図7

アルバータ腎臓病ネットワーク研究

カルガリー大学が構築した組織で可能なこと

病院、健診機関、などの保有する個人情報を基に把握した住民の健康状況（人種、社会的階層、高血圧、肥満、脂質異常、慢性腎臓病etc）が将来の死亡、疾患発症（心筋梗塞、脳卒中、透析患者）や医療費支出にどのように影響するのかを定量的に評価することを、アルバータ州在住住民で可能にした。

図8

個人情報保護対策
（英語を日本語に直訳）

アルバータ腎臓病ネットワーク（AKDN)では、個人情報保護のために種々の厳しい規制を実施しているが、主だった内容を簡単に列挙する

- AKDNデータベース利用に関しては、研究者権利と、データベース情報源の権限について、文書による徹底した確認作業を実施している

- 個人情報保護法に則って、下記行動規範を徹底している
  - 研究者への供給データは必ず匿名化実施ずみのものを用いる
  - カルガリー大学資料室内の蓄積データは、電子施錠された外部者立ち入り禁止地区内に置かれ、24時間のビデオ監視カメラが設置されている。また入室者は、署名をした上で入室のためのカードキーを受け取る。
  - サーバーは外部との接続が遮断されたセキュリティーゾーン内に設置され、プライベートネットワークアクセス権限のない者にはアクセス権が認められない。

図9

茨城県立健康プラザとその沿革

茨城県健康研究では、茨城県立健康プラザが市町村・県・国保連・研究者との連携を行い、研究事業の円滑な推進に大きく寄与しているとともに、報告書作成、保健教育教材作成、学術成果報告業務を担っている。

沿革:

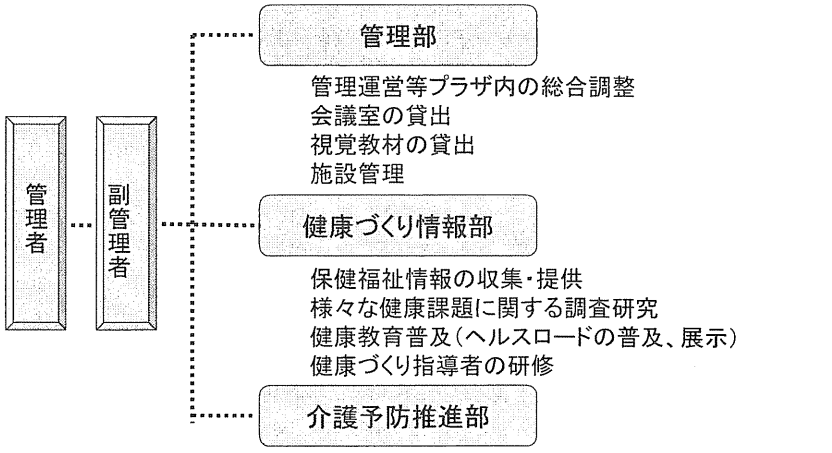
●平成3年4月　茨城県健康科学センター開設
（21世紀の超高齢化社会を迎えるにあたり、県民の健康づくりを積極的に推進するための中核施設として開設。）
水戸保健所・衛生研究所・精神保健福祉センター・茨城県健康科学センターは同一の敷地内で予防医学プラザを構成

