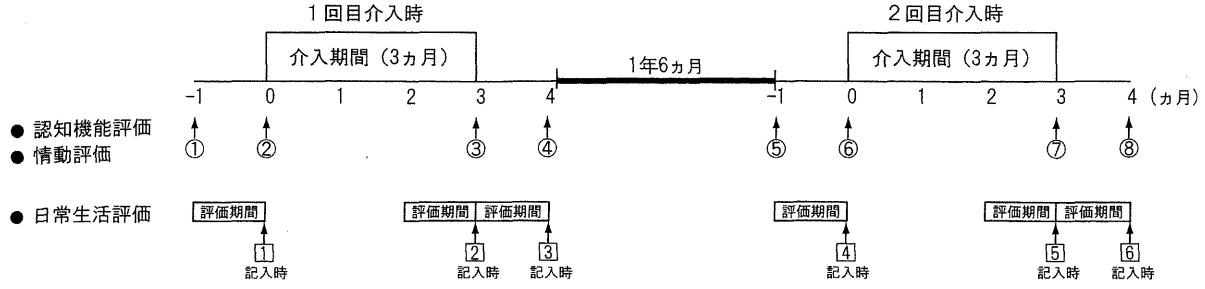

図2　各評価の評価時点

介入開始時を0ヵ月とした．認知機能評価と情動機能評価は①～⑧の時点に実施した．日常生活評価は，記入時の前1ヵ月間の評価期間の様子を評価し，1～6の記入時に評価用紙に記載した．

り，その際は再び100円単位の暗算に戻るなど遂行状況に応じて難易度を調節した．選択項目については，はじめは食べ物と花に関連したものから始まり，症例の関心の拡大に伴い，寿司編，魚編，スイーツ編なども実施した．例えば「花束の花を選ぶ」という目的で，「さくらは花束にはおかしいね．長持ちする花にしよう」とアイディアを出しながら適切な選択をする様子や「見舞いに持っていく果物」という目的では，「りんごが良いね．私は昔付き添い婦をしていたんだよ」と課題がきっかけで昔話をする姿が見られた．介入期間中盤に「今までは朝起きて今は朝か夕方かわからないときがあったが，最近頭がはっきりしてきた」と自らOTRに話した．

2. 認知機能に対する効果

結果を表1Aに示した．介入開始の1ヵ月前（初期評価）と介入開始直前の評価では，語想起（動物）の項目以外に顕著な差は見られず，介入開始前の認知機能は安定していた．

介入終了時は介入開始直前の評価に比べて，数唱（逆唱）を除いて全ての項目で得点の上昇，遂行時間の短縮が見られた．MMSEでは，見当識（6→9/10点）と遅延再生（0→1/3点）に得点上昇を認めた．また，三宅式の無関係対語や図形記憶に得点上昇を認めた．一方，FABの抑制コントロール（1→3/3点），語想起（1→2/3点），運動プログラミング（1→3/3点）で得点上昇を認めたが，順唱，逆唱に大きな変化を認めなかった．介入終了時の感想では，「数字だけ合わせるのではなく，中身を吟味するようになった．部屋でも考えることがあった」，「ぴんときやすくなった．介護さん（介護者）に言われることも答えるのが早くなった．前なら言いたいと思ってから言葉がなかなか出てこなかった」，「変化が自分でもわかる」と述べた．介入期間が終了して1ヵ月経過した時点での評価では，TMT-Aを除く全ての項目に得点の低下を認めたが，多くの項目で介入開始直前のレベルまでの低下とはならなかった．

3. 情動面に対する効果

結果を表1Bに示した．介入開始の1ヵ月前と介入開始直前の評価に差は見られず，介入開始前の情動機能に変動は少なかった．介入終了時は介入開始直前の評価に比べて，PGC得点の上昇，GDS得点の低下を認めた．介入終了時の感想では，「これをやるようになって他人の言動に腹が立たなくなった，おおらかになった気がする」と述べた．

4. 日常生活面に対する効果

結果を表1Cに示した．介入終了時の評価では，介入開始直前の評価と比べてN-ADLに著変はなかったが，NMスケールの記憶（7→9/10点），見当識（9→10/10点），会話（9→10/10点）の項目で得点上昇を認めた．介入終了時の感想では，「今まではみんな（介

表2 2回目介入時の認知機能・情動・日常生活評価

A. 認知機能					
		⑤介入開始の1ヵ月前（初期評価）	⑥介入開始直前	⑦介入終了時	⑧介入終了時から1ヵ月後
MMSE（点）		20	23	25	23
FAB（点）		11	12	15	13
語想起	語頭「か」（個）	2	3	4	5
	動物名（個）	7	9	8	7
数唱	順唱（点）	5	5	6	6
	逆唱（点）	5	5	5	5
TMT-A（秒）		116	62	69	97
三宅式	有対語（個）	9	10	10	10
	無対語（個）	4	1	4	3
図形記憶	即時再生（点）	3	2	7	6
	5分後再生（点）	0	0	7	0
B. 情動					
		⑤介入開始の1ヵ月前（初期評価）	⑥介入開始直前	⑦介入終了時	⑧介入終了時から1ヵ月後
GDS		5	4	3	4
PGC		13	14	15	12
C. 日常生活					
			④介入開始直前（初期評価）	⑤介入終了時	⑥介入終了時から1ヵ月後
N-ADL			37.5	40.5	40.5
NMスケール			43.0	44.5	44.5
CDR			0.5	0.25	0.25

＊表の構成は表1に準じる．⑤～⑧，④～⑥は図2の評価時点に相当する．

護者）が忙しいので黙っていることが多い生活だったが，これをやることで生活が変化した」と述べた．介護者からは「本人から（本取り組みが）とても楽しみだと聞いている．同じ質問，会話の繰り返しが減った．施設内で行われている歩行訓練や，華道，書道などの活動に表情良く参加することが増えた」と情報があった．

介入終了時から1ヵ月後の評価では，NMスケールの関心（10→7/10点），見当識（10→9/10点），会話（10→9/10点）の項目で得点の低下を認めた．その時点で症例に近況を尋ねると「イライラが最近戻ってきた，腹が立つ，人間関係でさみしい」と周囲や介護者に対する苦情を切々と述べた．

5. 2回目介入実施の効果

2回目介入開始の1ヵ月前に面談を実施したところ「最近はぼけたなと思う，ナースコールを押したあとになんだっけと思う」と話した．

介入期間では，目的の想起率がほぼ100%であったが，予算の想起は60～80%であったことから，遅延期間は3秒のままとした．暗算は50円単位でも80～100%の正解率となり1回目介入時よりも向上した．予算が余ると「これを追加するともっと良いね」とアイディアを出しながら楽しそうに行っていた．介入期間の中盤には，「やっぱりこれは良いですよ」，「お陰でぴんぴんと頭が早くまわる．（頭を）使わないとダメだよね」と話す．

認知機能・情動・日常生活の評価結果を表2に示した．介入終了時は介入開始直前の評価に

比べて，認知機能評価に関して，MMSEでは見当識（6→9/10点）と遅延再生（1→2/3点），FABでは抑制コントロール（0→3/3点）に得点上昇を認めた．「か」で始まる言葉の語想起では若干の上昇，図形記憶に上昇を認めた．これらの項目は，いずれも1回目介入時に得点上昇を認めた項目であり，得点上昇の程度には差があるものの再現性を認めた．情動面では，GDSとPGCにて若干の改善を認めたが，1回目のような顕著な変化を示さなかった．日常生活機能では，介入終了時，N-ADLの排泄（8→9.5/10点）の項目に得点上昇を認めた．NMスケールでは，関心（6→7/10点）と記憶（9→9.5/10点）の項目に得点上昇を認めた．記憶は1回目介入時にも得点上昇を認めた項目であり再現性を認めた．介入終了時の感想では，「物忘れがひどかったが，良くなっている気がする」，「相手の言うことや気持ちも感じられるようになった．そうするとこちらの意見も聞いてもらえる」，「これをやるとカンが働きやすくなる」，「人との関係でおかしいことを思わなくなった」と話した．

