Table 4 | Relative risks and 95% confidence intervals of mortality from all CVD and all causes relative to negative urinary protein and the lowest creatinine category or relative to negative urinary protein and GFR ⩾ 60 ml/min/1.73 m² category in men and women aged 40–79 years

Urinary protein / Creatinine	Creatinine and urinary protein categories: − / Low	+ or more / Low		− / High		+ or more / High		Urinary protein / GFR, ml/min/1.73 m²	GFR and urinary protein categories: − / ⩾60	+ or more / ⩾60		− / <60		+ or more / <60	
		RR	95% CI	RR	95% CI	RR	95% CI			RR	95% CI	RR	95% CI	RR	95% CI
Men															
Number at risk	28 731		792		761		134		28 812		804		680		122
All CVD															
No. of deaths	859	46		64		15			859	46		64		15	
Age-adjusted RR	1.00	1.74	(1.30–2.34)	1.64	(1.27–2.12)	2.75	(1.65–4.59)		1.00	1.74	(1.29–2.34)	1.66	(1.29–2.15)	2.79	(1.68–4.66)
Multivariable RR[a]	1.00	1.40	(1.03–1.88)	1.51	(1.16–1.96)	2.12	(1.27–3.55)		1.00	1.39	(1.03–1.88)	1.53	(1.18–1.98)	2.15	(1.28–3.60)
P for interaction				0.99								0.99			
All causes															
No. of deaths	3437	169		187		54			3440	171		184		52	
Age-adjusted RR	1.00	1.65	(1.41–1.92)	1.32	(1.14–1.53)	2.69	(2.06–3.52)		1.00	1.66	(1.42–1.94)	1.32	(1.14–1.54)	2.64	(2.01–3.48)
Multivariable RR[a]	1.00	1.49	(1.28–1.74)	1.33	(1.14–1.54)	2.49	(1.90–3.26)		1.00	1.50	(1.29–1.76)	1.33	(1.14–1.55)	2.44	(1.85–3.21)
P for interaction				0.23								0.31			
Women															
Number at risk	58 191		898		751		105		57 068		839		1874		164
All CVD															
No. of deaths	835	42		54		17			766	36		123		23	
Age-adjusted RR	1.00	2.40	(1.76–3.27)	1.87	(1.42–2.47)	7.03	(4.35–11.37)		1.00	2.45	(1.75–3.42)	1.72	(1.42–2.09)	5.00	(3.30–7.58)
Multivariable RR[a]	1.00	1.96	(1.43–2.68)	1.71	(1.29–2.26)	5.73	(3.52–9.34)		1.00	2.02	(1.44–2.83)	1.58	(1.30–1.93)	4.00	(2.62–6.10)
P for interaction				0.11								0.47			
All causes															
No. of deaths	2780	101		144		34			2626	90		298		45	
Age-adjusted RR	1.00	1.86	(1.53–2.27)	1.83	(1.54–2.16)	4.80	(3.42–6.73)		1.00	1.91	(1.55–2.35)	1.47	(1.30–1.66)	3.34	(2.49–4.49)
Multivariable RR[a]	1.00	1.69	(1.38–2.06)	1.71	(1.44–2.03)	4.09	(2.90–5.77)		1.00	1.74	(1.40–2.14)	1.40	(1.24–1.58)	2.89	(2.14–3.89)
P for interaction				0.13								0.42			

RR: relative risk, CI: confidence interval; GFR: glomerular filtration rate
Creatinine category: low (< 1.3 mg/dl in men and < 1.1 mg/dl in women) and high (⩾ 1.3 mg/dl in men and ⩾ 1.1 mg/dl in women).
[a]Adjusted for age, hypertension category, cigarette smoking, alcohol intake, diabetes mellitus, sex-specific quintiles of serum total cholesterol level, serum HDL-cholesterol level, and body mass index.

MATERIALS AND METHODS

Study population

The population surveyed included a total of 96 739 persons (32 904 men and 63 835 women) aged 40–79 years living in Ibaraki prefecture who participated in annual community-based health checkups in 1993. A total of 38 out of 85 communities in Ibaraki, Japan, were included in the present study. The participation rate of health checkups was 36.4% in the study areas, and was similar to 35.8% in Ibaraki prefecture in 1993. The study population consisted 3% of the census population living in Ibaraki prefecture. Persons with a history of stroke ($n = 958$), heart disease ($n = 4503$), and kidney disease ($n = 504$) were excluded from the study, and the data of 91 432 persons (30 764 men and 60 668 women) were used for the analysis. The study protocol was approved by the Ethics Committee of Ibaraki Prefectural Office.

Mortality surveillance

Mortality surveillance was conducted with systematic review of the death certificates and resident registration in cooperation with public health centers and municipal government offices. The underlying causes of death were coded according to the International Classification of Diseases, 9th revision (ICD-9, 1993–1994) and 10th revision (ICD-10, 1995–2003). The follow-up was conducted until the end of 2003. Only 2984 (3.3%) persons moved out of the communities during the follow-up, and 7070 (7.7%) persons died. Such individuals were censored at the date of moving out or death. The average follow-up period for all participants was 10.1 years.

Cause-specific mortality was also determined by stroke (ICD-9 codes 430–438; ICD-10 codes I60-I69), coronary heart disease (codes 410–414; I20-I25), all cardiovascular disease (codes 393–459; I00-I99), and non-cardiovascular disease (codes 001–392, 460–999; A00-H95, J00-Y89), separately.

Measurement of risk factors

Urinary protein and serum creatinine and other cardiovascular risk factors were measured at baseline survey when the participants were examined in 1993. Serum creatinine was measured by the modified method of Jaffe's reaction using the automated analyzer (RX-30, Nihon Denshi Inc., Tokyo, Japan). GFR was estimated by using the abbreviated equation developed at Cleveland Clinic laboratory for the Modification of Diet in Renal Disease (MDRD) Study as follows: GFR $(\mathrm{ml/min/1.73\,m^2}) = 186.3 \times \mathrm{age}^{-0.203} \times \mathrm{serum\ creatinine\ level}^{-1.154} \times (0.742 \text{ if female}) \times (1.212 \text{ if black subject})$.[24,25] Urinary protein was checked by dipstick urinalysis (Ames Hemacombisticks, Bayer-Sankyo, Tokyo). Trace-positive sample of proteinuria was re-examined using the sulfosalicylic acid test, and was divided into four groups (−, 1+, 2+, 3+). The result of '1+' or more was regarded as proteinuria.

