表1. ベースラインにおける各種所見

	非症例	全認知症	脳卒中既往	
			なし	あり
認知症例数	9028	426	289	137
年齢, y	50.9	61.4	61.4	61.2
男性, %	44.2	37.8	30.8	52.6
Body mass index, kg/m^2	23.5	23.7	23.8	23.7
過去喫煙, %	8.9	8.3	6.3	12.5
現在喫煙, %	32.2	26.9	23.3	34.6
過去飲酒, %	3.2	4.3	2.8	7.5
現在飲酒, %	36.5	27.3	21.1	40.3
収縮期血圧, mmHg	132.3	137.9	136.2	141.4
高血圧治療, %	12.5	28.4	24.9	35.8
糖尿病, %	5.7	8.2	9.2	6.4
血清総コレステロール, mg/dl	191.8	193.8	195.8	189.6
心房細動, %	0.6	0.7	0.7	0.7
心電図ST-T変化, %	6.7	10.1	8.0	14.6
高血圧性眼底変化, %	34.7	55.1	49.7	67.6
糖尿病性眼底変化, %	0.5	0.6	0.5	0.9
糸球体濾過量, $ml/min/1.73m^2$	87.4	78.5	78.2	79.0
尿蛋白陽性, %	2.4	2.6	2.8	2.2

表2. リスクファクターと認知症の関連

	全認知症	脳卒中既往	
		なし	あり
認知症例数	426	289	137
年齢, 1yr ‡	**1.20(1.18–1.22)**	**1.21(1.19–1.23)**	**1.19(1.16–1.22)**
男性 *	1.00(0.82–1.21)	0.74(0.57–0.95)	1.79(1.28–2.50)
Body mass index, 1kg/m^2 †	1.00(0.97–1.03)	1.00(0.96–1.03)	1.02(0.96–1.07)
過去喫煙 †	1.04(0.68–1.60)	0.94(0.53–1.67)	1.16(0.59–2.26)
現在喫煙 †	1.24(0.89–1.72)	1.26(0.84–1.89)	1.20(0.69–2.07)
過去飲酒 †	1.53(0.90–2.61)	1.00(0.47–2.17)	**2.74(1.25–5.98)**
現在飲酒 †	1.03(0.75–1.41)	0.78(0.52–1.16)	1.67(0.99–2.83)
収縮期血圧 (1標準偏差増) †	1.01(0.92–1.11)	0.92(0.82–1.04)	1.20(1.03–1.41)
高血圧治療 †	**1.25(1.01–1.55)**	1.01(0.77–1.33)	**1.89(1.32–2.70)**
糖尿病 †	1.39(0.92–2.08)	**1.62(1.01–2.61)**	0.97(0.44–2.11)
血清総コレステロール (1標準偏差増) †	0.95(0.86–1.05)	0.97(0.86–1.10)	0.91(0.76–1.09)
心房細動 †	1.26(0.40–3.93)	1.41(0.35–5.68)	1.03(0.14–7.36)
心電図ST-T変化 †	1.09(0.79–1.50)	0.79(0.52–1.22)	**1.89(1.17–3.06)**
高血圧性眼底変化 †	1.20(0.91–1.58)	0.95(0.69–1.32)	**2.13(1.24–3.63)**
糖尿病性眼底変化 †	3.04(0.76–12.2)	2.38(0.33–17.0)	4.06(0.57–29.1)
糸球体濾過量 (1標準偏差増) †	1.04(0.91–1.19)	1.03(0.88–1.21)	1.07(0.85–1.35)
尿蛋白陽性 †	1.58(0.87–2.88)	1.71(0.85–3.45)	1.32(0.42–4.16)

† 性・年齢を調整
‡ 性を調整
＊ 年齢を調整

（資料）平成 26 年度総括研究報告書

厚生労働科学研究費補助金（認知症対策総合研究事業）
総括研究報告書
認知症一次予防のための多角的データ利用による縦断研究

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研究要旨
本研究では、過去の食事調査データの整備を行い、認知症発症との関連を分析するためのデータベースを構築し、基本集計を行った。茨城県及び秋田県の農村地区の住民のうち、健診と同時に24時間思い出し法による食事調査を行った人の中から、要介護認知症の症例245人とその対照490人を対象にコホート内症例対照研究を行った。その結果、きのこ類や乳類、栄養素では食物繊維や一部の脂肪酸が要介護認知症と関連を示す可能性が示された。特に、食事中のアルファリノレン酸と要介護認知症との間に強い負の関連が認められた。本データベースをさらに詳細に検討することにより、認知症予防に役立つ食習慣に関する日本人独自のエビデンスの構築が期待される。

A. 研究目的

本研究では、従来の基本健康診査・特定健康診査の検査項目に加えて、食事調査等の付加的な検査・調査項目を実施してきた地域において、認知症の予防に役立つ生活習慣指導項目や、健診に追加することが有用な新しい検査項目を本格的な疫学研究として明らかにすることを目的としている。本年度は、特に過去の食事調査データの整備を行い、認知症発症との関連を分析するためのデータベースを構築し、基本集計を行った。

B. 研究方法

対象は、茨城県及び秋田県の農村地区の、1981年から1994年までの循環器健診・基本健診の受診者（年間約5,000人）のうち、健診と同時に24時間思い出し法による食事調査を行ったのべ5737人である。そのうち、2000年4月から2014年3月までに介護保険認定を受けた要介護認知症の症例と、その時点において認知症を発症していない生存者を対照として、食事調査実施者の中から、性、年齢、健診受診年、地域を1：2でマッチさせて無作為に選び出し、症例245人、対照490人の合計735人を分析対象とした。