考　察

1. G-DR課題の認知機能に対する効果

本研究よりG-DR課題を用いた訓練を軽度認知症患者に実施することで，介入終了時に語の流暢性，抑制コントロール，図形記憶，三宅式の無関係対語の記憶に向上を認めた．日常生活面での記憶，見当識，会話にも改善が得られた．さらに，症例自身からも認知・記憶機能の改善を示唆する感想を得た．ただ今回は，同一評価を複数回実施したため，反復効果による点数の上昇が考えられた．しかし，介入終了時から1ヵ月経過した時点での再評価では，多くの得点が下降していたことに加え，1年6ヵ月後に再介入を実施したところ，認知機能，日常生活評価のほぼ同様の項目で得点の再上昇を認めた．これらのことからG-DR課題を用いた訓練が認知機能や日常生活面の改善に寄与した可能性が高いと考えられる．近年，コンピューターを利用したリハビリテーション機器が積極的に開発されている．Klingbergら[21]，Westerbergら[22]は視空間性ワーキングメモリ課題を用いたトレーニングを開発し，ADHDや脳卒中後の記憶容量の増加に有意な効果があったことを報告している．またCiprianiら[23]は，注意・記憶・言語をトレーニングするneuropsychological training（NPT）を用いてアルツハイマー型認知症患者や軽度認知症患者に介入し，認知機能の改善が得られたことを報告している．これらの研究と比較して，今回用いた課題は実生活に密着した目的志向的内容を取り入れ，単なる記憶訓練ではなく患者自身の過去の記憶や経験を活かせる内容とした．また，文字だけではなく実際の写真を示しながら臨場感ある中で実施した．実際に症例が「こうしたらもっと良い」と目的と予算の範囲内で様々な工夫をしながら必要な項目を選択する様子や，特定の項目の選択をきっかけに昔話をすることがあった．さらに，目的や予算を忘れないで覚えておこうと集中力を高めて取り組んでいる様子が見られた．示された課題を記憶し，自身の記憶や経験を引き出しながら，課題の実現のために選択を行うという行為の継続が，注意・集中の向上に繋がり，抑制コントロールや記憶機能の改善に寄与したと考えられる．また，本課題は，要求する正解を一つとは限らず，患者の工夫やアイディアにより様々な正解を生み出すことができる．症例は「数字だけあわせるのではなく，中身を吟味するようになった．部屋でも考えることがあった」と話し，回を重ねるごとに選択肢をよく検討し様々なアイディアを出しながら選択するようになっていった．こうした過程が，思考の柔軟性を引き出し，語の流暢性の向上に寄与したと考えられる．

本課題の基盤は遅延反応課題でありワーキングメモリに関連した機能の改善を意図したが，逆唱やMMSEの計算問題などに顕著な変化は見出されなかった．本課題のワーキングメモリ機構への寄与については今後更なる検討が必要と考えられる．

2. G-DR課題の情動機能に対する効果

今回はGDSとPGCの得点の改善に加え，症例の感想からも訓練が進むにつれて腹立たしさなどの感情が減少している様子を認めた．前頭連合野は認知機能だけではなく，情動にも深く関与している[24]．一般に前頭連合野の外側部は認知機能に，内側部や眼窩部は情動に関わっていることが知られている．認知機能に関連する外側部と情動に関連する内側部や眼窩部領域は，相互に密接な神経線維連絡を持っており[25]，認知過程での情報処理により情動が影響される可能性や，逆に情動の変化により認知機能が影響されることが知られている[24]．本訓練は，この特徴を基盤に，症例の興味・関心のある内容を積極的に取り入れた．また，抑うつ傾向のあるアルツハイマー型認知症では結果を紙面などで具体的に示し前向きに評価することが有効なため[26]，個々の試行ごとに選択項目を振り返り，成功の強化やもうひと工夫したら良い点の確認を行った．症例は予算の把握が困難なことを次第に認識し，選択時に予算に気を配るようになった．なお，本訓練は，症例にとって適度な難易度になるよう課題を調節した．Klingbergら[21]も，視空間性ワーキングメモリ課題を用いたトレーニングの際，難易度を症例に合わせて調節したことが効果的であったと報告している．本訓練も，コンピューターを用いることで柔軟かつ簡易に個人の遂行能力や興味・関心に合わせて課題を抽出することができる環境を整え，症例の興味・関心を捉えながら，適度な負荷となるよう課題を適宜調整し，OTRと1対1の環境でじっくり進める枠組みとした．このことが症例の楽しさや達成感など情動面の変化を喚起し，認知機能を発揮しやすい状況を生み出したと考えられる．これは症例の「これをやるようになって他人の言動に腹が立たなくなった，おおらかになった気がする」という発言からも支持される．

一方，変化の少ない施設生活に，新たなOTRが新たな訓練を導入したことが症例の情動の変化に影響した可能性も考えられる．本訓練特有の反応ではなく，新規介入に対する反応であったことも否定できず，今後は本訓練の要素を取り入れないが何らかの新規介入を行うコントロール期間を設定し，本訓練の情動への効果を再検証する必要がある．

研究の限界

本研究はベースラインの安定を確認したうえで介入を行ったことに加え，2回目介入を行うなど効果の再現性を確認するよう努めた．しかし，遂行機能やワーキングメモリの要素を取り入れた本課題が前頭連合野の機能向上に直接寄与したのかについて言及するには，前頭連合野機能にアプローチしないコントロール課題を設定し，本課題と比較する必要があったと言える．今後は，このようなコントロール課題の設定を行い大規模な検証を行いたいと考えている．

結　　語

ワーキングメモリ，目的志向的行動制御など前頭連合野の基礎研究の成果を基盤にしたリハビリテーション訓練を開発した．認知症患者に試行した結果，注意集中の向上，思考の柔軟性，うつ傾向の改善に繋がる可能性が示唆された．本訓練の特徴である症例に合わせて難易度や内容をコンピューターで柔軟かつ簡易にテーラーメイドできる点や，単なる記憶訓練ではなく過去の記憶やアイディアを刺激する内容としている点が，認知と情動の両側面を刺激し，機能改善に寄与したと考えられる．

謝辞：本稿を終えるにあたり元札幌医科大学教授村上新治先生に深謝致します．本訓練のシステム構築に多大な御尽力，御配慮を頂きました吉田章彦氏に深謝致します．データ収集にご協力頂きました老人福祉施設看護介護課，機能訓練課の皆様に深謝いたします．様々なご助言ご指導頂きました札幌医科大学医学部医科知的財産管理学教室教授石埜正穂先生に深謝します．本研究は科研費（17700449，19700440；研究代表者：竹田里江），シーズ発掘試験発掘型（研究代表者：竹田里江）の助成を受けて実施した．