We measured several potential confounders: serum total cholesterol, serum HDL-cholesterol, plasma glucose level, blood pressure, use of antihypertensive medication, body mass index, cigarette

smoking, usual alcohol intake, history of kidney disease, and diabetes mellitus. Serum total cholesterol was measured by an enzyme method using an RX-30 device (Nihon Denshi Inc., Tokyo, Japan). HDL-cholesterol was measured with a phosphotungestic acid magnesium method using an MTP-32 device (Corona Electric, Ibaraki, Japan). The measurement of these lipids in the laboratory of Ibaraki Health Service Association was standardized by the laboratory of the Osaka Medical Center for Health Science and Promotion under the laboratory network program of the US Centers for Disease Control and Prevention (Atlanta, GA, USA).[26] Plasma glucose levels were measured using a glucose oxidase electrode method with a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan). Diabetes was determined by a plasma glucose level of $\geqslant 126$ mg/dl fasting, $\geqslant 200$ mg/dl in non-fasting, or with treatment of diabetes mellitus. BP was measured by trained observers using standard mercury sphygmomanometer on the right arm of seated participants who had rested for 5 min. Height in stocking feet and weight in light clothing were measured. body mass index was calculated as weight (kg) divided by the square of height (m). An interview was conducted to ascertain the number of cigarettes smoked per day, usual weekly intake of alcohol, which was converted to grams of ethanol per day, and histories of stroke, heart, and kidney diseases.

Statistical analysis

Differences in age-adjusted mean values and the prevalence of potential confounding factors between two categories of urinary protein (−, + or more) and among six categories of serum creatinine levels ($\leqslant 0.8$, 0.9, 1.0, 1.1, 1.2, $\geqslant 1.3$ mg/dl for men, and $\leqslant 0.6$, 0.7, 0.8, 0.9, 1.0, $\geqslant 1.1$ mg/dl for women) were tested by the analysis of covariance and χ^2 test, respectively. When the overall difference was significant ($P<0.05$), we compared confounding factors between the lowest category and the other categories of creatinine levels. The relative risk of death and its 95% confidence interval (CI) were calculated with reference to the risk for persons with creatinine level $\leqslant 0.8$ mg/dl in men and $\leqslant 0.6$ mg/dl in women. Participants were stratified into six categories of GFR levels (<60, 60–79, 70–79, 80–89, 90–99, $\geqslant 100$ ml/min/1.73 m^2) and the RR and its 95% CI of death were also calculated with reference to the risk for persons with GFR level $\geqslant 100$ ml/min/1.73 m^2 in both men and women. These estimates were adjusted for age and other potential confounding factors using the Cox proportional hazards model. Potential confounding factors were hypertension category (normal BP, high-normal BP, grade 1 hypertension (mild), grade 2 hypertension (moderate), grade 3 hypertension (severe)),[27] anti-hypertensive treatment (yes vs no), cigarette smoking (never-smokers, ex-smokers, current 1–19, 20–29, and $\geqslant 30$ no./day), diabetes mellitus (fasting blood glucose $\geqslant 126$ mg/dl or non-fasting blood glucose $\geqslant 200$ mg/dl or treatment for diabetes), usual alcohol intake (never, former, current <56 g/day, and $\geqslant 56$ g/day in ethanol), sex-specific quintiles of body mass index , serum total cholesterol, and serum HDL-cholesterol.

The analysis was also conducted according to the combination of the presence of proteinuria with serum creatinine category (<1.3, $\geqslant 1.3$ mg/dl for men and <1.1, $\geqslant 1.1$ mg/dl for women) and GFR category (<60, $\geqslant 60$ ml/min/1.73 m^2). The significance of the interaction for serum creatinine and GFR were tested in the multivariable models using the interaction terms of urinary protein (−, + or more) × creatinine category and urinary protein × GFR category, respectively.

Furthermore, gender-specific population attributable risks of reduced GFR or proteinuria were calculated as follows:[28] population attributable risk $= p(RR-1)/(p(RR-1)+1)$, where p is the proportion of the population that is exposed, and RR is the relative risk of population that is exposed. The relative risks were calculated with reference to the risk for persons with GFR $\geqslant 60$ ml/min/1.73 m^2 and for those with proteinuria (+ or more) for both sexes. All statistical analyses were conducted using SAS, version 8.02 (SAS Institute, Inc., Cary, NC, USA).

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（3）健康日本21地方計画策定支援を目的とした地域診断ツールの開発

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要約：

目的　健康日本 21 の市区町村計画策定を支援するために，危険因子への介入による死亡率低下予測が可能な地域診断ツールを開発する。

方法　地域における死亡率低下割合の予測に必要な相対危険度と回帰係数を算出するために，茨城県健診受診者生命予後追跡調査のデータを用いて，1993 年度の基本健康診査を受診した 40 歳～69 歳の男性 25,201 人，女性 51,776 人を対象とし，2002 年までの死亡を追跡した。総死亡率，全循環器疾患死亡率，脳血管疾患死亡率，虚血性心疾患死亡率，全がん，および肺がん死亡率に対する喫煙（吸う），多量飲酒（1 日 3 合以上），肥満（Body Mass Index: BMI≧30），高血圧（収縮期≧160mmHg，拡張期≧100mmHg，高血圧治療中），高コレステロール（240mg/dl 以上，ただし 50 歳以上の女性は 260mg/dl 以上，高脂血治療中），低 HDL コレステロール（35mg/dl 未満），糖尿病（空腹時 126mg/dl 以上，非空腹時 200mg/dl 以上，糖尿病治療中）の相対危険度を Cox 比例ハザードモデルにより算出した。また，BMI，収縮期血圧，総コレステロール，HDL コレステロール，血糖について，二次項を含めた Cox 比例ハザードモデルにより回帰係数を算出した。これらの結果を基に，効果分画により，危険因子の変化による死亡率低下割合が予測可能なツールを Microsoft EXCEL を用いて開発した。