●平成17年4月　茨城県健康科学センターから茨城県立健康プラザに名称変更（新たに介護予防推進事業を加えた）

●平成18年4月　健康プラザの管理・運営業務を「（財）茨城県総合健診協会」による指定管理事業とした

図10

茨城県立健康プラザ概要：組織と業務



H23年現在職員は22名

図11

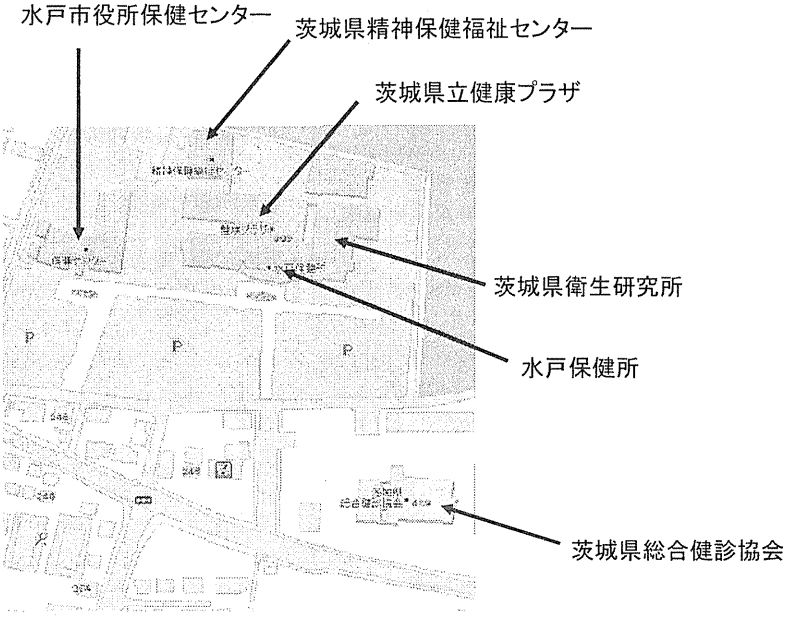


図12

茨城県健康研究

Ibaraki Prefectural Health Study

（事業名：健診受診者生命予後追跡調査事業，他）

- 茨城県内38市町村の基本健康診査受診者9万8千人を対象とした前向きコホート調査
- 地域の健康管理上の課題を明らかにして、健診の事後指導、健康教育を効果的に進めるための基礎資料を得ることを目的として平成10年度着手
- 県の主導で行なった調査としては、全国初の大規模な疫学調査

図13

研究組織（事業実施体制）

茨城県保健福祉部保健予防課	予算管理、体外的調整
健康いばらき推進協議会 健診受診者生命予後追跡調査事業検討部会	事業内容の検討
茨城県立健康プラザ	集計解析、報告書作成、事業の企画
共同研究機関 自治医科大学、筑波大学、独協医科大学、大阪大学、国立環境研究所 市町村 保健所 健診機関 （財）茨城県総合健診協会 （財）日立メディカルセンター 取手北相馬保険医療センター取手医師会病院 茨城県国民健康保険団体連合会	