エンドポイントは、痴呆性（認知症）老人の日常生活自立度を用い、IIa度以上を要介護認知症とした。この基準は過去の検討において、精神科医の診断に対して感度83%、特異度96%を有することがわかっている。要介護認知症の発症について、各食事項目と、それから算出した各栄養素の1標準偏差増加あたりの条件付オッズ比を、条件付多重ロジステ

ィックモデルを用いて分析した。共変量として、喫煙、高血圧、糖尿病を調整した。栄養素の算出に当たっては、日本食品標準成分表2010、日本食品標準成分表準拠アミノ酸成分表2010、及び五訂増補日本食品標準成分表脂肪酸成分表を用いた。

（倫理面への配慮）

血液の保存・研究利用については、健診時に本人より口頭又は文書により了承を得ているほか、ホームページ上でも公開している。また本研究は当該自治体の保健事業の一環として実施するものとして、自治体の首長・保健担当者からの同意を得ている。研究の遂行に当たっては、対象地域の自治体職員との協働を基本とし、当該自治体職員の協力のもとで連結可能匿名化されたデータベースを用いた。研究の概要や結果については、自治体の広報や研究機関のウェブサイト等に掲載する。本研究の実施にあたっては、筑波大学、大阪大学及び大阪がん循環器病予防センターの倫理委員会の承認を得た。

C. 研究結果

食品群別に見た認知症の多変量調整条件付オッズ比（95%信頼区間）は、きのこ類が 1 標準偏差増加あたり 0.77 (0.62-0.96)、乳類が 0.87 (0.74-1.03)、菓子類が 0.80 (0.66-0.97)、調味料及び香辛料類が 0.84 (0.69-1.03)などであった。（表１）

総摂取エネルギーや三大栄養素、ミネラル、ビタミン、食塩については、要介護認知症との関連はなかった。食物繊維については、水溶性で 1 標準偏差増加あたり 0.81 (0.67-0.97)、不溶性で 0.84 (0.70-1.02)、総量で 0.82 (0.68-0.99)と、いずれも負の関連または傾向を示した。（表２）

個々のアミノ酸成分については、要介護認知症と関連するものはなかった。（表３）

脂肪酸組成については、総量、飽和、一価不飽和、多価不飽和として見た場合は有意な関連はみられなかったが、一価不飽和脂肪酸と n-6 系多価不飽和脂肪酸は、有意ではないが負の傾向が認められた。（表４）

個々の脂肪酸として見た場合（表４）、飽和脂肪酸ではトリデカン酸、アンテイソペンタデカン酸、イソプルミチン酸がいずれも負の傾向、一価不飽和脂肪酸では、オレイン酸が負の傾向、イコセン酸とドコセン酸がいずれも有意な正の関連を示した。n-6 系多価不飽和脂肪酸ではリノール酸が負の傾向、n-3 系多価不飽和脂肪酸ではアルファリノレン酸が負の関連を示した。エイコサペンタエン酸やドコサヘキサエン酸については有意な関連を示さなかった。

D. 考察

本研究では、これまで数十年間にわたり脳血管疾患の予防対策を実施してきた地域において、健康診査や栄養調査等の過去の調査・検査データと、介護保険データを一体化させたデータベースを構築することにより、コホート内症例対照研究を行い、要介護認知症の予防に役立つ生活指導・健診検査項目を明らかにすることを目的とした。特に本年度は、

食事調査のデータに焦点を当て、データセットの構築を行い、基本集計を行った。

その結果、きのこ類や乳類、栄養素では食物繊維や一部の脂肪酸が要介護認知症と関連を示す可能性が示された。特に、血清中のアルファリノレン酸と要介護認知症との間に負の関連があることは、本研究の先行研究で初めて明らかになった知見であるが（山岸他，第68回日本公衆衛生学会総会，2009)、今回新たに食事中のアルファリノレン酸についても同様に負の関連があることが明らかになった。また、食事中の食物繊維は、水溶性、不溶性に関わらず、要介護認知症と負の関連が認められた。そのほか、負の傾向を示した３種の飽和脂肪酸はいずれも乳類に多く含まれることから、乳類と要介護認知症との負の関連はこれらの脂肪酸が関与している可能性が高い。一方、菓子類や調味料・香辛料と要介護認知症との間に負の関連が示されたことや、イコセン酸やドコセン酸と正の関連が示されたこと、またこれまで負の関連が多く報告されてきた、魚に多く含まれる長鎖n-3系多価不飽和脂肪酸との関連が示されなかったことなどは、明確な理由は不明である。ただし、菓子類については、チョコレートの摂取が認知症の抑制につながるとする仮説が最近提唱されており、本研究結果と関連する可能性がある。いずれにしても、今回の分析は基本集計であることから、今後４分位分析など詳細な分析を全ての項目について行う予定である。

本研究では、本年度、上記の研究を含め、種々の調査・検査データと、介護保険データを多角的に活用したデータベースを構築し、数々の分析を行って研究を総括した。食事調査以外の本研究の総括については、平成24～26年度総合研究報告書を参照されたい。

E. 結論

過去の食事調査データと認知症発症との関連を分析するためのデータベースを構築し、基本集計を行った。きのこ類や乳類、栄養素では食物繊維や一部の脂肪酸が要介護認知症と関連を示す可能性が示された。今後、本データベースをさらに詳細に検討することにより、認知症予防に役立つ食習慣に関する日本人独自のエビデンスの構築が期待される。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