成績　本ツールの開発により，地域での現在の危険因子保有者の割合（曝露人口割合），平均値・標準偏差と目標とするそれらの値を入力することにより，その目標を達成した場合の死亡率の低下割合をシミュレーションできるようになった。本研究の対象集団において，各危険因子の保有者割合が半減した場合，および各検査値の分布が変化した場合の死亡率の低下割合を推定した結果，喫煙率が半減した場合，男性では総死亡率が 10%低下する可能性が示された。高血圧者の割合が半減した場合，男性では全循環器疾患死亡率が 12%，女性では 11%低下する可能性が示された。また，収縮期血圧の平均値を 10%低下させた場合，男性では全循環器疾患死亡率が 22%，女性では 18%低下する可能性が示された。

結論　本ツールは，都道府県と市区町村が連携して地域診断を推進するための，一つのツールとなり得る。

（4）住民健診（基本健康診査）の結果に基づいた脳卒中・虚血性心疾患・全循環器疾患・がん・総死亡の予測

（野田博之，磯　博康，西連地利己，入江ふじこ，深澤伸子，鳥山佳則，太田仁史，能勢忠男．日本公衆衛生雑誌 2006; 53(4): 265-276）

要約：

目的　大規模なコホート研究により，住民健診の検査結果とその後の死亡との関連を分析し，

パソコン上で簡便に使用でき，日常診療，保健活動に役立つ予測ツールを作成する。

方法　茨城県内の 38 市町村における 1993 年度，40-79 歳の住民健診受診者のうち，血圧値のない者また脳卒中および心疾患の既往者を除く 92,277 人（男性 31,053 人，女性 61,224 人）を対象として，住民健診の検査項目とその後の死亡（脳卒中，虚血性心疾患，全循環器疾患，がん，総死亡）との関連を，COX 比例ハザードモデルを用いて解析した。検査項目の 12 項目のうち，男女別に変数減少法を用いて予測項目を絞り推定モデルを決定した。

成績　2001 年までの平均 8.0 年の追跡期間に，総死亡 5,260 人（脳卒中 710 人，虚血性心疾患 389 人，がん 2,322 人）を認めた。推定モデルにおける予測因子は，男性では，総死亡に関して全項目（高齢，収縮期血圧高値，高血圧治療歴，HDL-コレステロール低値，クレアチニン低値および高値，肝機能異常，糖尿病，Body Mass Index(BMI)低値，現在喫煙，多量飲酒，尿蛋白異常）で有意な関連を示した。全循環器疾患に関しては，高齢，収縮期血圧高値，高血圧治療歴，総コレステロール低値および高値，HDL-コレステロール低値，クレアチニン高値，糖尿病，BMI 低値，現在喫煙，尿蛋白異常で，がんに関しては高齢，高血圧治療歴，HDL-コレステロール低値，クレアチニン低値，肝機能異常，糖尿病，BMI 低値，現在喫煙，多量飲酒，尿蛋白異常で有意な関連を示した。また，男性の脳卒中に関しては，高齢，収縮期血圧高値，高血圧治療歴，HDL-コレステロール低値，クレアチニン高値，肝機能異常，BMI 低値，現在喫煙で，虚血性心疾患に関しては高齢，収縮期血圧高値，総コレステロール高値，HDL-コレステロール低値，糖尿病，現在喫煙，尿蛋白異常で有意な関連を示した。女性では有意な関連を示さない項目がいくつかあったものの，選択された項目の傾向は男性とほぼ変わらなかった。

結論　脳卒中，虚血性心疾患，がんの予防の健康教育において使用できる，5 年以内の死亡率を推定する簡便なパソコン予測ツールを作成した。本ツールは受診者の動機付けに繋がり，健康教育に有用と期待される。

3．今後の研究計画

既に平成 17 年度末に，旧 38 市町村中 34 市町村の平成 16,17 年の住民基本台帳と照合作業を行い，受診後 11-12 年目までの死亡・転出者の検索を終了している。

18 年度末までに，残り 4 市町村の死亡・転出者の検索を終了する予定である。

なお，現在，平成 16,17 年の人口動態死亡票磁気テープの目的外使用を厚生労働省に申請中である。

また，平成 18 年度に研究班に提出したデータセットの内容は，平成 5 年の受診者の健診成績と平成 17 年末までの死亡日（死因を除く），転出日である。

Ⅱ．分担研究報告

1. JACC Study

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A. 研究の目的

日本人の生活習慣（例えば、喫煙習慣、食習慣、運動習慣など）は最近大きく変化している。それに伴い、がんによる死亡数、死亡率は、ともに年々増加しており、がんの有効な治療法を研究するだけでなく、日本人における適切ながん予防法を確立することが必要である。

1980 年代後半、当時の青木國雄教授（名古屋大学医学部予防医学）を中心にがんの疫学研究者が集まり、日本人におけるがん発生関連要因を大規模なコホート研究により検討することを目的に JACC Study は開始された。このコホート研究は、約 12 万人の一般住民を追跡することにより、最近の日本人の生活習慣ががんとどのように関連しているかを明らかにすることを目的としている。その後、循環器疾患の疫学研究者もコホート研究に参画し、現在では循環器疾患をエンドポイントとした追跡研究も行っている。

B. 研究対象と方法

ベースライン調査は全国 45 地区に住む住民を対象に、1988 年から 90 年の間に自記式問診票で生活習慣、既往歴などの調査を行い、調査時に 40～79 歳だった 110,792 名（男 46,465 名、女 64,327 名）を追跡対象とした。45 地区のうち、22 地区では地区内に居住する該当年齢の全ての住民を対象とし、20 地区では老人保健法に基づく基本健康診査を受診した住民を対象とした。2 地区では、基本健康診査の受診者に加えてボランティアの参加者をも対象とし、残り 1 地区は被爆者検診受診者を対象とした。ベースライン時に対象者中約 3.9 万人については血清を採取し、1 人チューブ 5 本（1 本あたり約 300 μ l）に分注し、-80℃で保管した。全ての情報は、各施設でコンピュータに電子情報として入力され、氏名や住所を除き個別の ID を付与した電子情報が事務局（名古屋大学医学部予防医学）に送付された。当時はまだ観察型の疫学研究参加に際して説明・同意手順を経ることは稀であったが、原則として、調査票の表紙に「調査への協力のお願い」として研究の説明をし、対象者に署名を依頼した。ただし、一部の地区では、地域の代表者への説明と了解の返事をもって、研究を実施した。