文　献

1) 山内俊雄・編：精神疾患と認知機能．新興医学出版社，東京，2009.
2) 博野信次：痴呆のリハとケアのあり方．高次脳研究 23：206-214，2003.
3) Clare L. Wilson BA. Carter G. Breen K. Gosses A. et al: Intervening with everyday memory problems in Dementia of Alzheimer Type: An errorless learning approach. J Clin Exp Neuropsychol 22: 132-146, 2000.
4) 竹田里江，村上新治：啓蒙活動，検診，作業療法を統合した認知症早期発見・援助事業とその効果．作業療法 27：275-282，2008.
5) 飯干紀代子，浜田博文，白浜育子，相星さゆり，猪鹿倉武：アルツハイマー型痴呆患者に対する記憶訓練―日常生活上の問題点に即したアプローチ―．失語症研究 22：65-71，2002.
6) 頼田綾子，小森憲治郎，池田　学，繁信和恵，田辺敬貴：初老期に発症したアルツハイマー病に対するリハビリテーションの試み．認知リハビリテーション 2003，認知リハビリテーション研究会，新宿，2003，pp.139-145.
7) 船橋新太郎：前頭葉の謎を解く．京都大学出版会，京都，2005.
8) 一原里江，船橋新太郎：作業記憶の脳内機構．Clinical Neuroscience 21：804-806，2003.
9) Funahashi S. Bruce CJ. Goldman-Rakic PS: Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J Neurophysiol 61: 331-349, 1989.
10) Ichihara-Takeda S. Funahashi S: Activity of primate orbitofrontal and dorsolateral prefrontal neurons: Task-related activity during an oculomotor delayed-response task. Exp Brain Res 181: 409-425, 2007.
11) Mushiake H. Saito N. Sakamoto K. Itoyama Y. Tanji J: Activity in the lateral prefrontal cortex reflects multiple steps of future events in action plans. Neuron 50: 631-641, 2006.
12) D'Esposito M. Aguirre GK. Zarahn E. Ballard D. Shin RK. et al: Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res 7: 1-13, 1998.
13) Watanabe M: Reward expectancy in primate prefrontal neurons. Nature 382: 629-632, 1996.
14) Ichihara-Takeda S. Funahashi S: Reward-period activity in primate dorsolateral prefrontal and orbitofrontal neurons is affected by reward schedules. J Cogn Neurosci 18: 212-226, 2006.
15) Ichihara-Takeda S. Funahashi S: Activity of primate orbitofrontal and dorsolateral prefrontal neurons: Effect of reward schedule on task-related activity. J Cogn Neurosci 20: 563-579, 2008.
16) Callicott JH. Mattay VS. Bertolino A. Finn K. Coppola R. et al: Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex 9: 20-26, 1999.
17) 石合純夫：高次脳機能障害学．医歯薬出版，東京，2003.
18) Wechsler D（杉下守弘・訳）：日本版ウエクスラー記憶検査法（WMS-R）．日本文化科学社，東京，2001.
19) 今村陽子：臨床高次脳機能評価マニュアル．新興医学出版社，東京，2000.
20) 矢冨直美：日本老人における老人用うつスケール（GDS）短縮版の因子構造と項目特性の検討．老年社会科学 16：29-36，1994.
21) Klingberg T. Fernell E. Olesen P. Johnson M. Gustafsson P. et al: Computerized training of working memory in children with ADHD-A randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 44: 177-186, 2005.
22) Westerberg H. Jacobaeus H. Hirvikoski T. Clevberger P. Ostensson ML. et al: Computerized working memory training after stroke—A pilot study. Brain Injury 21: 21-29, 2007.
23) Cipriani G. Bianchetti A. Trabucchi M: Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on pa-

tients affected by mild cognitive impairment. Arch Gerontol Geriatr 43: 327-335, 2006.
24) 船橋新太郎，竹田里江：前頭葉・視床背側核系と情動行動．神経研究の進歩 50：89-97, 2006.
25) Cavada C. Company T. Tejedor J. Cruz-Rizzolo RJ. Reinoso-Suarez F: The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10: 220-242, 2000.
26) 竹田里江，村上新治，土岐めぐみ，石合純夫：漢字の読みに障害を呈したアルツハイマー型認知症者に対する領域特異的訓練の効果―前頭葉腹内側部に血流低下を示した症例に対する介入―．作業療法 28：69-79, 2009.

Effects of cognitive rehabilitation using computers on a dementia patient: Development and trial of a tailor-made training program based on prefrontal function

By

Satoe Ichihara-Takeda[*1,*2] Kazuyoshi Takeda[*3] Nozomu Ikeda[*1]
Kiyoji Matsuyama[*1] Sumio Ishiai[*2] Shintaro Funahashi[*4]

From

[*1] Department of Occupational Therapy, School of Health Sciences, Sapporo Medical University
[*2] Department of Rehabilitation, School of Medicine, Sapporo Medical University
[*3] Department of Psychiatry, National Center Hospital, National Center of Neurology and Psychiatry
[*4] Kokoro Research Center, Kyoto University

We developed a cognitive rehabilitation program based on the prefrontal cortex functions such as the working memory, planning and decision making. The program is adjustable according to each individual's interest and capability. The present study attempted to clarify the effect of this cognitive rehabilitation program by introducing appropriate tasks to a dementia patient. The results showed improvement in verbal fluency, inhibition control and verbal and spatial memory functions. In addition, the daily activities and emotional functions also improved. The contents of this training simulated our daily life activities for our past memories and ideas. The degree of difficulty is adjustable according to individual interest and capability. These results indicate that these characteristics contributed to the improvements of the patient's cognitive and emotional functions.

Key words: Dementia, Prefrontal cortex, Rehabilitation, Computer, Tailor-made

J Epidemiol 2012;22(3):222-229
doi:10.2188/jea.JE20110083

Original Article

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

Daigo Yoshida[1], Toshiharu Ninomiya[1,2], Yasufumi Doi[1,2], Jun Hata[1,2], Masayo Fukuhara[1,2], Fumie Ikeda[1,2], Naoko Mukai[1,2], and Yutaka Kiyohara[1]

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Received August 15, 2011; accepted November 28, 2011; released online February 18, 2012

ABSTRACT

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

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

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

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

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

INTRODUCTION

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

METHODS

Study population

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

Address for correspondence. Toshiharu Ninomiya, MD, PhD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan (e-mail: nino@envmed.med.kyushu-u.ac.jp).

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

Ethical considerations

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

Questionnaire

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

Definition of functional disability

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

Cause of disability

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

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

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

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

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

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

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

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

Statistical analysis

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

RESULTS

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

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

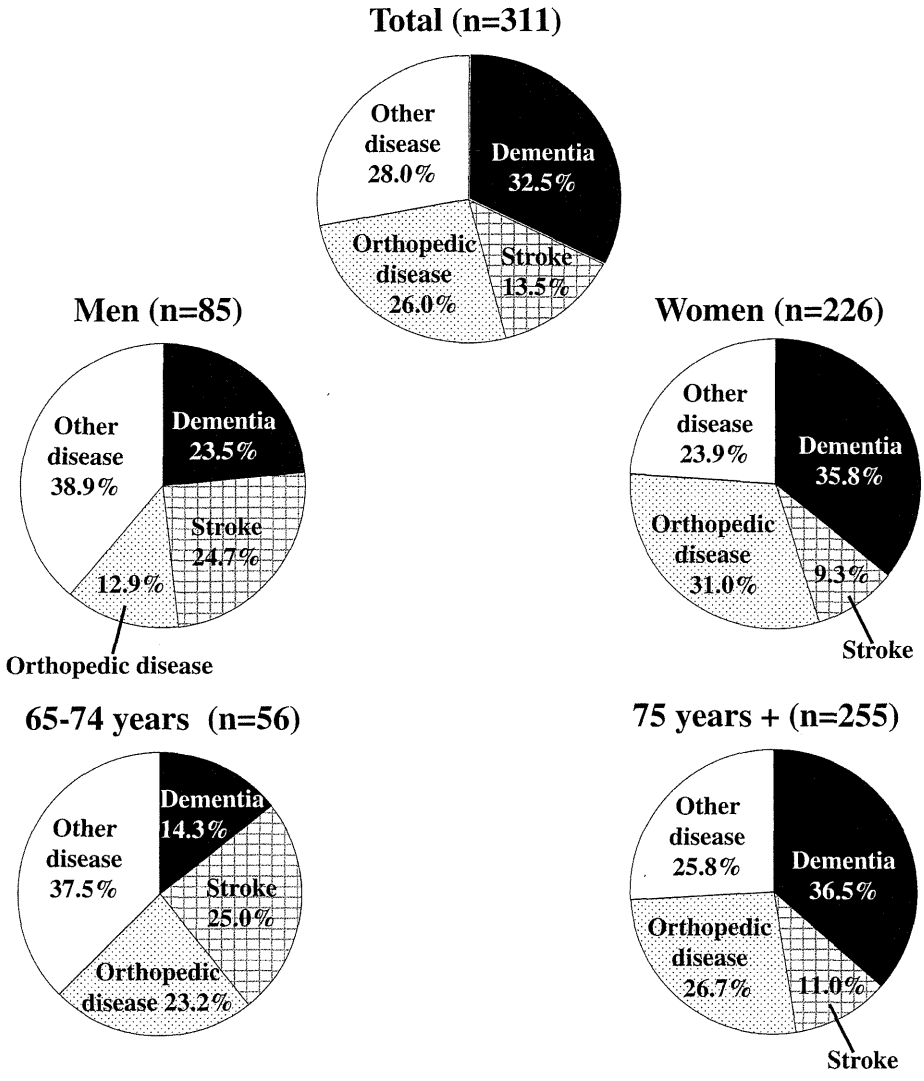

Figure 1. Causes of functional disability by sex and age (Hisayama Study, 2005).