なし

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表1　各食品群に関する認知症の多変量調整条件付オッズ比

	1SD増加当たり多変量オッズ比
穀類	1.17 (0.91–1.50)
いも及びでん粉類	0.90 (0.76–1.07)
砂糖及び甘味類	0.97 (0.82–1.15)
豆類	1.07 (0.91–1.25)
種実類	1.10 (0.93–1.30)
野菜類	0.91 (0.77–1.07)
果実類	1.09 (0.92–1.30)
きのこ類	0.77 (0.62–0.96)
藻類	1.06 (0.91–1.24)
魚介類	1.01 (0.85–1.21)
肉類	1.03 (0.86–1.22)
卵類	1.08 (0.93–1.26)
乳類	0.87 (0.74–1.03)
油脂類	0.98 (0.83–1.16)
菓子類	0.80 (0.66–0.97)
し好飲料類	1.04 (0.86–1.25)
調味料及び香辛料類	0.84 (0.69–1.03)

地域、性、年齢、健診受診年をマッチ、喫煙、高血圧、糖尿病を調整

表2 各栄養素に関する認知症の多変量調整条件付オッズ比

	1SD増加当たり多変量オッズ比
Total energy intake	0.85 (0.69–1.05)
Water	0.99 (0.80–1.24)
Protein	1.03 (0.79–1.35)
Protein:the sum of amino acid residues	1.05 (0.83–1.32)
Lipid	0.88 (0.71–1.10)
Carbohydrate	1.12 (0.79–1.61)
Ash	0.93 (0.75–1.15)
Sodium	0.99 (0.80–1.21)
Potassium	0.87 (0.72–1.06)
Calcium	0.91 (0.76–1.09)
Magnesium	0.92 (0.75–1.13)
Phosphorus	1.01 (0.79–1.29)
Iron	0.98 (0.81–1.18)
Zinc	1.04 (0.78–1.39)
Copper	0.93 (0.72–1.21)
Manganese	1.05 (0.86–1.28)
Iodine	0.83 (0.61–1.14)
Selenium	0.97 (0.82–1.14)
Chromium	1.03 (0.87–1.22)
Molybdenum	1.09 (0.86–1.36)
Retinol	1.01 (0.87–1.18)
Carotein	0.98 (0.83–1.15)
α Carotein	0.97 (0.82–1.15)
β Carotein	0.98 (0.84–1.16)
β Cryptoxanthin	1.01 (0.82–1.25)
β Carotene equivalents	0.98 (0.84–1.16)
Retinol activity equivalents	1.01 (0.87–1.17)
Vitamin D	1.08 (0.91–1.28)
α Tocopherols	0.93 (0.78–1.12)
β Tocopherols	0.89 (0.75–1.06)
γ Tocopherols	0.88 (0.74–1.06)
δ Tocopherols	0.90 (0.75–1.08)
Vitamin K	0.91 (0.76–1.08)
Thiamin	1.00 (0.82–1.21)
Riboflavin	0.87 (0.71–1.06)
Niacin	1.13 (0.93–1.37)
Vitamin B_6	1.05 (0.86–1.29)
Vitamin B_{12}	1.14 (0.97–1.34)
Folate	0.91 (0.76–1.08)
Pantothenic acid	0.84 (0.66–1.07)
Biotin	0.97 (0.81–1.16)
Ascorbic acid	0.97 (0.81–1.15)
Fatty acids	0.87 (0.70–1.09)
Cholesterol	1.05 (0.89–1.25)
Total fiber	0.82 (0.68–0.99)
Soluble fiber	0.81 (0.67–0.97)
Insoluble fiber	0.84 (0.70–1.02)
Salt	0.99 (0.80–1.21)

地域、性、年齢、健診受診年をマッチ、喫煙、高血圧、糖尿病を調整

表3 各アミノ酸に関する認知症の多変量調整条件付オッズ比

	1SD増加当たり多変量オッズ比
Isoleucine	1.03 (0.83–1.29)
Leucine	1.03 (0.82–1.30)
Lysine	1.02 (0.83–1.25)
Sulfur containing amino acid	1.06 (0.84–1.35)
Methionine	1.04 (0.83–1.31)
Cysteine	1.11 (0.85–1.44)
Aromatic amio acid	1.05 (0.83–1.34)
Phenylalanine	1.05 (0.82–1.33)
Tyrosine	1.07 (0.84–1.35)
Threonine	1.04 (0.83–1.31)
Toriptofan	1.07 (0.84–1.36)
Valine	0.04 (0.82–1.32)
Histidine	1.11 (0.92–1.32)
Arginine	1.11 (0.88–1.40)
Alanine	1.08 (0.85–1.36)
Asparatic acid	1.05 (0.84–1.32)
Glutamic acid	0.98 (0.78–1.23)
Glycine	1.11 (0.89–1.39)
Purorin	0.96 (0.78–1.19)
Serine	1.07 (0.84–1.36)
Ammonia	1.15 (0.93–1.43)