対照地域のうち 31 地区では、ベースライン調査から約 5 年後に中間調査を実施し、ベースライン調査対象者のうち約 5 万人の方から回答を得た。中間調査では、既往歴、食習慣や喫煙習慣について、特に 5 年間の変化に注目して調査を行った。

死亡情報は、1-2 年ごとに総務省に人口動態統計資料の目的外利用申請を行い、死亡小

票をベースに 死亡年月日、死因を把握している。対象地区からの転出は各施設で市町村と協力して調査を進めている。24 地区(対象数 63,357 名)では、地域のがん登録や主要病院への照会などにより、がんの罹患情報（部位、組織型、罹患年月日、手術の有無など)も把握する。全ての情報は氏名や住所など個人を容易に特定できる情報を外し、個別 ID を付与して事務局に送付される。このコホート研究全体については、2000 年に名古屋大学医学部倫理審査委員会で倫理審査を受け、承認を得た。

C. 研究成果

1. 閉経年齢と虚血性心疾患死亡との関連

目的：白人女性において報告のある閉経年齢と虚血性心疾患の関連を、日本人において明らかにする。

方法：文部科学省大規模コホート研究において、40～79 歳の閉経後女性 37,965 人（循環器疾患、がんの既往者除く）を対象として、1988-90 年から 1999 年末まで平均 10 年間追跡した。初経年齢、閉経年齢ならびに出産可能期間と虚血性心疾患死亡との関連について、年齢、肥満度、高血圧の既往、糖尿病の既往、喫煙状況、飲酒量、婚姻暦、教育歴および閉経種別を調整した相対危険度(95%信頼区間)を算出した。死因は ICD10 に従って分類した。

結果：10 年間の追跡期間中、全脳卒中の死亡は 487 人、虚血性心疾患は 178 人であった。初経年齢、閉経年齢並びに出産可能期間は、いずれも全体としては虚血性心疾患死亡との関連は認められなかった。しかしながら、初経年齢が 17 歳以上の者を対照とした場合、13 歳以下の者では虚血性心疾患死亡の相対危険度は 1.32(0.93-1.87, p=0.10)であった。また、対象を調査時 40-64 歳の者に限定した上で、閉経年齢が 49 歳以上の者を対照とした場合、49 歳未満の者での相対危険度は 1.85(0.92-3.73, p=0.08)であった。

結論：日本人中年女性においても、白人と同様に、早期閉経が虚血性心疾患リスクを高める可能性が示された。

Original Article

Relationships of Age at Menarche and Menopause, and Reproductive Year with Mortality from Cardiovascular Disease in Japanese Postmenopausal Women: The JACC Study

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BACKGROUND: Early menopause is associated with increased risk of coronary heart disease in Caucasian women. However, this association has not been examined in Asian women.
METHODS: We conducted a 10-year cohort study of 37,965 Japanese post-menopausal women aged 40-79 years in the Japan Collaborative Cohort (JACC) Study. Causes of death were determined based on the International Classification of Disease.
RESULTS: There were 487 mortality of stroke and 178 mortality of coronary heart disease. Late menarche or early menopause, or shorter duration of reproductive period was not associated with risk of mortality from coronary heart disease. However, compared with women with age at menarche ≤13 years, those with age at menarche ≥17 years tended to have increased risk of mortality from stroke: the multivariable hazard ratio was 1.32 (95% confidence interval [CI]: 0.93-1.87, p = 0.10). Compared with women with age at menopause of ≥49 years, those with age at menopause of <49 years tended to have increased risk of coronary heart disease among women aged 40-64 years; the multivariable hazard ratio was 1.85 (95% CI: 0.92-3.73, p = 0.08).
CONCLUSIONS: The possible association between early menopause and coronary heart disease among middle-aged women was consistent with the result of observational studies for Caucasian women, and can be explained by a protective effect of endogenous estrogen on the development of atherosclerosis.
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Key words: Coronary Disease, Cerebrovascular Disorders, Menopause, Menarche, Follow-Up Studies.

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Several prospective studies have indicated that women who experience natural menopause at an early age have a higher risk of coronary heart disease;[1-4] however, the relation between exogenous estrogen use for post-menopausal women and risk of coronary heart disease are controversial. Exogenous estrogen use for post-menopausal women has been associated with reduced risk of coronary heart disease.[5-7] On the other hand, clinical trials demonstrated no benefit of hormone replacement therapy on risk of coronary heart disease.[8,9] A recent prospective study has indicated that age at natural menopause was unrelated to stroke mortality.[10] These findings are based on studies in Caucasian women, and no study has examined the potential effect of menstrual variables on the risk of coronary heart disease among Asian women.

Previous prospective studies indicated that serum total cholesterol levels were higher in post-menopausal women and in women on hormone replacement therapy than in premenopausal women.[11,12] Endothelial dysfunction is pronounced after menopause possibly due to the reduction of endogenous estrogen.[13] Using urinary cGMP excretion, a second messenger of nitric oxide, to estimate endothelial function, we have reported that nitric oxide bioactivity declined with higher serum total cholesterol levels in a general population; this relationship was more evident among post-menopausal women.[14] Our *a priori* hypothesis was that early menopause and shorter duration of reproductive year are associated with an increased risk of mortality from coronary heart disease, and that these associations are more pronounced in younger age groups at baseline.

A large prospective cohort study with 10 years of follow-up was used to examine the relationship between a broad range of age at menarche, age at menopause, and duration of reproductive period with mortality from stroke, coronary heart disease, and total cardiovascular disease among Japanese post-menopausal women.

METHODS

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study) began in 1988-1990, when 110,792 individuals (46,465 men and 64,327 women) aged 40-79 years living in 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires about their lifestyles and medical histories, and women were also asked for age at menarche, age at menopause, and type of menopause.[15] Late menarche was defined as the age at menarche ≥17 years and early menopause was defined as the age at menopause ≤44 years. Duration of reproductive year was defined as the number of years between age at menarche and menopause. Informed consent was obtained from these individuals when they completed the questionnaire. Follow-up surveys were conducted annually to verify the vital status of the participants. We excluded 23,785 premenopausal women, and 2,577 women who had a history of stroke, coronary heart disease or cancer at baseline. Therefore, 37,965 women were enrolled in the present study.