図14

茨城県における基本健康診査の委託先（集団検診分、平成5年度）

市町村の健診の9割を3つの健診機関が受託

平成5年度以降毎年25万人の健診情報が電子化されて保存

（財）日立メディカルセンター
8市町村　3.2万人

（財）茨城県総合健診協会
73市町村　21.1万人

北相馬保険医療センター取手医師会病院
4市町村　1.4万人

図15

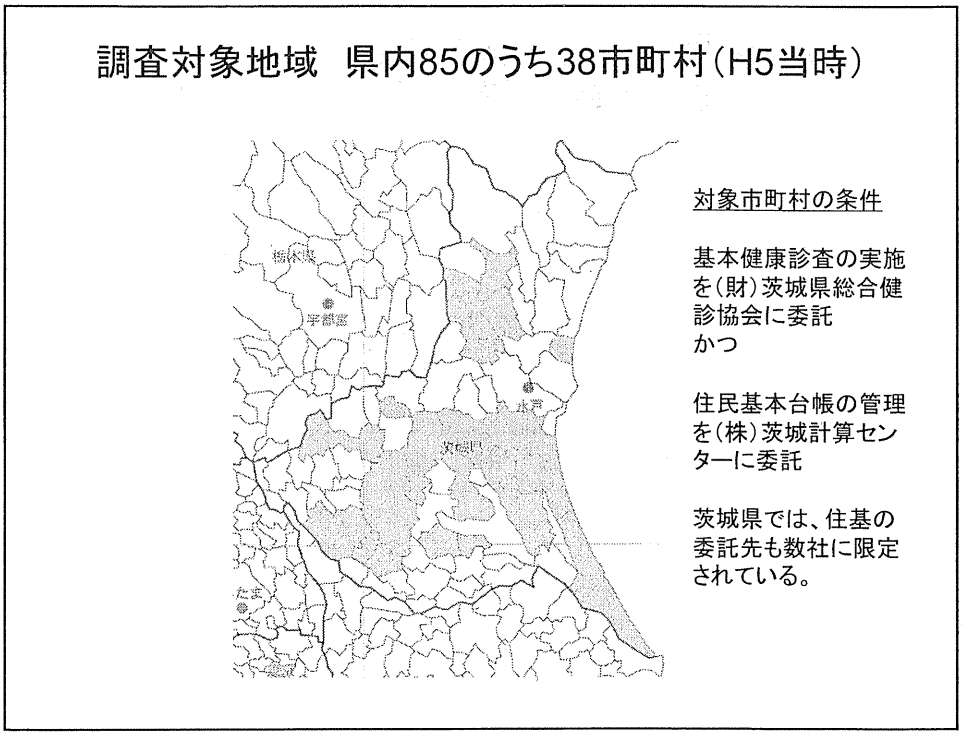

調査対象地域　県内85のうち38市町村（H5当時）
対象市町村の条件
基本健康診査の実施を（財）茨城県総合健診協会に委託
かつ
住民基本台帳の管理を（株）茨城計算センターに委託
茨城県では、住基の委託先も数社に限定されている。

図16

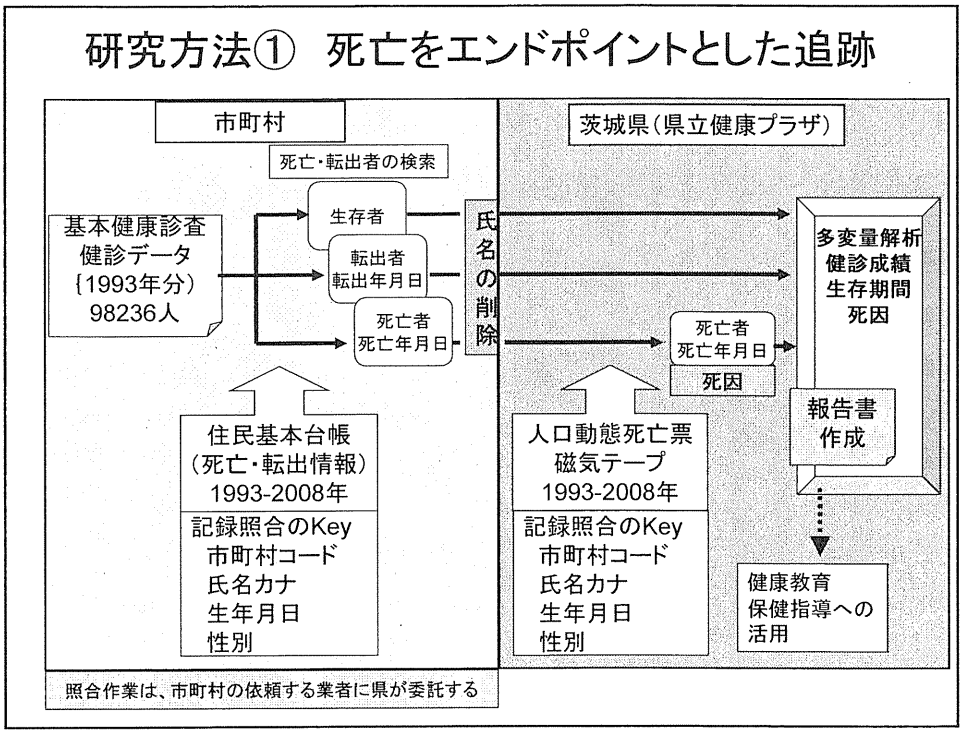
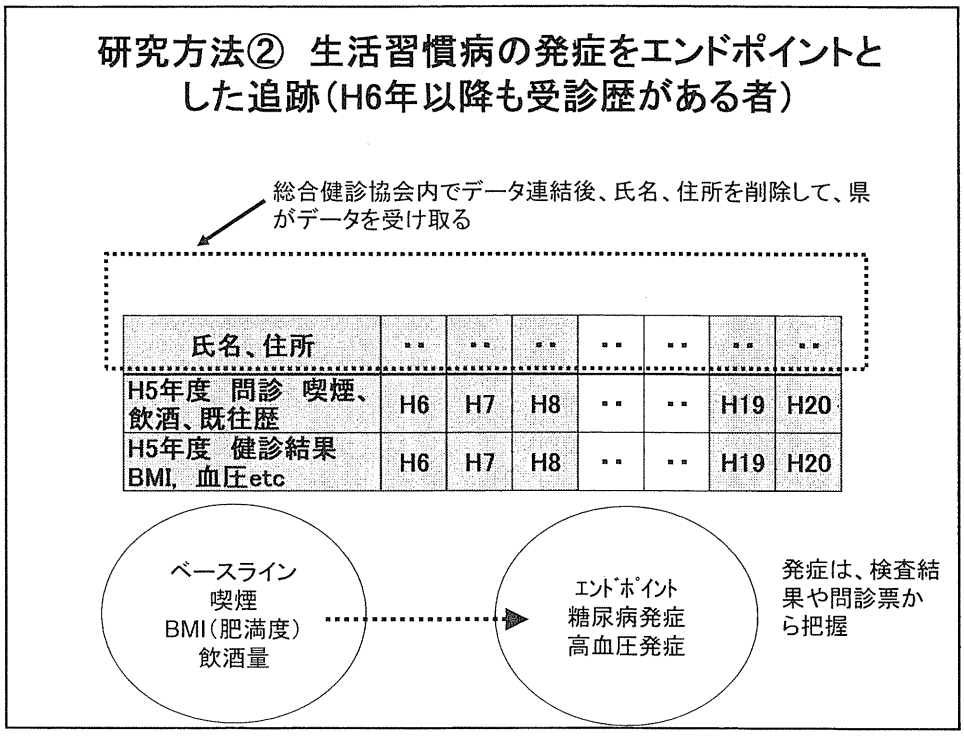