地域、性、年齢、健診受診年をマッチ、喫煙、高血圧、糖尿病を調整

表4 各脂肪酸に関する認知症の多変量調整条件付オッズ比

	1SD増加当たり多変量オッズ比
Saturated fatty acids	0.90 (0.73–1.10)
Butyric acid	0.90 (0.76–1.06)
Hexanoic acid	0.90 (0.76–1.06)
Heptanoic acid	0.87 (0.74–1.03)
Octanoic acid	0.93 (0.79–1.10)
Decanoic acid	0.90 (0.76–1.06)
Lauric acid	1.03 (0.87–1.21)
Tridecanoic acid	0.87 (0.74–1.03)
Myristic acid	1.00 (0.84–1.20)
Pentadecanoic acid	0.94 (0.79–1.12)
Antiso-pentadecanoic acid	0.88 (0.75–1.04)
Palmitic acid	0.88 (0.71–1.10)
Iso-Palmitic acid	0.88 (0.75–1.04)
Heptadecanoic acid	0.91 (0.75–1.10)
Antiso-heptadecanoic acid	0.88 (0.75–1.04)
Stearic acid	0.90 (0.74–1.10)
Arachidic acid	0.89 (0.73–1.08)
Behenic acid	0.97 (0.82–1.15)
Lignoceric acid	0.97 (0.83–1.15)
Monounsaturated fatty acids	0.90 (0.73–1.11)
Decenoic acid	0.88 (0.75–1.04)
Myristoleic acid	0.85 (0.68–1.06)
Pentadeaenoic acid	1.05 (0.90–1.22)
Palmitoleic acid	0.99 (0.81–1.20)
Heptadecenoic acid	0.96 (0.79–1.16)
Oleic acid	0.82 (0.66–1.01)
Icosenoic acid	1.18 (1.01–1.37)
Docosenoic acid	1.18 (1.02–1.38)
Tetracosenoic acid	1.14 (0.97–1.34)
Polyunsaturated fatty acids	0.89 (0.73–1.09)
n-6 polyunsaturated fatty acids	0.86 (0.70–1.04)
n-3 polyunsaturated fatty acids	1.02 (0.86–1.22)
Hexadecadienoic acid	1.06 (0.91–1.25)
Hexadecatrienoic acid	0.97 (0.82–1.14)
Hexadecatetraenoic acid	1.03 (0.88–1.22)
Linoleic acid	0.85 (0.70–1.04)
α Linolenic acid	0.81 (0.66–1.00)
γ Linolenic acid	1.12 (0.96–1.32)
Octadecatetraenoic acid	1.14 (0.98–1.33)
Eicosadienoic acid	1.10 (0.91–1.33)
Eicosatrienoic acid	0.96 (0.79–1.18)
Eicosatetraenoic acid	1.14 (0.97–1.33)
Arachidonic acid	1.03 (0.86–1.24)
Eicosapentaenoic acid	1.08 (0.91–1.27)
Henicosapentaenoic acid	1.10 (0.94–1.29)
Docosadienoic acid	1.01 (0.86–1.18)
Docosatetraenoic acid	1.14 (0.96–1.35)
Docosapentaenoic acid (n-3)	1.07 (0.91–1.26)
Docosapentaenoic acid (n-6)	1.05 (0.89–1.23)
Docosahexaenoic acid	1.10 (0.93–1.29)

地域、性、年齢、健診受診年をマッチ、喫煙、高血圧、糖尿病を調整

［Ⅱ］研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Yamagishi K, Ikeda A, Moriyama Y, Chei CL, Noda H, Umesawa M, Cui R, Nagao M, Kitamura A, Yamamoto Y, Asada T, Iso H; for the CIRCS Investigators	Serum coenzyme Q10 and risk of disabling dementia: the Circulatory Risk in Communities Study (CIRCS)	***Atherosclerosis***	237	400-403	2014

［Ⅲ］研究成果の刊行物・別刷

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C-reactive protein levels and risk of disabling dementia with and without stroke in Japanese: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Objective: Studies have shown that elevated high-sensitivity C-reactive protein (hs-CRP) predicts stroke, which is a risk factor for dementia. It remains, however, unclear whether hs-CRP increases risk of dementia.

Methods: A prospective nested case–control study of Japanese 40–69 years of age was conducted using frozen serum samples collected from approximately 7531men and women who participated in cardiovascular risk surveys from 1984 to 1994 in one community and 1989–1995 in another community under the Circulatory Risk in Communities Study (CIRCS). Two control subjects per case were matched by sex, age, community, and year of serum storage. The hs-CRP was measured using a latex particle-enhanced immunonephelometric assay.

Results: Between 1999 and 2013, we identified 275 disabling dementia cases (96 cases with history of stroke and 179 without it). There was a positive association between hs-CRP levels and risk of dementia with history of stroke. No significant association was observed between hs-CRP levels and risk of dementia without history of stroke. After adjustment for hypertension, diabetes and other confounding variables, the positive association remained statistically significant. The multivariable odds ratios associated with 1-SD increment of log hs-CRP were 1.02 (0.87–1.20) for total dementia, 1.35 (1.02–1.79) for dementia with history of stroke, and 0.89 (0.72–1.10) for dementia without history of stroke.

Conclusion: Elevated hs-CRP levels were associated with increased risk of disabling dementia in individuals with history of stroke but not in those without it.

1. Introduction

As a consequence of a rapidly growing elderly population, the number and proportion of individuals with dementia is dramatically expanding worldwide. In Japan, where the elderly population has been increasing faster than in other countries, it is projected that the number of elderly with dementia will increase from 30 million in 2010 to 36 million in 2020 [1]. This has led to intense efforts to identify factors that distinguish persons who are at higher or lower risk for developing dementia.

Cardiovascular diseases are the leading cause of disability and death in Japan [2,3] and Japanese populations have a higher incidence of stroke compared to western populations [4]. Patients with history of stroke have a 5 fold increased risk of developing dementia compared with patients without it [5]. Cardiovascular risk factors profiles for dementia with history of stroke and dementia

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without it may be different. The pooled results from a meta-analysis study revealed that midlife total cholesterol was positively associated with risk of dementia without history of stroke, but not dementia with it [6]. However, follow-up studies of elderly (65 years or older) found that low-density lipoprotein (LDL) cholesterol was associated with risk of dementia with history of stroke (with a relative risk range from 2.5 to 2.6) for the highest compared with the lowest quartile of LDL cholesterol but not in dementia without it [7,8]. Elevated high sensitive C-reactive protein (hs-CRP), an acute-phase reactant and a marker of systemic inflammation, has been associated with risk of stroke in western [9,10] and Japanese populations [11,12]; however, the connection between elevated serum hs-CRP levels and risk of developing dementia still remains controversial.