Baseline Surveillance of Mortality from Cardiovascular Disease

Follow-up surveys were conducted annually to determine the vital status of the participants, and the investigators conducted systematic review of death certificates, all of which were forwarded to the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of deaths was coded according to the International Classification of Diseases (ICD), 9th Revision from 1988 through 1994, and 10th Revision from 1995 through 1999 for the National Vital Statistics. Registration of death is required by the Family Registration Law in Japan and is believe to be followed across Japan. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from public health centers, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. The follow-up was conducted until the end of 1999, and the average follow-up period of time for the participants was 10.0 years. The Ethics Committee of the University of Tsukuba approved the present study in advance.

Cause-specific mortality of cardiovascular disease was determined based on the ICD-9th revision and ICD-10th revision as follows: total cardiovascular disease (ICD-9th revision, codes 390 to 459, ICD-10th revision, codes I01 to I99), coronary heart disease (410 to 414, I20 to I25), total stroke (430 to 438, I60 to I69), and stroke subtypes such as subarachnoid hemorrhage (430 and I60), intraparenchymal hemorrhage (431 and I61), and ischemic stroke (433 and I63).

Statistical Analyses

Statistical analyses were based on mortality rates of stroke, coronary heart disease and total cardiovascular disease during the follow-up from 1988-90 through 1999. For each participant, follow-up was calculated from the date of filling out the baseline questionnaire through time of death, moving out of the community, or the end of 1999, whichever was first. The hazard ratio of mortality from cardiovascular disease was defined as the death rate among participants in categories of age at menarche (≤13, 14, 15, 16, and ≥17 years), age at menopause (≤44, 45-46, 47-48, 49-50, and ≥51 years), and duration of reproductive year (≤27, 28-30, 31-33, 34-36, and ≥37 years). We used categories of age at menarche ≤13 years, age at menopause ≥51 years, and duration of reproductive period ≥37 years as the reference. The category of early age at menarche and menopause or shorter duration of reproductive period was defined as the approximately lowest deciles.

Age-adjusted means and proportions of selected cardiovascular risk factors and psychological factors were presented among the categories of age at menarche, age at menopause, and duration of reproductive period, using analysis of covariance or chi-square tests. Testing for a linear trend across the age at menarche, age at menopause, and duration of reproductive period categories was

conducted by linear regression or logistic regression model, using a median variable of age at menarche, age at menopause, and duration of reproductive period in each category. The age- and multivariable-adjusted hazard ratios and the 95% confidence intervals (CIs) were calculated after adjustment for age and potential confounding factors by using the Cox proportional hazards model. The confounding variables included smoking status (never, ex-, current 1-19, and ≥20 cigarettes/day), alcohol intake categories (never, ex-, current ethanol 1-22, 23-45, 46-68, and ≥69 g/day), marital status (married, widowed, divorced, single), type of menopause (natural, surgical, or unknown), education (primary school, junior high school, high school, college or more), histories of hypertension (no, yes) and diabetes (no, yes). The analysis was repeated stratified by baseline age-subgroup (age at 40 to 64 years and age at 65 to 79 years).

RESULTS

During the 10-year follow-up of 37,965 post-menopausal women aged 40-79 years, 1,010 women died of total cardiovascular disease. These deaths included 487 from stroke including 111 subarachnoid hemorrhages, 99 intraparenchymal hemorrhages, 167 ischemic stroke, and 178 from coronary heart disease.

Table 1 shows mean age and age-adjusted mean values and prevalence of selected cardiovascular risk factors by five categories of age at menarche and menopause, and duration of reproductive period. Women with age at menarche ≥17 years were older, smoked more, were less hypertensive and diabetic, had

Table 1. Age-adjusted characteristics of 37,965 women aged 40-79 years.

	Age at menarche (year)					
	≤13	14	15	16	≥17	P for trend
No. at risk	5,595	7,336	8,578	7,387	9,069	
Age (average, year)	59.1	60	61.1	62.8	63	<0.001
Body mass index (average, kg/m²)	23.3	23	22.9	23	22.8	0.05
Smoker (%)	4.7	4.1	4.4	5.1	5.5	<0.001
History of hypertension (%)	29.7	27.7	28	27.7	25.9	<0.001
History of diabetes (%)	5.9	5.4	4.3	4.3	4	<0.001
Ethanol intake (average, g/day)	10	9.3	10	10	10.1	0.59
College or higher education (%)	11	9.6	8.8	8.5	7.8	<0.001
Married (%)	77.8	79.6	79.6	81.1	80.8	<0.001
	Age at menarche (year)					
	≤44	45-46	47-48	49-50	≥51	
No. at risk	5,084	3,975	6,274	10,209	12,423	
Age (average, year)	59.7	61.7	61.4	61.9	61.7	<0.001
Body mass index (average, kg/m²)	22.9	22.7	22.9	22.9	23.1	0.06
Smoker (%)	6.7	5.1	5	4.4	4.1	<0.001
History of hypertension (%)	27.2	24.6	26.9	27.8	29	<0.001
History of diabetes (%)	5.6	4.5	4.4	4.4	4.8	0.63
Ethanol intake (average, g/day)	12	9.9	9.2	9.4	9.7	0.001
College or higher education (%)	8.4	8.1	7.9	8.8	10.2	<0.001
Married (%)	76.8	78.6	79.3	80.4	81.5	<0.001
	Duration of reproductive period (year)					
	≤27	28-30	31-33	34-36	≥37	
No. at risk	4,204	4,387	8,298	11,731	9,345	
Age (average, year)	60.6	61.5	61.7	61.3	61.6	<0.001
Body mass index (average, kg/m²)	22.9	22.7	22.9	22.9	23.3	0.03
Smoker (%)	6.7	5.8	4.9	4.4	3.8	<0.001
History of hypertension (%)	26.4	25.2	27	27.8	29.8	<0.001
History of diabetes (%)	5.5	4.2	4.2	4.6	5.3	0.17
Ethanol intake (average, g/day)	12.2	10	9.7	9.2	9.8	0.002
College or higher education (%)	7.9	8.4	7.5	9.1	10.8	<0.001
Married (%)	78	77.9	78.8	81	81.1	<0.001

The study began in 1988 to 1990 at baseline, followed until the end of 1999.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality from cardiovascular disease according to age at menarche, menopause, and duration of reproductive period.