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

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

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

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

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

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

[a]P value for comparison between sexes.

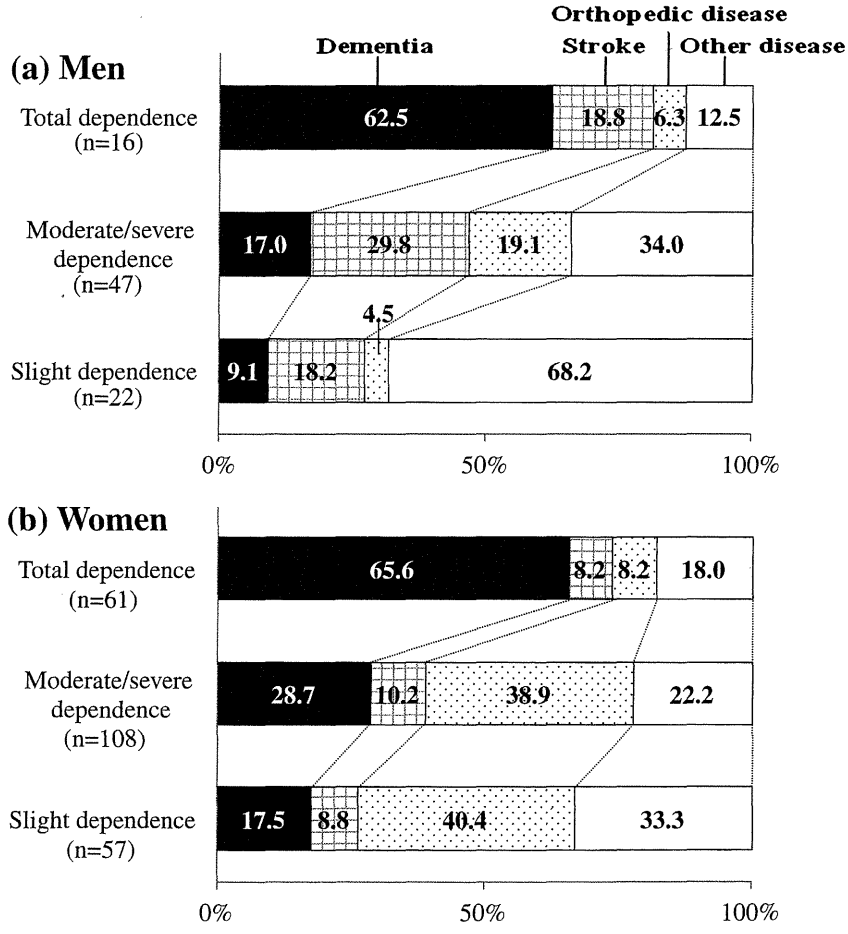

Figure 2. Causes of functional disability by severity of disability in men and women (Hisayama Study, 2005). Total dependence: Berthel Index score = 0–20. Moderate/severe dependence: Berthel Index score = 25–90. Slight dependence: Berthel Index score = 95.

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

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

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

DISCUSSION

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

Prevalence of disability

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

Sex differences in disability

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

Cause of disability

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

Place of residence and severity of disability

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

these subjects had dementia and were bedridden. The increase in patients hospitalized or staying in health care facilities is a major social and economic burden in Japan. Therefore, it is imperative to establish effective strategies for preventing the development of dementia and subsequent deterioration of ADL.

Study strengths and limitations

The strength of our study is that selection bias was minimized by including more than 90% of all Hisayama residents aged 65 years or older and by examining subjects staying in hospitals and health care facilities. In addition, cardiovascular events and dementia were evaluated using not only questionnaires but also detailed clinical information, as these parameters are main endpoints of the ongoing Hisayama Study.[15,23] A limitation is that this was a cross-sectional study. Consequently, causal relationships cannot be inferred between underlying diseases and functional disability.

Conclusion

Our study revealed that functional disability is common among Japanese elderly adults and that dementia is the most frequent cause of disability, especially in persons with total dependence. Stroke is a major cause of disability in men and in individuals aged 65 to 74 years (the young old). In countries such as Japan, where the elderly population is increasing rapidly, it is important to establish effective prevention strategies for dementia and stroke to reduce the risk of disability and extend healthy life expectancy in later life.

ACKNOWLEDGMENTS

This study was supported in part by Grants-in-Aid for Scientific Research (Nos. 20591063, 21590698, 22590892, 23590797, and 23590798) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare of Japan (Comprehensive Research on Aging and Health: H20-Chouju-004; Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H22-Junkankitou [Seishuu]-Ippan-005 and H23-Junkankitou [Seishuu]-Ippan-005). The authors thank the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

Conflicts of interest: None declared.

REFERENCES

1. The Statistics Bureau, Director-General for Policy Planning (Statistical Standards) & Statistical Research and Training Institute. Population Estimates. Available from: http://www.stat.go.jp/english/data/jinsui/tsuki/index.htm.
2. Fried LP, Guralnik JM. Disability in older adults: evidence regarding significance, etiology, and risk. J Am Geriatr Soc. 1997;45:92–100.
3. Mathers CD, Sadana R, Salomon JA, Murray CJ, Lopez AD. Healthy life expectancy in 191 countries, 1999. Lancet. 2001; 357:1685–91.
4. Rose AM, Hennis AJ, Hambleton IR. Sex and the city: differences in disease- and disability-free life years, and active community participation of elderly men and women in 7 cities in Latin America and the Caribbean. BMC Public Health. 2008;8:127.
5. Melzer D, McWilliams B, Brayne C, Johnson T, Bond J. Profile of disability in elderly people: estimates from a longitudinal population study. BMJ. 1999;318:1108–11.
6. Ng TP, Niti M, Chiam PC, Kua EH. Prevalence and correlates of functional disability in multiethnic elderly Singaporeans. J Am Geriatr Soc. 2006;54:21–9.
7. Millán-Calenti JC, Tubío J, Pita-Fernández S, González-Abraldes I, Lorenzo T, Fernández-Arruty T, et al. Prevalence of functional disability in activities of daily living (ADL), instrumental activities of daily living (IADL) and associated factors, as predictors of morbidity and mortality. Arch Gerontol Geriatr. 2010;50:306–10.
8. Jang SN, Kim DH. Trends in the health status of older Koreans. J Am Geriatr Soc. 2010;58:592–8.
9. Tang Z, Wang HX, Meng C, Wu XG, Ericsson K, Winblad B, et al. The prevalence of functional disability in activities of daily living and instrumental activities of daily living among elderly Beijing Chinese. Arch Gerontol Geriatr. 1999;29:115–25.
10. Koyano W, Shibata H, Haga H, Suyama Y. Prevalence and outcome of low ADL and incontinence among the elderly: five years follow-up in a Japanese urban community. Arch Gerontol Geriatr. 1986;5:197–206.
11. Shimada K, Ozawa T, Matsubayashi K. Dependency of the aged in the community. Lancet. 1993;342:1241.
12. Hayakawa T, Okayama A, Ueshima H, Kita Y, Choudhury SR, Tamaki J. Prevalence of impaired activities of daily living and the impact of stroke and lower limb fracture in elderly persons in Japan. CVD Prevention. 2000;3:187–94.
13. Okochi J. Increase of mild disability in Japanese elders: a seven year follow-up cohort study. BMC Public Health. 2005;5:55.
14. Ministry of Health, Labour and Welfare. Comprehensive Survey of Living Conditions: Percentage distribution of major causes due to need of assistance or care by sex, 2007. Available from: http://www.mhlw.go.jp/english/database/db-hss/cslc-tables.html.
15. Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, Kiyohara Y. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation. 2008;118: 2672–8.
16. Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, 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.
17. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42:703–9.
18. Katoh S, Simogaki H, Onodera A, Ueda H, Oikawa K, Ikeda K, et al. Development of the revised version of Hasegawa's