In the Honolulu-Asia Aging study [13], 1050 Japanese American men (mean age = 54–58 years) were followed-up for 25 years, those with elevated serum hs-CRP in midlife were associated with higher risk of developing dementia in later life (OR:2.8, 95% CI 1.6–5.1). The Rotterdam study [14] and the Conselice Study of Brain Aging [15] also found an association between elevated hs-CRP levels and increased risk of dementia. The pooled hazard ratio from meta-analysis for hs-CRP and the incidence of dementia was 1.5 (95% CI 1.1–1.9) [16]. However, in the Women's Health Study [17], hs-CRP levels were not associated with cognitive function in older women (age 60–90 years) and in the 90 + Study [18], hs-CRP was not associated with dementia in the oldest elderly individuals. Other prospective studies [19,20] also failed to find such an association. In contrast, in the Framingham Heart Study [21] elevated serum hs-CRP levels were associated with reduced risk of dementia, however, after adjusting for additional risk factors such as *APOE4* allele, the results were no longer statistically significant. To date, age-stratified analysis on the association between hs-CRP levels and risk of dementia with history of stroke and without it has not been undertaken with a large Japanese cohort.

Inflammatory process may directly or indirectly relate to dementia risk via their role in initiation of athero- and arteriolesclerotic lesions in the cerebral vascular system, and may contribute to the development of dementia. Our hypothesis is that elevated hs-CRP levels, a biomarker of inflammation, increased risk of dementia with history of stroke. We measured hs-CRP from stored serum samples of two Japanese communities of the Circulatory Risk in Communities Study (CIRCS), and examined the association between hs-CRP levels and risk of disabling dementia with history of stroke and without it.

2. Materials and methods

2.1. Subjects

The present study was an ancillary study of the CIRCS. The details of this study have been described previously [22]. Participants in the present study were recruited from all residents who participated in cardiovascular risk surveys in two communities of CIRCS. The surveyed populations comprised approximately 7531 men and women 40–69 years old who participated in the surveys between 1984 and 1994 in a mid-eastern rural community (Kyowa; $n = 5349$) and between 1989 and 1995 in northeastern rural community (Ikawa; $n = 2182$). These two cohorts have been followed up with annual cardiovascular surveys and surveillance for incidence and mortality of stroke and coronary heart disease systematically, as described elsewhere. We excluded persons aged 70 old or older at baseline, since serum hs-CRP is likely to be an indicator of advanced age rather than inflammatory process for the elderly [23–25]. Within these two cohorts, elderly persons aged ≥ 65 years with disabling dementia requiring care were identified under the national long-term care insurance program, between 1999 and 2005 in Kyowa, and between 1999 and 2013 in Ikawa. We did not have information on cognitive function prior to dementia. The mean duration of follow-up was 14 years, with 6 being the minimum and 24 the maximum. Informed consent was obtained by community leaders and by individual participants verbally, which was common practice in Japanese communities at that time. The Ethics Committees of the Osaka Center for Cancer and Cardiovascular Disease Prevention and University of Tsukuba approved the study procedures.

2.2. Long-term care insurance program for elderly aged ≥65

Details of the national long-term care insurance program for elderly aged ≥65 have been reported elsewhere [26,27]. In brief, the insurance program began in Japan from April 2000. This program was essentially an extension of the national health insurance system, and partially relied on subsidies from general revenue from the national government, prefectures and municipalities. All individuals aged ≥40 are required to pay a supplement to their health insurance, which is transferred to a long-term care fund. The payment is directly withdrawn from their monthly income, shared with the employer or deducted from their public pension. All individuals are able to receive long-term care through their resided municipalities when they turn 65 and also if they have disabling dementia and/or reduced capacity for daily living.

2.3. Case selection

The cases were selected among subjects aged ≥65 years between 1999 and 2005 in Kyowa, between 1999 and 2013 in Ikawa, who were regarded as suffering from dementia under the long-term insurance program. The dementia status was classified into six ranks (0–V) and was reported by their primary care physicians according to a standardized physicians' manual issued by the Health and Welfare Bureau for the Elderly of Japan [28]. The dementia status was usually updated annually and was reviewed until the patients were withdrawn due to death or move out of the study area. Individuals without dementia were classified as rank 0. Individuals who were diagnosed with mild cognitive dysfunction, but who had no dementia-related symptoms or behavioral disturbance and were capable of living independently, were classified as rank I. Individuals who had moderate dementia-related behavioral disturbance and cognitive impairment with slight dependence were classified as rank II. Individuals who had moderate to severe dementia-related behavioral disturbance and cognitive impairment with moderate dependence were classified as rank III. Individuals who had severe dementia-related behavioral disturbance and cognitive impairment with heavy dependence were classified as rank IV. Finally, individuals with severe dementia-related behavioral disturbance and cognitive impairment who required medical treatment were classified as rank V. Individuals who were ranked II or greater for the first time were regarded as incident disabling dementia cases in the present analysis. The validation for the cut-off point was determined by neuropsychiatrists of the subjects' cognitive functions (attention, memory, visuospatial function, language and reasoning) based on their aging-associated cognitive decline, as defined by the International Psychogeriatric Association [29]. The calculated sensitivity and specificity values were 36% and 90%, respectively, from the preliminary validation study of 34 disabling subjects. [30].

2.4. History of stroke identification

The history of stroke was obtained from the annual cardiovascular surveys and/or surveillance of the cardiovascular disease

registration system [11] from 1981 to the present. In the present study, 90% of stroke occurrence was confirmed based on CT or MRI using standardized criteria [11,31]. The determination of stroke without imaging studies was conducted based on the clinical criteria [32]. Stroke was defined as rapid-onset focal neurological disorder persisting for ≥ 24 h, or until death. Transient ischemic attack was not included.