	Age at menarche (year)				
	≤13	14	15	16	≥17
Person-years	55,608	73,075	85,672	73,992	90,747
			Total stroke deaths		
No.	42	83	90	127	145
Age-adjusted HR (95% CI)	1.00	1.28 (0.89-1.86)	1.04 (0.72-1.50)	1.46 (1.03-2.07)	1.36 (0.96-1.92)
Multivariable HR (95% CI)	1.00	1.29 (0.89-1.88)	1.03 (0.71-1.49)	1.42 (1.00-2.02)	1.32 (0.93-1.87)
			Coronary heart disease deaths		
No.	18	21	45	36	58
Age-adjusted HR (95% CI)	1.00	0.74 (0.39-1.38)	1.15 (0.67-1.99)	0.91 (0.51-1.60)	1.19 (0.70-2.03)
Multivariable HR (95% CI)	1.00	0.77 (0.41-1.45)	1.22 (0.70-2.11)	0.98 (0.55-1.73)	1.28 (0.75-2.20)
			Total cardiovascular disease deaths		
No.	96	165	212	230	307
Age-adjusted	1.00	1.11 (0.86-1.42)	1.05 (0.82-1.34)	1.13 (0.89-1.43)	1.23 (0.97-1.54)
Multivariable HR (95%CI)	1.00	1.13 (0.88-1.45)	1.06 (0.83-1.35)	1.13 (0.89-1.44)	1.22 (0.96-1.53)
			Total stroke deaths		
	≤44	45-46	47-48	49-50	≥51
Person-years	50,463	39,803	62,599	102,134	124,094
			Total stroke deaths		
No.	67	54	104	129	133
Age-adjusted HR (95% CI)	1.19 (0.89-1.60)	1.07 (0.78-1.47)	1.40 (1.08-1.81)	1.03 (0.81-1.32)	1.00
Multivariable HR (95% CI)	1.21 (0.89-1.64)	1.08 (0.78-1.49)	1.38 (1.07-1.79)	1.01 (0.80-1.29)	1.00
			Coronary heart disease deaths		
No.	23	16	33	40	66
Age-adjusted HR (95% CI)	0.80 (0.50-1.30)	0.62 (0.36-1.08)	0.87 (0.57-1.33)	0.63 (0.42-0.93)	1.00
Multivariable HR (95% CI)	0.78 (0.47-1.29)	0.63 (0.36-1.09)	0.87 (0.57-1.33)	0.62 (0.42-0.92)	1.00
			Total cardiovascular disease deaths		
No.	139	111	190	265	305
Age-adjusted HR (95% CI)	1.07 (0.88-1.32)	0.96 (0.77-1.19)	1.12 (0.93-1.34)	0.92 (0.78-1.09)	1.00
Multivariable HR (95% CI)	1.08 (0.88-1.34)	0.97 (0.78-1.21)	1.10 (0.92-1.32)	0.91 (0.77-1.07)	1.00
	Duration of reproductive period (year)				
	≤27	28-30	31-33	34-36	≥37
Person-years	41,725	43,941	83,127	117,275	93,026
			Total stroke deaths		
No.	55	68	143	120	101
Age-adjusted HR (95% CI)	1.08 (0.77-1.50)	1.19 (0.87-1.62)	1.36 (1.06-1.76)	0.88 (0.68-1.18)	1.00
Multivariable HR (95% CI)	1.07 (0.77-1.51)	1.18 (0.86-1.61)	1.33 (1.03-1.72)	0.86 (0.66-1.13)	1.00
			Coronary heart disease deaths		
No.	20	23	39	50	46
Age-adjusted HR (95% CI)	0.83 (0.49-1.41)	0.85 (0.52-1.41)	0.79 (0.51-1.21)	0.79 (0.53-1.18)	1.00
Multivariable HR (95% CI)	0.84 (0.49-1.45)	0.86 (0.52-1.42)	0.81 (0.53-1.24)	0.80 (0.54-1.20)	1.00
			Total cardiovascular disease deaths		
No.	119	132	265	275	219
Age-adjusted HR (95% CI)	1.06 (0.85-1.33)	1.05 (0.85-1.31)	1.16 (0.97-1.38)	0.93 (0.78-1.11)	1.00
Multivariable HR (95% CI)	1.07 (0.85-1.35)	1.05 (0.85-1.31)	1.15 (0.96-1.38)	0.93 (0.78-1.11)	1.00

Multivariable adjustment: age, body mass index (kg/m^2), histories of hypertension and diabetes, current smoking, ethanol intake, marital status, college or higher school, and type of menopause.

Categories of age at menarche ≤13 years, age at menopause ≥51 years, and duration of reproductive period ≥37 years as the reference groups.

The study began in 1988-1990 at baseline, followed until the end of 1999.

Table 3. Multivariable hazard ratios (HRs) and 95% confidence intervals of mortality from coronary heart disease according to age at menopause stratified by age at the baseline survey.

	Age at menopause (year)				
	≤44	45-46	47-48	49-50	≥51
	Age at baseline survey = 40-64 years				
No	6	4	8	6	11
Multivariable HR	1.82 (0.61-5.41)	1.49 (0.47-4.75)	1.61 (0.64-4.07)	0.72 (0.27-1.97)	1.00
	Age at baseline survey = 65-79 years				
No	17	12	25	34	55
Multivariable HR	0.65 (0.37-1.15)	0.51 (0.27-0.96)	0.74 (0.46-1.19)	0.59 (0.39-0.91)	1.00

Multivariable adjustment: age, body mass index (kg/m^2), history of hypertension and diabetes, current smoking, ethanol intake, marital status, college or higher school, and type of menopause.
The study began in 1988-1990 at baseline, followed until the end of 1999.

lower mean body mass index and lower education level compared with those with lower age at menarche categories. Women with age at menopause ≥51 years were older and more hypertensive, had a higher level of education, and were more likely to be married, but smoked less compared with those in lower age at menopause categories. Women with a longer duration of reproductive period were older and more hypertensive, had higher mean body mass index, and were higher education level, and were more likely to be married, but smoked less.