dementia scale (HDS-R). Jpn J Geriatr Psychiatry. 1991;2: 1339–47 (in Japanese).
19. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for clinician. J Psychiatr Res. 1975;12:189–98.
20. Cederfeldt M, Gosman-Hedström G, Sävborg M, Tarkowski E. Influence of cognition on personal activities of daily living (P-ADL) in the acute phase: the Gothenburg Cognitive Stroke Study in Elderly. Arch Gerontol Geriatr. 2009;49:118–22.
21. Fransen M, Anderson C, Chalmers J, Chapman N, Davis S, MacMahon S, et al. Effects of a perindopril-based blood pressure-lowering regimen on disability and dependency in 6105 patients with cerebrovascular disease: a randomized controlled trial. Stroke. 2003;34:2333–8.
22. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Stroke. 2000;31:811–6.
23. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, et al. Midlife and Late-life blood pressure and dementia in Japanese elderly: the Hisayama Study. Hypertension. 2011;58: 22–8.
24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed, revised. Washington, DC: American Psychiatric Association; 1987.
25. 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. Neurology. 1984;34:939–44.
26. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250–60.
27. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. Stroke. 2003;34:2349–54.
28. Katz S, Ford AB, Moskowitz RW, Jackson BA, Laffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychological function. JAMA. 1963;185:914–9.
29. von Strauss E, Agüero-Torres H, Kåreholt I, Winblad B, Fratiglioni L. Women are more disabled in basic activities of daily living than men only in very advanced ages: a study on disability, morbidity, and mortality from the Kungsholmen Project. J Clin Epidemiol. 2003;56:669–77.
30. Demura S, Sato S, Minami M, Kasuga K. Gender and age differences in basic ADL ability on the elderly: comparison between the independent and the dependent elderly. J Physiol Anthropol Appl Human Sci. 2003;22:19–27.
31. Guralnik JM, Kaplan GA. Predictors of healthy aging: prospective evidence from the Alameda County Study. Am J Public Health. 1989;79:703–8.
32. Oman D, Reed D, Ferrara A. Do elderly women have more physical disability than men do? Am J Epidemiol. 1999; 150:834–42.
33. Wray LA, Blaum CS. Explaining the role of sex on disability: a population-based study. Gerontologist. 2001;41:499–510.
34. Sauvaget C, Yamada M, Fujiwara S, Sasaki H, Mimori Y. Dementia as a predictor of functional disability: a four-year follow-up study. Gerontology. 2002;48:226–33.
35. Agüero-Torres H, Fratiglioni L, Guo Z, Viitanen M, von Strauss E, Winblad B. Dementia is the major cause of functional dependence in the elderly: 3-year follow-up data from a population-based study. Am J Public Health. 1998;88:1452–6.
36. Kamiyama T, Muratani H, Kimura Y, Fukiyama K, Abe K, Fujii J, et al. Factors related to impairment of activities of daily living. Intern Med. 1999;38:698–704.
37. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health. 1994;84:351–8.
38. Boult C, Kane RL, Louis TA, Boult L, McCaffrey D. Chronic conditions that lead to functional limitation in the elderly. J Gerontol. 1994;49:M28–36.
39. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol. 2009;8: 1006–18.

Self-Reported Dietary Intake of Potassium, Calcium, and Magnesium and Risk of Dementia in the Japanese: The Hisayama Study

Mio Ozawa, MSc,[*] *Toshiharu Ninomiya, MD, PhD,*[*†] *Tomoyuki Ohara, MD, PhD,*[*‡] *Yoichiro Hirakawa, MD,*[*†] *Yasufumi Doi, MD, PhD,*[*†] *Jun Hata, MD, PhD,*[*†] *Kazuhiro Uchida, MSc,*[§] *Tomoko Shirota, PhD,*[§] *Takanari Kitazono, MD, PhD,*[†] *and Yutaka Kiyohara, MD, PhD*[*]

OBJECTIVES: To investigate whether higher intake of potassium, calcium, and magnesium reduces the risk of incident dementia.

DESIGN: Prospective cohort study.

SETTING: The Hisayama Study, in Japan.

PARTICIPANTS: One thousand eighty-one community-dwelling Japanese individuals without dementia aged 60 and older.

MEASUREMENTS: A 70-item semiquantitative food frequency questionnaire was used to assess potassium, calcium, and magnesium intakes. Hazard ratios (HRs) for the development of all-cause dementia and its subtypes were estimated using Cox proportional hazards model.

RESULTS: During a 17-year follow-up, 303 participants experienced all-cause dementia; of these, 98 had vascular dementia (VaD), and 166 had Alzheimer's disease (AD). The multivariable-adjusted HRs for the development of all-cause dementia were 0.52 (95% confidence interval [CI] = 0.30–0.91), 0.64 (95% CI = 0.41–1.00), and 0.63 (95% CI = 0.40–1.01) for the highest quartiles of potassium, calcium, and magnesium intake, respectively, compared with the corresponding lowest quartiles. Similarly, the HRs for the development of VaD were 0.20 (95% CI = 0.07–0.56), 0.24 (95% CI = 0.11–0.53), and 0.26 (95% CI = 0.11–0.61) for the highest quartiles of potassium, calcium, and magnesium intake, respectively. There was no evidence of a linear association between these mineral intakes and the risk of AD.

CONCLUSION: Higher self-reported dietary intakes of potassium, calcium, and magnesium reduce the risk of all-cause dementia, especially VaD, in the general Japanese population. **J Am Geriatr Soc 60:1515–1520, 2012.**

Key words: dementia; Alzheimer's disease; vascular dementia; potassium; calcium; magnesium

Recent evidence has emerged to indicate that dietary modification has an important role in preventing life style-related diseases.[1] In several prospective studies, higher intake of potassium, calcium, and magnesium reduced the risk of developing hypertension and stroke.[2–4] These findings raise the possibility that these mineral intakes may be effective at reducing the burden of cardiovascular risk factors and subsequent vascular diseases.

Dementia is one of the causes of disability and premature death in elderly adults[5,6] and is a high-priority public health concern worldwide.[7] Cerebrovascular disease is one of the causes of vascular dementia (VaD).[8] In addition, recent epidemiological studies have suggested that cardiovascular risk factors may play at least a partial role in Alzheimer's disease (AD), which has traditionally been considered a primarily neurodegenerative disorder.[8,9] Therefore, it is reasonable to assume that the intake of these minerals exerts beneficial effects on cerebro- and cardiovascular diseases and their risk factors, leading to a subsequent reduction in the risk of dementia, but few studies have assessed the effects of mineral intake on the risk of dementia. To clarify this issue, a prospective cohort study was performed to evaluate risk factors for the development of dementia in Japanese elderly individuals. The aim of this study was to elucidate the effects of dietary

From the [*]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [†]Department of Medicine, and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [‡]Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; and [§]Department of Health Promotion, School of Health and Nutrition Sciences, Nakamura-Gakuen University, Fukuoka, Japan.

Address correspondence to Toshiharu Ninomiya, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812–8582, Japan. E-mail: nino@intmed2.med.kyushu-u.ac.jp

DOI: 10.1111/j.1532-5415.2012.04061.x

JAGS 60:1515–1520, 2012

0002-8614/12/$15.00

intakes of potassium, calcium, and magnesium on the development of dementia and its subtypes in a general population of Japanese elderly adults.

PARTICIPANTS AND METHODS

Study Population

The Hisayama Study is a population-based prospective cohort study of cerebro- and cardiovascular diseases established in the town of Hisayama, located in a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. Full community surveys of health status and neurological conditions of the residents aged 40 and older have been repeated annually since 1961.[10] In 1985, a comprehensive survey of cognitive impairment, including a neuropsychological test (Hasegawa dementia scale[11]) was performed in the elderly adults of the town.[12] In addition, the study team and local physicians or members of the Health and Welfare Office of Hisayama performed annual health examinations and established a daily monitoring system to obtain information on any stroke and dementia that participants developed. In 1988, 1,228 residents aged 60 and older (participation rate 91.1%) underwent a screening examination for the present study. Based on these data, 35 residents who had already had dementia at baseline were identified. After excluding these residents with dementia, 111 residents for whom dietary questionnaires were not available, and one resident with no blood sample, 1,081 participants (457 men and 624 women) were enrolled in this study. This study was conducted with the approval of the Kyushu University institutional review board for clinical research. Written informed consent was obtained from all participants.