研究方法①　死亡をエンドポイントとした追跡
市町村
死亡・転出者の検索
基本健康診査
健診データ
(1993年分)
98236人
生存者
転出者
転出年月日
死亡者
死亡年月日
氏名の削除
住民基本台帳
(死亡・転出情報)
1993-2008年
記録照合のKey
市町村コード
氏名カナ
生年月日
性別
茨城県（県立健康プラザ）
死亡者
死亡年月日
死因
人口動態死亡票
磁気テープ
1993-2008年
記録照合のKey
市町村コード
氏名カナ
生年月日
性別
多変量解析
健診成績
生存期間
死因
報告書
作成
健康教育
保健指導への
活用
照合作業は、市町村の依頼する業者に県が委託する

図17


研究方法② 生活習慣病の発症をエンドポイントとした追跡(H6年以降も受診歴がある者)
総合健診協会内でデータ連結後、氏名、住所を削除して、県がデータを受け取る
氏名、住所
H5年度 問診 喫煙、飲酒、既往歴
H5年度 健診結果 BMI, 血圧etc
H6
H7
H8
H19
H20
ベースライン
喫煙
BMI(肥満度)
飲酒量
ｴﾝﾄﾞﾎﾟｲﾝﾄ
糖尿病発症
高血圧発症
発症は、検査結果や問診票から把握