Table 2 shows age- and multivariable-adjusted hazard ratios of mortality from stroke, coronary heart disease, and total cardiovascular disease according to age at menarche and menopause, and duration of menstruation. Women with age at menarche ≥17 years had tented to increase risk of mortality from stroke; the respective multivariable hazard ratio was 1.32 (95% CI: 0.93-1.87, p = 0.10). The risk of mortality from coronary heart disease and total cardiovascular disease was not significantly increased among women with later ages at menarche. Also, women with later ages at menarche were not at an increased risk of mortality from intraparenchymal hemorrhages, subarachnoid hemorrhages, or ischemic stroke (not shown in the table).

Early menopause was not associated with the higher risk of mortality from stroke, coronary heart disease, or total cardiovascular disease. No significant association was observed between the duration of menstruation and mortality from stroke, coronary heart disease, and total cardiovascular disease. The proportion of menopause by surgery was 8.5% (3,242/37,965) among total subjects. When we excluded them from the analyses, the results did not change materially (not shown in the table).

The associations between age at menopause and coronary heart disease were further examined when stratified by age at baseline survey (Table 3). We found no excess risk of mortality associated with early menopause in either subgroup of ages 40-64 and 65-79 years. However, compared to women with age at menopause ≥49 years, those with age at menopause <49 years tended to have increased risk of mortality from coronary heart disease in the age subgroup of 40-64 years, but not in the older ages: the multivariable hazard ratio was 1.85 (95% CI: 0.92-3.73, p = 0.08) and 0.84 (95% CI: 0.60-1.19, p = 0.32), respectively.

DISCUSSION

In this large prospective study of Japanese menopausal women, late age at menarche tended to be associated with increased risk of mortality from stroke among total subjects aged 40 to 79 years, and early menopause tended to be associated with increased risk of mortality from coronary heart disease among younger ages of 40 to 64 years.

Mechanisms for the possible association between late menarche and stroke are not clear at present. Women with late age at menarche were older, smoked more, and were less educated in the present study. These characteristics have been associated with risk of stroke among Japanese.[16-20] One-year case-fatality of ischemic stroke was 2-fold higher for Finnish women with lower income and 3-fold higher in those with lower education than those with higher socioeconomic status.[21] A follow-up study showed that women with late age at menarche were likely to have lower body mass index and to be less obese among women aged 45 to 52 years.[22] Further, our recent prospective study indicated that women with body mass index <18.5 kg/m^2 had 2-fold higher risk of mortality from total stroke.[23] Other potential confounding socioeconomic conditions such as income levels, which were not examined in the present study, may explain the association. Alternatively, the association could be due to chance.

Previous case-control studies reported that age at menarche (<13 vs. ≥13 years, or <15 vs. ≥15 years old) was associated with the 2-to 3-fold higher prevalence of subarachnoid hemorrhage,[24,25] and the 5-fold higher prevalence of intraparenchymal hemorrhage.[25] However, the present study showed that earlier age at menarche was not significantly associated with the risk of mortality form subarachnoid hemorrhage or intraparenchymal hemorrhage.

Early menopause tended to increase the risk of mortality from coronary heart disease among post-menopausal women aged 40 to

64 years, but not among those aged 65 to 79 years in the present study. This result is consistent with the finding that early menopause was associated with higher risk of mortality from coronary heart disease among American and European women.[1,2,26] In studies of Norwegian and Dutch women, this association was more evident in women of younger ages than those of older ages.[1,26] One of the reasons for the larger impact of early menopause at younger ages may be a longer duration of elevated serum total or LDL-cholesterol levels along with endogenous estrogen depletion.[27] Depletion of estrogen itself may have an adverse effect of the development of atherosclerosis due to endothelial dysfunction[13,28] and increased platelet aggregability.[29]

Observational studies have reported that the use of hormone replacement therapy was associated with reduced risk of coronary heart disease.[5-7] Clinical trials, however, demonstrated no benefit of hormone replacement therapy on the risk of coronary heart disease.[8,9] However, a potential benefit of estrogen therapy was found for young postmenopausal women aged 50-59 years.[9]

In the Nurses Health Study, early menopause was associated with a higher risk of coronary heart disease among current smokers, but not among never-smokers.4 This interaction was not found in the present study, where a very low prevalence (5%) of current smoking in our cohort made it difficult to evaluate the interaction reliably.

The strengths of the present study include its prospective design and large sample size. The limitations are that first we used the self-report of age at menarche and menopause. We did not test the reliability of these variables. However, previous studies using two-year repeated questionnaires showed that 81 to 88% of post-menopausal women reported concordant responses for age at menarche[30] and for age at menopause.[30,31] Second, we excluded 23,785 premenopausal women at baseline: 94.3% of these women were aged 40-64 years. Thus, for the younger age group, women with an early menopause would be over represented in the data set analyzed. This, however, is unlikely to introduce a serious bias in the evaluation of association between age at menopause and cardiovascular disease because the actual distribution of exposure variables may be irrelevant for the evaluation.

Mechanisms for the association between late menarche and mortality from stroke are uncertain, and could be due to chance. The possible association between early menopause and coronary heart disease among young women in the present study was consistent with the results in Caucasian women, which can be explained by a protective effect of endogenous estrogen on the development of atherosclerosis.

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2. 血清総コレステロール値と脳卒中・虚血性心疾患死亡リスク

目的：血清総コレステロール値の高値が虚血性心疾患リスクを高めることは既に確立した知見であるが、脳卒中並びに病型別脳卒中リスクとの関連は一定していない。本研究ではJACC 研究の一部して、nested case-control study の手法を用いた分析を行った。

方法：文部科学省大規模コホート研究において、40～79 歳の男女 38,158 人（男性 13,382 人、女性 24,776 人、循環器疾患、がんの既往者除く）を対象として、1988-90 年から 1999 年末まで平均 10 年間追跡した。その間に発生した脳卒中死亡者 345 人（うち脳出血死亡者 76 人）、虚血性心疾患死亡者 150 人に対して、性、年齢、地域、採血年度を 1:1 で一致させた対照集団を設定した。血清総コレステロール値と脳卒中・虚血性心疾患死亡の関連については、収縮期血圧値、HDL コレステロール値、飲酒量、喫煙状況及び糖尿病を調整したオッズ比(95%信頼区間)を算出した。死因は ICD10 に従って分類した。