Follow-Up Survey

The participants were followed up for 17 years, from December 1988 to November 2005, through the daily monitoring system and annual health examinations.[13] Health status was checked yearly by letter or telephone call for any participant who did not undergo a regular examination or who had moved out of town.[14] Comprehensive screening surveys of cognitive function including neuropsychological tests (the Hasegawa dementia scale,[11] its revised version,[15] or the Mini-Mental State Examination[16]) were conducted in 1992, 1998, and 2005. When new neurological symptoms, including cognitive impairment, were suspected, the physicians and psychiatrists from the study group carefully evaluated the participant. During the follow-up period, there were no participants whose medical condition or vital status could not be ascertained.

Diagnosis of Dementia

The criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*,[17] were used to define the diagnosis of dementia. Participants diagnosed with AD met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[18] and participants diagnosed with VaD met the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences.[19] The diagnostic procedure was reported previously.[20] During the 17-year follow-up period, 303 participants (103 men and 200 women) developed dementia, and 518 (47.9%) died. Of those with dementia, 261 (86.1%) were evaluated using brain imaging, and 155 (51.2%) underwent autopsy; both were performed in 143. Thus, 273 participants in all (90.0%) had some kind of morphological examination. Of participants with dementia, 25 with AD and 18 with VaD had other coexisting subtypes of dementia, of whom 14 had mixed AD and VaD. These cases were counted as events in the analyses for each subtype. Finally, 166 participants experienced AD and 98 VaD.

Nutritional Survey

At the baseline examination, a dietary survey was conducted using a 70-item semiquantitative food frequency questionnaire concerning food intake.[21] The validity of this questionnaire has been reported elsewhere.[22] The questionnaire was administered before initiation of this study, and trained dieticians and nutritionists questioned each participant during the examination. Average food intake per day was calculated from the weekly frequency of various foods and the amount of each food portion. Nutritional intake was calculated using the fourth revision of the Standard Tables of Food Composition in Japan.[23] Magnesium intake was calculated from a previously developed magnesium inclusion table.[24] Each nutritional element was adjusted for energy intake using the residual method.[25] The correlation between the food frequency questionnaire and food records was 0.53 for potassium and 0.42 for calcium but was not investigated for magnesium. The validity of magnesium could not be assessed, because there was no standardized table of food compositions for magnesium in Japan in 1988.

Risk Factor Measurement

At baseline, each participant completed a self-administered questionnaire covering medical history, antidiabetic and antihypertensive treatments, educational status, alcohol consumption, smoking habits, and physical activity. History of stroke was determined 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, including medical records, neurological examination, and brain imaging. A low educational level was defined as <7 years of formal education. Smoking and drinking habits were classified as currently used or not. Regular exercise was defined as engaging in sports or other forms of exertion three or more times a week during leisure time. Blood pressure was measured three times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 minutes. 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 greater, 2-hour postload glucose concentrations or postprandial glucose concentrations of 11.1 mmol/L or greater, or current use of insulin or oral medication for diabetes mellitus.

Statistical Analysis

Participants were divided into quartiles of potassium, calcium, and magnesium intake. Age- and sex-adjusted mean values or frequencies of potential risk factors for dementia between the lowest and the highest mineral intakes were compared using analysis of covariance for continuous variables and a logistic regression model for dichotomous variables. Participants were censored at date of death or date of the end of follow-up for survival analyses. The age- and sex-adjusted or multivariable-adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) of intake levels of minerals for the development of dementia were estimated using the Cox proportional hazards model. The assumption of the proportional hazards was checked graphically using the log cumulative hazard plots for outcomes according to the intake levels of each mineral. All measured variables of known or suspected risk factors for dementia were selected as potential confounders. The median values of food intake between the lowest and highest quartiles of mineral intakes were compared using the Student *t*-test. SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used to perform all statistical analyses.

RESULTS

Table 1 compares the age- and sex-adjusted mean values or frequencies of possible risk factors for dementia of the lowest and highest quartiles of dietary potassium, calcium, and magnesium intake at baseline. Participants with the highest intakes of potassium, calcium, and magnesium were more likely to be female and more educated than those with the lowest intakes. The prevalence of diabetes mellitus was higher in participants in the highest quartiles of mineral intakes, and the prevalence of smoking and alcohol intake were lower in the highest-intake quartile for each mineral. The intakes of vitamin C, cholesterol, fatty acids, saturated fatty acid, monounsaturated fatty acid, and polyunsaturated fatty acid were all higher in the highest quartile than in the lowest for each mineral. Strong correlations between these mineral intakes were observed (Pearson correlation coefficient (r) = 0.65 between potassium and calcium, r = 0.85 between potassium and magnesium, and r = 0.76 between calcium and magnesium).

The age- and sex-adjusted and multivariable-adjusted HRs and their 95% CIs for the development of all-cause

Table 1. Age- and Sex-Adjusted Potential Risk Factors for Dementia According to Lowest and Highest Quartiles of Self-Reported Dietary Potassium, Calcium, and Magnesium Intake at Baseline

	Potassium Intake		Calcium Intake		Magnesium Intake	
Risk Factors	Q1 (lowest) (n = 270)	Q4 (highest) (n = 270)	Q1 (lowest) (n = 270)	Q4 (highest) (n = 270)	Q1 (lowest) (n = 270)	Q4 (highest) (n = 270)
Age, mean	69	69	69	69	69	69
Female, %	37.1	68.3[a]	44.3	60.1[a]	42.5	69.2[a]
Education ≤6 years, %	16.8	8.8[a]	17.0	9.1[b]	14.7	8.2[b]
History of stroke, %	4.6	3.6	4.1	4.7	4.4	4.0
Systolic blood pressure, mmHg, mean	139	139	141	139	140	140
Diastolic blood pressure, mmHg, mean	76	76	76	77	76	77
Hypertension, %	52.7	53.8	64.7	56.2	53.7	57.7
Diabetes mellitus %	10.3	20.5[a]	9.6	22.6[a]	13.0	21.5[b]
Total cholesterol, mg/dL, mean	207	213	201	218[a]	202	215[a]
Body mass index, kg/m^2, mean	22.0	22.8[a]	22.1	22.5	21.9	22.6[b]
Smoking habits, %	30.3	18.8[a]	27.8	19.0[b]	30.7	16.6[a]
Alcohol intake, %	31.4	22.4[b]	29.7	23.2[b]	30.7	24.7[b]
Regular exercise, %	20.0	19.7[b]	21.2	18.9	21.0	21.9[a]
Dietary intake per day, mean						
Energy, kcal	1,651	1,745[b]	1,716	1,725	1,665	1,718
Vitamin C, mg	51	114[a]	70	91[a]	56	106[a]
Cholesterol, mg	209	251[a]	192	274[a]	208	256[a]
Saturated fatty acid, g	11.2	13.5[a]	10.2	14.5[a]	10.8	13.8[a]
Monounsaturated fatty acid, g	16.8	20.2[a]	16.2	21.1[a]	17.1	20.1[a]
Polyunsaturated fatty acid, g	12.9	18.9[a]	12.5	19.7[a]	13.3	18.5[a]

Age is sex-adjusted; sex is age-adjusted.
P < .01[a], .05[b] vs Q1.

dementia, VaD, and AD according to intakes of potassium, calcium, and magnesium are shown in Table 2. The HR of all-cause dementia decreased significantly with higher intake of each mineral after adjusting for age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking; alcohol intake; regular exercise; and intakes of energy, vitamin C, cholesterol, saturated fatty acid, monounsaturated fatty acid, and polyunsaturated fatty acid (all *P* for trend <.05). With regard to subtypes of dementia, the multivariable-adjusted HRs of VaD were significantly lower with higher intakes of potassium, calcium, and magnesium (all *P* for trend <.01), although the multivariate-adjusted HRs of AD were significantly lower in the third quartile of potassium intake and in the second and third quartile of magnesium intake, but there was no evidence of a significant linear association (all *P* for trend >.09). Because the intakes of the three minerals were strongly correlated, the risks of all-cause dementia and its subtypes in participants with the highest intakes of all three minerals (n = 143) were compared with those with the lowest intakes of these minerals (n = 154). Participants with the highest intakes of all three minerals had 71% (95% CI = 8–91%) lower risk of VaD after adjusting for the above-mentioned potential confounders.

