, may also have favorable influence against dementia by reducing fat and improving insulin resistance.[40,41]

The strengths of the current study include its longitudinal, population-based, prospective design; the long follow-up period; perfect follow-up of subjects; and the ability to perform a morphological examination of the brains of most dementia cases using autopsy and neuroimaging, although some potential limitations 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 are likely to have introduced some misclassification of food intake, and such misclassifications would weaken the relationship found in the study, biasing the results toward the null hypothesis. Finally, because dairy products are not part of traditional Japanese diets and represent a degree of westernization of lifestyle, the possibility of bias introduced by unmeasurable confounding factors cannot be eliminated.

In conclusion, these findings emphasize the need to consider higher intake of milk and dairy as a potentially protective factor against all-cause dementia, AD, and probably VaD in an elderly Japanese population. Further research will be necessary to clarify the relationship between milk and dairy intake and the risk of developing all-cause dementia and its subtypes in other prospective cohort studies and intervention trials.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by