結果：脳卒中、とりわけ脳出血の患者では、対照群に比べて血清総コレステロールの平均値が低かった。脳出血のオッズ比は、血清総コレステロール値が 160mg/dl 未満の群において、それ以上の群よりも高かった。一方、虚血性心疾患については、血清総コレステロールが 160mg/dl 未満の群を対照とした場合、260mg/d 以上の群において、オッズ比が有意に高かった。

考察：血清総コレステロールの低値は脳出血の死亡と関連する一方、高値は虚血性心疾患の死亡リスクを高めることが日本人において明らかとなった。

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Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: The JACC study

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Abstract

The relation between serum total cholesterol and coronary heart disease is well established, but the relations with total stroke and stroke subtypes are controversial. We conducted a nested case–control study as part of the JACC study. A total of 39,242 subjects, 40–79 years of age, provided serum samples at baseline between 1988 and 1990. During the 10-year follow-up, 345 deaths from total strokes (including 76 intraparenchymal hemorrhages) and 150 deaths from coronary heart diseases were recorded. The control subjects were matched for sex, age, community, and year of serum storage, and further adjusted for systolic blood pressure, high density lipoprotein (HDL)-cholesterol, ethanol intake category, smoking status, and diabetes. Serum total cholesterol levels were measured using an enzymatic method. Cases with total stroke and more specifically intraparenchymal hemorrhage had lower mean values of serum total cholesterol levels compared with control subjects. The risk of mortality from intraparenchymal hemorrhage was significantly higher for persons with low total cholesterol levels [less than 4.14 mmol/l (160 mg/dl)] than with those with higher levels. The risk of mortality from coronary heart disease for persons with serum total cholesterol levels more than or equal to 6.72 mmol/l (260 mg/dl) was significantly higher than those with levels less than 4.14 mmol/l (160 mg/dl). Low serum total cholesterol levels are associated with high mortality from intraparenchymal hemorrhage while high levels are associated with high mortality from coronary heart disease among Japanese.

Keywords: Stroke; Coronary heart disease; Total cholesterol; Follow-up studies

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1. Introduction

It is well known that high serum total cholesterol levels correlate positively with increased risk of coronary heart disease [1,2]. However, the relations with stroke and stroke subtypes are controversial. Prospective studies of Americans [3], Europeans [4], and Japanese-American men [5] indicate a positive association between serum cholesterol concentration and risk of ischemic stroke. While a study of Japanese showed no association of serum total cholesterol with risk of ischemic or total stroke [6]. On the other hand, prospective studies of Japanese men and women [7], Japanese-American men [8], American men [3], elderly American men [9], Swedish women [10], and Scottish men and women [11], but not all [12] showed that serum total cholesterol levels was inversely associated with risk of intraparenchymal hemorrhage.

The aim of present study was to examine comprehensively the relationships between serum cholesterol levels and mortality from total stroke, stroke subtypes, and coronary heart disease among Japanese men and women. We conducted a nested control-study in a large prospective cohort study.

2. Methods

2.1. Surveyed populations

We carried out a nested case–control study as part of the Japan collaborative cohort study for evaluation of cancer risk sponsored by Monbusho (JACC study), which began in 1988–1990, in which 110,792 individuals (46,465 men and 64,327 women, age 40–79 years) living in 45 areas across Japan, participated in municipal health screening examinations and completed self-administered questionnaires about their lifestyles and medical histories of previous cardiovascular disease and cancer [13]. Informed consent was obtained from the participating individuals when they completed the questionnaire, and a total of 39,242 subjects (13,839 men and 25,403 women) from 37 areas, i.e. 35.4% of total subjects in 45 areas have agreed to provide blood samples. Subsequently, we excluded 457 men and 627 women who had a history of cardiovascular disease or cancer at baseline. Thus, a total of 38,158 subjects (13,382 men and 24,776 women) were enrolled in the present study. The Ethics Committee of the University of Tsukuba approved the present study.

2.2. Mortality surveillance

The participants were followed up to determine mortality of cardiovascular disease occurring by the end of 1999. For mortality surveillance in each community, investigators conducted systematic review of the death certificates, all of which were forwarded to the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of death was coded according to the *International Classification of Diseases* (*ICD*), 9th revision, for deaths from 1988 to 1994, and the 10th revision from deaths from 1995 to 1999 for the National Vital Statistics. Registration of death is required by the Family Registration Law in Japan and is believed to be followed across Japan. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case.

The cause-specific mortality of cardiovascular disease was determined based on the ICD-9th revision and ICD-10th revision as follows: total stroke (ICD-9th revision, codes 430–438; ICD-10th revision, codes I60–I69); coronary heart disease (410–414, I20–I25). Further subgrouping of total strokes was also conducted as follows: intraparenchymal hemorrhage (431, I61), subarachnoid hemorrhage (430, I60) and ischemic stroke (433–434, I63). For each case, one control subject was selected randomly from participants without mortality from stroke or coronary heart disease, matched for sex, age (±2 years) community, and year of serum storage at serum collection.

2.3. Determination of biochemical variables

The venous blood was collected at baseline, and serum was prepared from blood samples as soon as possible after blood collection at laboratories in near the surveyed municipalities. For each participant, the serum was divided into 3–5 tubes (100–500 μl per tube). Fasting status at the time of blood was not recorded and the serum was stored for 13–15 years at −80 °C. Serum total cholesterol and HDL-cholesterol were measured using enzymatic method by an automatic analyzer (Hitachi 7600-210, Hitachi Medical Corp., Hitachi, Japan) in Kotobiken Medical Laboratories, Inc., Ibaraki-ken, Japan, by trained staff blinded to case–control status. The standardization of lipid measurement was performed through the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN) [14].

2.4. Statistical analysis

We tested the interaction of serum total cholesterol levels with sex by using an interaction term generated by multiplying the cholesterol levels with sex. There were, however, no significant interactions between them (p for interaction, >0.05). Thus, we analyzed association between serum total cholesterol levels with cardiovascular disease for total subjects, adjusting for sex.

The paired Student's t-test was used to compare the mean values of baseline cardiovascular risk factors and serum total cholesterol levels between mortality cases and control subjects. The χ^2-test was used to compare proportions of cases and control subjects. The odds ratios of total stroke, stroke subtype, and coronary heart disease were estimated according to seven categories of serum total cholesterol

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