2.5. Control selection

We employed risk set sampling [33] of controls, i.e. matching each case of dementia randomly with two of all other individuals with no diagnosis of dementia in the study cohort who were alive and resident within the same community on the date of diagnosis of dementia for the case, age (±2 years) and who had the same gender as the control. The vital status of controls was assessed before control selection.

2.6. Determination of serum high-sensitivity C-reactive protein

Non-fasting venous blood was collected in a 7- to 10- mL plain tube and allowed to stand for <30 min for serum separation. The serum samples were aliquoted immediately and placed on dry ice at the survey sites and then stored at −80 °C until analysis. Serum hs-CRP was measured using latex particle-enhanced immunonephelometric assays on the BN Prospec nephrometer Behring II (Dade Behring). In this method, monoclonal anti-CRP antibodies coated with polystyrene particles formed a complex with CRP present in the measured study sample. The amount of scattered light was directly proportional to the size of the antigen–antibody complex and reflected the hs-CRP concentration present in the study sample [34]. For results under the measurement limit of hs-CRP; hs-CRP>0.500 mg/dL or hs-CRP< 0.004 mg/dL, the values of 0.500 mg/dL or 0.004 mg/dL were used respectively.

2.7. Determination of confounding variables

Confounding variables were collected in the same year of blood collection. An interview was conducted to ascertain histories of cigarette smoking, ethanol intake and medication use for hypertension and diabetes. Height in stocking feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Systolic and diastolic blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Use of antihypertensive medication was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg and as taking antihypertensive medication. Serum total cholesterol was measured by enzymatic method. Serum glucose was measured by the hexokinase method. Borderline diabetes was defined as a fasting glucose of 6.1–6.9 mmol/L and/or a non-fasting glucose level of 7.8–11.0 mmol/L, without medication use for diabetes. Diabetes was defined as a fasting glucose level of ≥7.0 mmol/L and/or a non-fasting glucose level of ≥11.0 mmol/L and/or use of medication for diabetes. Atrial fibrillation was defined using Minnesota Codes 8-3-1 or 8-3-2 in electrocardiogram.

2.8. Statistical analysis

The unpaired student's *t* test and Wilcoxon rank sum test were used to compare the mean values of baseline dementia risk factors and median variables of hs-CRP between incident cases and control subjects. The χ^2 test was used to compare proportions between cases and control subjects. Potential confounding factors according to hs-CRP quartiles were investigated using the analysis of variance for continuous variables and χ^2 test for categorical variables. The conditional odds ratios (OR) and 95% confidence intervals (CI) for disabling dementia, dementia with stroke and dementia without stroke were estimated according to quartiles of hs-CRP levels and 1-SD increment of log transformed hs-CRP (antilog of SD = 3.3 mg/dL) of control subjects with conditional logistic regression models. Adjustment was made for systolic blood pressure (mmHg), use of antihypertensive medication (yes and no), BMI (kg/m^2), ethanol intake (never, former, current: less than 46 g/day, and 46 g/day or more ethanol), cigarette smoking status (never, ex-, and current smokers; 20 cigarettes/day or less, and more than 20 cigarettes/day), serum total cholesterol levels (mmol/L), borderline diabetes (yes and no) and diabetes (yes and no). Linear regression was employed to test for linear trends across the hs-CRP categories by using a median variable of hs-CRP for each hs-CRP category. The significance of the interactions for sex, use of antihypertensive medication (yes and no) and diabetes (yes and no) were tested using cross-product terms of sex, use of antihypertensive medication and diabetes with hs-CRP levels. All probability values of statistics were two- tailed, and values of $P < 0.05$ were regarded as statistically significant. The SAS statistical package version 9.1.3 (Statistical Analysis System Inc., Cary, NC) was used for analyses.

3. Results

Table 1 shows the risk characteristics of total dementia cases, dementia cases with history of stroke and dementia cases without history of stroke compared with control subjects. The average age for both cases and control of total dementia and dementia subtypes was 63 years. The proportion of men was higher in dementia with history of stroke (46%) than dementia without it (27%). Mean systolic blood pressure levels, diastolic blood pressure levels and median hs-CRP levels were higher in dementia with history of stroke than in controls; however this trend was not observed in dementia without it. The prevalence of diabetes was higher in total dementia than in controls, and these cases-controls differences were more evident in dementia with history of stroke than dementia without it.

During the follow-up period, we identified 275 dementia cases, comprising 96 dementia cases with a history of stroke and 179 dementia cases without such history.

Table 2 shows age-, sex-, community-, and survey year-matched and multivariable-adjusted odds ratios (95% CI) for total and subtypes of dementia according to quartiles of hs-CRP levels and 1-SD increment in log transformed hs-CRP levels. There was a significant association between elevated hs-CRP levels and dementia with history of stroke. After adjustment for hypertension, diabetes and other confounding variables, these positive associations remained statistically significant. The multivariable odds ratios associated with 1-SD increment of hs-CRP were 1.02 (0.87–1.20) for total dementia, 1.35 (1.02–1.79) for dementia with history of stroke, and 0.89 (0.72–1.10) for dementia without history of stroke. The multivariable odds ratios of dementia with history of stroke for the highest vs. lowest quartiles of hs-CRP levels were 0.99 (0.61–1.60) for total dementia, 2.72 (1.12–6.64) for dementia with history of stroke, and 0.63 (0.34–1.14) for dementia without history of stroke.

We examined potential effect modification by stratifying the analyses for use of antihypertensive medication (yes and no) and diabetes (yes and no) (data not shown) for dementia with history of stroke. There were no statistically significant interactions between hs-CRP levels and use of antihypertensive medication (p for interaction = 0.48) or diabetes (p for interaction = 0.12).

Table 1
Risk characteristics among cases and control subjects of total dementia stratified by the presence of stroke history.