The food intake characteristics of participants in the lowest quartiles of all three mineral intakes were compared with the characteristics of those in the highest quartiles (Table 3). Participants in the highest quartiles tended to eat more potatoes, soybeans and soybean products, vegetables, fruits and fruit juices, algae, fish, eggs, and milk and dairy products and had lower intakes of rice, meat, sugar,

Table 2. Development of All-Cause Dementia, Vascular Dementia, and Alzheimer's Disease According to Quartile of Self-Reported Dietary Potassium, Calcium, and Magnesium Intake

Variable	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
All-cause dementia					
Potassium, mg/d	≤1,856	1,857–2,149	2,150–2,559	≥2,560	
Events/participants, n/n	77/270	80/270	76/271	70/270	
HR (95% CI)[a]	1	0.77 (0.56–1.07)	0.70 (0.51–0.97)	0.65 (0.46–0.91)	.01
HR (95% CI)[b]	1	0.69 (0.49–0.99)	0.58 (0.38–0.87)	0.52 (0.30–0.91)	.02
Calcium, mg/d	≤431	432–531	532–638	≥638	
Events/participants, n/n	74/270	78/270	85/271	66/270	
HR (95% CI)[a]	1	0.99 (0.72–1.37)	0.86 (0.63–1.19)	0.77 (0.55–1.07)	.08
HR (95% CI)[b]	1	0.91 (0.64–1.28)	0.77 (0.53–1.11)	0.64 (0.41–1.00)	.04
Magnesium, mg/d	≤147	148–169	170–195	≥196	
Events/participants, n/n	79/270	74/270	72/271	78/270	
HR (95% CI)[a]	1	0.66 (0.48–0.92)	0.56 (0.40–0.77)	0.69 (0.50–0.95)	.02
HR (95% CI)[b]	1	0.61 (0.43–0.86)	0.50 (0.34–0.75)	0.63 (0.40–1.01)	.04
Vascular dementia					
Potassium, mg/d	≤1,856	1,857–2,149	2,150–2,559	≥2,560	
Events/participants, n/n	31/270	29/270	26/271	12/270	
HR (95% CI)[a]	1	0.86 (0.51–1.45)	0.74 (0.43–1.27)	0.36 (0.18–0.70)	.003
HR (95% CI)[b]	1	0.74 (0.41–1.36)	0.48 (0.24–0.98)	0.20 (0.07–0.56)	.003
Calcium, mg/d	≤431	432–531	532–638	≥638	
Events/participants, n/n	32/270	25/270	24/271	17/270	
HR (95% CI)[a]	1	0.81 (0.48–1.38)	0.66 (0.39–1.14)	0.52 (0.29–0.94)	.02
HR (95% CI)[b]	1	0.59 (0.34–1.04)	0.43 (0.23–0.81)	0.24 (0.11–0.53)	<.001
Magnesium, mg/d	≤147	148–169	170–195	≥196	
Events/participants, n/n	35/270	23/270	23/271	17/270	
HR (95% CI)[a]	1	0.55 (0.32–0.94)	0.48 (0.28–0.82)	0.42 (0.23–0.76)	.003
HR (95% CI)[b]	1	0.44 (0.25–0.79)	0.34 (0.17–0.67)	0.26 (0.11–0.61)	.002
Alzheimer's disease					
Potassium, mg/d	≤1,856	1,857–2,149	2,150–2,559	≥2,560	
Events/participants, n/n	34/270	45/270	41/271	46/270	
HR (95% CI)[a]	1	0.82 (0.52–1.30)	0.71 (0.44–1.13)	0.79 (0.50–1.25)	0.3
HR (95% CI)[b]	1	0.69 (0.42–1.14)	0.52 (0.29–0.93)	0.56 (0.26–1.20)	.09
Calcium, mg/d	≤431	432–531	532–638	≥638	
Events/participants, n/n	34/270	43/270	50/271	39/270	
HR (95% CI)[a]	1	1.11 (0.70–1.74)	0.96 (0.61–1.49)	0.89 (0.56–1.42)	.48
HR (95% CI)[b]	1	1.00 (0.61–1.63)	0.92 (0.55–1.54)	0.87 (0.47–1.62)	.61
Magnesium, mg/d	≤147	148–169	170–195	≥196	
Events/participants, n/n	36/270	39/270	42/271	49/270	
HR (95% CI)[a]	1	0.67 (0.42–1.07)	0.62 (0.39–0.97)	0.80 (0.52–1.25)	.45
HR (95% CI)[b]	1	0.58 (0.35–0.95)	0.53 (0.31–0.92)	0.72 (0.38–1.37)	0.4

[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; alcohol intake; regular exercise; and energy, vitamin C, cholesterol, saturated fatty acid, monounsaturated fatty acid, and polyunsaturated fatty acid intake.

HR = hazard ratio; CI = confidence interval.

Table 3. Comparisons of the Amounts of Each Food Group Consumed Between the Lowest and Highest Quartiles for Intake of All Three Minerals (Potassium, Calcium, and Magnesium)

Food Group	Median (Interquartile Range) Lowest Quartile (n = 143)	Highest Quartile (n = 154)	*P*-Value
Rice	235.8 (196.2–281.4)	144.4 (103.3–170.5)	<.001
Breads	1.05 (−2.5–17.7)	1.36 (−0.8–40.9)	.32
Noodles and other cereals	1.78 (−3.4–14.0)	2.77 (−0.96–25.8)	.31
Potatoes	9.46 (3.96–718.9)	20.2 (9.9–42.1)	<.001
Soybeans and soybean products	44.7 (16.4–62.3)	123.2 (84.6–171.8)	<.001
Miso	13.9 (9.3–15.7)	14.4 (11.8–15.3)	.50
Pickles	25.9 (8.6–44.9)	29.0 (8.94–59.3)	.11
Green vegetables	41.7 (27.8–59.3)	124.2 (91.2–147.4)	<.001
Other vegetables	93.9 (71.0–141.8)	255.9 (182.4–295.4)	<.001
Fruits and fruit juices	34.4 (12.2–64.4)	80.1 (49.6–146.5)	<.001
Algae	0.48 (0.21–0.93)	1.39 (0.88–1.98)	<.001
Fish	20.4 (10.7–33.6)	41.5 (29.7–60.8)	<.001
Meat	20.1 (10.6–30.8)	13.9 (6.8–24.7)	.01
Eggs	26.0 (13.6–45.9)	38.6 (20.7–48.8)	.01
Milk and dairy products	25.7 (−5.0–68.9)	197.3 (121.3–250.5)	<.001
Fats and oils	19.7 (15.6–35.8)	18.3 (14.4–23.2)	.13
Sugar and confectioneries	23.1 (15.5–36.3)	18.6 (12.4–26.3)	<.001
Alcoholic beverages	47.8 (−18.0–202.6)	8.1 (−18.8–68.2)	.01
Salt	12.4 (9.1–15.2)	11.2 (8.8–14.4)	.29

confectioneries, and alcoholic beverages. Comparable patterns of food intakes were found when food intakes of participants in the highest and lowest quartiles of each mineral were compared separately.