	No	Age y	Men, %	Systolic BP, mm Hg	Diastolic BP, mm Hg	Antihypertensive medication use, %	BMI, kg/m2	Ethanol intake, g/d	Current smokers, %	Serum cholesterol mmol/L	Impaired glucose tolerance %	Diabetes mellitus %	Atrial fibrillation %	Median hs-CRP (mg/dL)
Total dementia														
Cases	275	62.8 ± 5.2	33.8	137.2 ± 18.4‡	79.9 ± 10.8*	32.4	23.9 ± 3.5	0.48 ± 0.90	23.3	200.1 ± 32.9	16.7	10.2*	0.4	0.041
Control subjects	550	62.6 ± 5.2	33.8	132.7 ± 16.7	78.1 ± 10.5	30.9	23.9 ± 3.2	0.43 ± 0.84	19.1	198.2 ± 33.3	15.6	5.3	0.4	0.042
Dementia with history of stroke														
Cases	96	62.4 ± 4.3	45.8	140.8 ± 19.9‡	82.5 ± 10.5‡	39.6	23.7 ± 3.3	0.65 ± 0.97	29.2	198.2 ± 32.8	16.7	9.4*	1.1	0.050*
Control subjects	192	62.2 ± 4.4	45.8	132.1 ± 16.1	78.0 ± 11.4	32.3	23.8 ± 3.1	0.57 ± 0.97	26.0	193.0 ± 32.8	17.7	2.6	0.5	0.036
Dementia without history of stroke														
Cases	179	63.1 ± 5.6	27.4	135.4 ± 17.3	78.6 ± 10.8	28.5	24.0 ± 3.6	0.39 ± 0.85	20.1	201.1 ± 32.4	16.8	10.6	0	0.037
Control subjects	358	62.8 ± 5.6	27.4	132.9 ± 17.1	78.1 ± 10.0	30.2	24.0 ± 3.2	0.35 ± 0.75	15.4	201.0 ± 33.2	14.5	6.7	0.3	0.044

Data are shown as mean ± SD, frequency as a number (%).
hs-CRP levels are expressed as median (interquartile range).
P values for differences from control subjects : *$P < 0.05$, ‡$P < 0.001$.

4. Discussion

The present study is the first study to provide evidence that elevated hs-CRP levels were associated with increased risk of disabling dementia in individuals with history of stroke. These associations remained unchanged even after adjustment for risk factors of dementia and the matching variable of age, sex, years of serum storage, and community. In addition, this association does not vary according to use of antihypertensive medication or whether a person has diabetes. However, no significant association was observed between hs-CRP levels and risk of disabling dementia in individuals without history of stroke.

The most important findings in the present study were that elevated hs-CRP in midlife was associated with the increased risk of developing dementia in individuals with history of stroke but not in individuals without such history. The evidence from Honolulu—Asia Aging study [13] indicated that elevated hs-CRP levels in midlife increased the risk of developing dementia in later life. That study, however, did not stratify individuals with dementia by stroke history but included stroke as a mediating variable in their model. Previous prospective studies [13–15] of hs-CRP and dementia showed a 1.5–2.8-fold increased risk of dementia with elevated hs-CRP levels whereas other studies [20,21] failed to find such associations. Again, those studies did not stratify individuals with dementia by stroke history. The inconsistent results across previous studies may suggest that the interaction effect of hs-CRP and cardiovascular disease on developing dementia was often insufficiently considered. One reason to explain our findings is the fact that Japan populations have the higher incidence of stroke compared to Western countries [4]. The comparatively larger number of stroke cases in our sample could account for the positive association we found between hs-CRP levels and dementia in individuals with history of stroke, and a result not found in studies conducted in Western countries.

Inflammatory process may directly or indirectly relate to dementia risk via their role in the initiation of athero- and arteriolesclerotic lesions in cerebrovascular system [25], which subsequently may increase risk of developing dementia in individuals with stroke history. High CRP facilitates the formation of foam cells in the process of atherogenesis [25] and also impairs endothelial function by attenuating the production of nitric oxide [35]. Both processes contribute the cognitive decline in older adults [36]. In addition, increased myo-inositol signal is a neurochemical abnormality associated with cognitive decline and Alzheimer's disease [37]. A recent cross-sectional study found that higher serum CRP was associated with higher ratio of cerebral myo-inositol/creatine concentrations in cognitively normal middle-aged adults, suggesting the linkage of high CRP to neurochemical changes [38].

Previous cohort studies reported that CRP levels were positively associated with risk of vascular dementia [13–15] but not associated with risk of Alzheimer's disease [13–15,21,39]. These findings corresponded to our present result that CRP levels were positively associated with risk of dementia with history of stroke, but not with dementia without history of stroke, presumably Alzheimer's disease. Although the carrying of *APOE4 allele* is a major risk factor for Alzheimer's disease [40] and *APOE4* carriers had lower levels of CRP compared to non *APOE4 allele* carriers [41–43], the effect of *APOE4 allele* to the association between CRP levels and Alzheimer's disease still remains murky. In the ULSAM-study [39] CRP levels were not associated with Alzheimer's disease after accounted for *APOE* genotype (*APOE4* allele carriers *versus* non carries). However, in a cohort study of Mexican Americans aged 60-101, CRP levels were found inversely associated with the risk of Alzheimer's disease (HR:0.74 (95% CI 0.35–0.90)) in *APOE4* carriers (13% of total subjects) and were positively associated with

Table 2
Odd ratios (95% confidence intervals) of total dementia, stratified by the presence of stroke history according to quartiles of serum hs-CRP levels of control subjects.

	Quartiles of hs-CRP, mg/dL					OR for 1SD increment of log hs-CRP
	1 (low)	2	3	4 (high)	*P* for trend	
Serum hs-CRP						
Median (mg/L)	0.01	0.03	0.06	0.152		
Range (mg/L)	0.002–0.016	0.017–0.041	0.042–0.088	0.090–3.11		
Total dementia						
No. of case	55	83	74	63		
No. of control	134	141	138	137		
Age-, sex, and community-matched OR	1.00	1.44 (0.95–2.18)	1.32 (0.86–2.04)	1.13 (0.73–1.74)	0.69	1.06 (0.92–1.22)
Multivariable OR[a]	1.00	1.34 (0.86–2.07)	1.16 (0.73–1.85)	0.99 (0.61–1.60)	0.82	1.02 (0.87–1.20)
Dementia with history of stroke						
No. of case	11	34	24	27		
No. of control	49	56	44	43		
Age-, sex, and community-matched OR	1.00	2.71 (1.22–6.03)*	2.43 (1.06–5.60)*	2.72 (1.21–6.10)*	0.02	1.33 (1.04–1.71)*
Multivariable OR[a]	1.00	2.15 (0.90–5.15)	2.06 (0.82–5.21)	2.72 (1.12–6.64)*	0.04	1.35 (1.02–1.79)*
Dementia without history of stroke						
No. of case	44	49	50	36		
No. of control	85	85	94	94		
Age-, sex, and community-matched OR	1.00	1.10 (0.66–1.83)	1.04 (0.62–1.74)	0.74 (0.44–1.27)	0.27	0.94 (0.78–1.12)
Multivariable OR[a]	1.00	1.08 (0.64–1.84)	0.93 (0.54–1.62)	0.63 (0.34–1.14)	0.11	0.89 (0.72–1.10)

*$P < 0.05$.
[a] Adjusted for systolic blood pressure, antihypertensive medication use, borderline diabetes, diabetes, BMI, alcohol intake categories, cigarette smoking status, serum total cholesterol levels as well as matching for sex, age, community, year of serum stored, and fasting status.

the risk of Alzheimer's disease (HR 1.24 (95% CI 1.29–1.40)) in non *APOE4* carriers [43].

The strengths of the present study were its prospective design, the comprehensive nature of cardiovascular surveys, storage of serum blood samples and the large number of strokes confirmed by imaging studies. These allowed us to investigate the association between hs-CRP levels and risk of dementia with history of stroke and without such history and to adjust for important potential confounding variables. Moreover, because we used annual cardiovascular surveys that were carried out at least 5 years before the endpoint determination, severe dementia was unlikely to be present at the time of the risk factor assessment. This would enhance our confidence that elevated hs-CRP was not influenced by subclinical dementia.

There are some limitations of the current study. First, we did not have the data of *APOE* genotype, and could not examine an effect modification by *APOE4* allele. Further studies are required to confirm the potential effect of CRP levels on Alzheimer's disease in the presence and absence of *APOE4* allele. Second, we did not assess the cognitive functions of studied subjects at baseline. Therefore, we cannot completely exclude the effects of co-existing subclinical dementia at the time of blood serum collection. However, participants were presumed fit and able to attend the annual cardiovascular checkup for data collection. We conducted another analysis that excluded 6 cases that attended the annual cardiovascular survey within at least 5 years of the diagnosis of dementia, and the results remained unchanged (data not shown). Third, we had a systematic survey and surveillance for stroke incidence, but did not obtain the imaging study results for 10% of the stroke cases because CTs and MRIs were not common at local hospitals in the early 1980s. However, the diagnosis for stroke based only on clinical evidence (excluding medical imaging) was found to be in agreement with 97% of the autopsy results in a previous Japanese study [32]. Therefore, false-negative stroke cases were less likely to exist in our dementia cases. Fourth, we used frozen serum to estimate hs-CRP levels and we did not examine long-term changes in hs-CRP levels in stored serum samples. However, hs-CRP levels were reported to be stable at −70 °C which were stored for 8–11years [44]. Finally, these findings are based on a single measure of hs-CRP. CRP levels of subjects in the general population tend to be stable, although CRP levels may spike occasionally in the presence of minor or subclinical infections, inflammation or trauma [45].

In conclusion, elevated hs-CRP levels were associated with increased risk of dementia among those with history of stroke. No significant association was observed among those without history of stroke. The current study highlights that the risk of developing dementia in the elderly could be predicted in part through CRP measures.

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Disclosure

None.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Appendix I

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Center for Cancer and Cardiovascular Disease Prevention, University of Tsukuba, Osaka

University, and Ehime University. The CIRCS investigators who contributed to this study are as follows: Masahiko Kiyama, Masakazu Nakamura, Takeo Okada, Kenji Maeda, Masatoshi Ido, Masayuki Yao, Mitsugu Kajiura, Yoshinori Ishikawa, Masamitsu Konishi, Takashi Shimamoto, Hideki Ozawa, Minoru Iida, and Yoshio Komachi, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka; Yoshihiko Naito, Mukogawa Women's University, Nishinomiya; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Masakazu Nakamura, National Cerebral and Cardiovascular Center, Suita; Tomoko Sankai, Kazumasa Yamagishi, Mitsumasa Umesawa, ChoyLye Chei and Minako Tabata, University of Tsukuba, Tsukuba; Hiroyasu Iso, Akihiko Kitamura, Hironori Imano, Renzhe Cui, Hiroyuki Noda, Satoyo Ikehara, Yuji Shimizu, Isao Muraki, Masanori Nagao and Minako Maruyama, Osaka University, Suita; Takeshi Tanigawa and Ai Ikeda, Juntendo University, Tokyo; Tetsuya Ohira, Fukushima Medical University, Fukushima; Isao Saito, Susumu Sakurai, Shinichi Hitsumoto, Kotatsu Maruyama, and Eri Eguchi, Ehime University, Tōon.

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