DISCUSSION

The present study demonstrated that higher self-reported dietary intakes of potassium, calcium, and magnesium reduced the risk of all-cause dementia and VaD but not of AD. Several longitudinal studies have reported the preventive effects of dietary intakes of these minerals on the risk of stroke,[3,4] but to the best of the knowledge of the authors of the current study, this is the first prospective cohort study showing that higher self-reported dietary intakes of potassium, calcium, and magnesium are associated with a lower risk of dementia. The separate effects of each mineral on dementia were not distinguished because these minerals were strongly correlated with one another. Furthermore, the possibility that some other factors contained in the foods than the minerals themselves caused the favorable effects on dementia cannot be excluded. Nevertheless, these findings may provide intriguing information on the beneficial effects of a diet rich in these minerals against dementia in Japanese.

The mechanism through which the risk of VaD decreased with higher intakes of these minerals is unclear. Hypertension has been recognized as a strong risk factor for vascular diseases, including VaD.[26] There is some evidence of the antihypertensive effects of these mineral intakes,[2] but the adjustment for hypertension had little effect on the association between each mineral intake and the risk of VaD in the present study. As alternative mechanisms, it has been reported that these minerals may have some favorable effects against vascular diseases through inhibition of free radical formation and platelet aggregation, improvement of dyslipidemia, and an increase in insulin sensitivity.[27–29] Further investigation will be needed to clarify this issue.

In the present study, the risk of AD tended to decrease with higher self-reported dietary mineral intakes, but there was no clear evidence of a significant linear association. As was discussed, the self-reported dietary mineral intakes are likely to have some type of favorable effects on atherosclerotic cardiovascular diseases such as stroke and VaD, but AD has been considered a primarily neurodegenerative disorder caused by amyloid deposition, although recent epidemiological studies have suggested the partial involvement of cardiovascular risk factors in AD development.[8,9] Therefore, these self-reported dietary mineral intakes may have had only a modest benefit in reducing the risk of AD.

Some potential limitations of this study should be noted. First, information regarding dietary nutrient intake derived from a semiquantitative food frequency questionnaire may be not be fully valid. Additionally, dietary intake was assessed only once, at baseline. These

limitations could lead to misclassification of mineral intake to some extent. Such misclassification would weaken the association found in the present study, biasing the results toward the null hypothesis. Second, the validity of magnesium intake estimation made using a semiquantitative food frequency questionnaire has not been explored, although given the high correlations between magnesium intake and calcium (0.76), potassium (0.65), and fiber intakes (0.63), it is likely that the findings on magnesium are meaningful. Finally, the lack of information about the use of supplements containing potassium, calcium, or magnesium may have reduced the accuracy of the findings to some extent.

In conclusion, the present study demonstrated that self-reported dietary intakes of potassium, calcium, and magnesium were associated with lower risks of all-cause dementia and VaD in the general Japanese elderly population. Although plausible mechanisms to account for these associations remain unclear, these findings imply that consuming foods high in potassium, calcium, and magnesium may reduce the risk of late-life onset of dementia, especially VaD. Further epidemiological and clinical studies are warranted to determine whether a diet rich in these minerals can lessen the future risk of dementia.

ACKNOWLEDGMENTS

The authors thank the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

Conflict of Interest: This study was supported in part by Grants-in-Aid for Scientific Research 20591063, 21590698, 22590892, and 22300116 from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by a Health and Labor Sciences Research Grant of the Ministry of Health, Labor and Welfare of Japan (Comprehensive Research on Aging and Health: H20-Chouju-004).

Author Contributions: Mio Ozawa: study concept, design, interpretation of data, statistical analysis, and writing of the manuscript. Toshiharu Ninomiya: data collection, interpretation of data, and writing of the manuscript. Tomoyuki Ohara, Yoichiro Hirakawa, Yasufumi Doi, and Jun Hata: data collection and interpretation of data. Kazuhiro Uchida and Tomoko Shirota: nutritional data collection and interpretation of data. Takanari Kitazono: interpretation of data. Yutaka Kiyohara was the study coordinator and contributed to securing of funds, study concept, interpretation of data, and writing of the manuscript.

Sponsor's Role: The supporting sources had no role in study design or conduct of the study; collection, management, analysis, or interpretation of data; writing of the report; or the decision to submit the manuscript for publication.

REFERENCES

1. Ammerman AS, Lindquist CH, Lohr KN, Hersey J. The efficacy of behavioral interventions to modify dietary fat and fruit and vegetable intake: A review of the evidence. Prev Med 2002;35:25–41.
2. Houston MC, Harper KJ. Potassium, magnesium, and calcium: Their role in both the cause and treatment of hypertension. J Clin Hypertens 2008;10:3–11.
3. Larsson SC, Virtanen MJ, Mars M et al. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. Arch Intern Med 2008;168:459–465.
4. Iso H, Stampfer MJ, Manson JE et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke 1999;30:1772–1779.
5. Sauvaget C, Yamada M, Fujiwara S et al. Dementia as a predictor of functional disability: A four-year follow-up study. Gerontology 2002;48:226–233.
6. Bowen JD, Malter AD, Sheppard L et al. Predictors of mortality in patients diagnosed with probable Alzheimer's disease. Neurology 1996;47:433–439.
7. Ferri CP, Prince M, Brayne C et al. Global prevalence of dementia: A Delphi consensus study. Lancet 2005;366:2112–2117.
8. Knopman DS. Cerebrovascular disease and dementia. Br J Radiol 2007;80: S121–S127.
9. Newman AB, Fitzpatrick AL, Lopez O et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study Cohort. J Am Geriatr Soc 2005;53:1101–1107.
10. Kubo M, Kiyohara Y, Kato I et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: The Hisayama Study. Stroke 2003;34:2349–2354.
11. Hasegawa K, Inoue K, Moriya K. An investigation of dementia rating scale in a general population of Japanese elderly [Japanese]. Seishin Igaku 1974;6:965–969.
12. Sekita A, Ninomiya T, Tanizaki Y et al. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: The Hisayama Study. Acta Psychiatr Scand 2010;122:319–325.
13. Yoshitake T, Kiyohara Y, Kato I et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: The Hisayama Study. Neurology 1995;45:1161–1168.
14. Ohmura T, Ueda K, Kiyohara Y 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;36:1198–1203.
15. Katoh S, Simogaki H, Onodera A et al. Development of the revised version of Hasegawa's Dementia Scale (HDS-R) [Japanese]. Jpn J Geriatr Psychiatry 1991;2:1339–1347.
16. 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;12:189–198.
17. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. Revised. Washington, DC: American Psychiatric Association, 1987.
18. McKhann G, Drachman D, Folstein M et al. 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. Neurology 1984;34:939–944.
19. Román GC, Tatemichi TK, Erkinjuntti T et al. Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
20. Ohara T, Doi Y, Ninomiya T et al. Glucose tolerance status and risk of dementia in the community: The Hisayama Study. Neurology 2011; 77:1126–1134.
21. Kiyohara Y, Shinohara A, Kato I et al. Dietary factors and development of impaired glucose tolerance and diabetes in a general Japanese population: The Hisayama Study. J Epidemiol 2003;13:251–258.
22. Shirota T, Yoshizumi E. A study on convenient dietary assessment [Japanese]. Jpn J Public Health 1990;37:100–108.
23. Resources Council of Science and Technology Agency. Standard Tables of Food Composition for in Japan, 4th Ed. [Japanese]. Tokyo: Ministry of Finance Printing Bureau, 1982.
24. Shirota T, Kitano T, Sugawara K et al. Comparison of measured dietary consumption of minerals (Ca, P, Mg, Fe, Cu) with calculated values be weighting methods [Japanese]. Kyushu Jissen Eiyo Kenkyukai Houkokusyo 1991;3:63–68.
25. Willett W, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
26. Sharp SI, Aarsland D, Day S et al. Hypertension is a potential risk factor for vascular dementia: Systematic review. Int J Geriatr Psychiatry 2011;26:661–669.
27. Young DB, Lin H, McCabe RD. Potassium's cardiovascular protective mechanisms. Am J Physiol 1995;268:R825–R837.
28. Karanja N, Morris CD, Illingworth DR et al. Plasma lipids and hypertension: Response to calcium supplementation. Am J Clin Nutr 1987;45:60–65.
29. Mooren FC, Krüger K, Völker K et al. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects—a double-blind, placebo-controlled, randomized trial. Diabetes Obes Metab 2011;13:281–284.