Ⅲ．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

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yokokawa H, Yasumura S, Tanno K, Ohsawa M, Onoda T, Itai K, Sakata K, Kawamura K, Tanaka F, Yoshida Y, Nakamura M, Terayama Y, Ogawa A, Okayama A.	Serum low-density lipoprotein to high-density lipoprotein ratio as a predictor of future acute myocardial infarction among men in a 2.7-year cohort study of a Japanese northern rural population.	J Atheroscler Thromb	18	89-98	2011
Fujishima Y, Ohsawa M, Itai K, Kato K, Tanno K, Turin TC, Onoda T, Endo S, Okayama A, Fujioka T.	Serum selenium levels in hemodialysis patients are significantly lower than those in healthy controls	Blood Purification	32	43-47	2011
Koeda Y, Nakamura M, Tanaka F, Onoda T, Itai K, Tanno K, Ohsawa M, Makita S, Ishibashi Y, Koyama T, Yosida Y, Omama S, Ogasawara K, Ogawa A, Kuribayashi T, Okayama A.	Serum C-reactive protein levels and death and cardiovascular events in mild to moderate chronic kidney disease.	Int Heart J	52	180-4	2011
大澤　正樹, 板井　一好, 丹野　高三, 藤島　洋介, 加藤　香廉, 岡山　明, 遠藤　重厚, 小野田　敏行, 坂田　清美, 中村　元行, 栗林　徹, 藤岡　知昭.	透析患者の血清中ヒ素濃度の検討-健常対照との比較、血清ヒ素濃度が心筋梗塞ならびに虚血性脳卒中罹患リスクに与える影響	日循予防誌	46巻1号	180-196	2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Fujishima Y, Ohsawa M, Itai K, Kato K, Tanno K, Turin TC, Onoda T, Endo S, Okayama A, Fujioka T.	Serum selenium levels are inversely associated with death risk among hemodialysis patients.	Nephrol Dial Transplant	26	3331-8	2011
Ohsawa M, Kato K, Tanno K, Itai K, Fujishima Y, Okayama A, Turin TC, Onoda T, Suzuki K, Nakamura M, Kawamura K, Akiba T, Sakata K, Fujioka T.	Seropositivity for anti-HCV core antigen is independently associated with increased all-cause, cardiovascular, and liver disease-related mortality in hemodialysis patients.	J Epidemiol	21	491-499	2011
Nakamura M, Tanaka F, Takahashi T, Makita S, Ishisone T, Onodera M, Ishibashi Y, Itai K, Onoda T, Ohsawa M, Tanno K, Sakata K, Shinichi O, Ogasawara K, Ogawa A, Kuribayashi T, Okayama A.	Sex-specific threshold levels of plasma B-type natriuretic peptide for prediction of cardiovascular event risk in a Japanese population initially free of cardiovascular disease.	Am J Cardiol	108	1564-9	2011

Ⅳ．研究成果の刊行物・別冊

Original Article

Serum Low-Density Lipoprotein to High-Density Lipoprotein Ratio as a Predictor of Future Acute Myocardial Infarction Among Men in a 2.7-Year Cohort Study of a Japanese Northern Rural Population

Hirohide Yokokawa[1], Seiji Yasumura[1], Kozo Tanno[2], Masaki Ohsawa[2], Toshiyuki Onoda[2], Kazuyoshi Itai[2], Kiyomi Sakata[2], Kazuko Kawamura[3], Fumitaka Tanaka[4], Yuki Yoshida[5], Motoyuki Nakamura[4], Yasuo Terayama[6], Akira Ogawa[7], and Akira Okayama[8]

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[2]Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Morioka, Japan
[3]Iwate Health Service Association, Morioka, Japan
[4]Division of Cardiology, Department of Internal Medicine and Memorial Heart Center, School of Medicine, Iwate Medical University, Morioka, Japan
[5]Department of Critical Care Medicine, School of Medicine, Iwate Medical University, Morioka, Japan
[6]Division of Neurology, Department of Internal Medicine, School of Medicine, Iwate Medical University, Morioka, Japan
[7]Department of Neurosurgery, School of Medicine, Iwate Medical University, Morioka, Japan
[8]The First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo, Japan

Aim: To examine and compare the predictive value of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TC/HDL-C and LDL-C/HDL-C ratios for future cardiovascular outcomes in the general Japanese population.
Methods: A total of 24,566 eligible participants aged 18 years or older, without cardiovascular disease, were enrolled through multiphase health screening and divided into quartile groups based on lipoprotein levels or ratios. Primary endpoints of the study were definitive acute myocardial infarction (AMI) and ischemic stroke, and cases of sudden death with unknown causes were not included. We used Cox proportional hazard models to examine the relationships between the quartiles and incidences of AMI or ischemic stroke, adjusting for traditional risk factors.
Results: Mean age was 63.7 years for males and 60.7 years for females. Mean follow-up period was 2.7 years, and 40 cases of AMI and 182 cases of ischemic stroke were recorded. The hazard ratio (HR) for AMI was significantly higher in the top quartile of the LDL-C/HDL-C ratio and LDL-C levels, and third quartile of TC among male participants. The HR of male participants with a LDL-C/HDL-C ratio of 2.6 or higher was significantly higher than other quartiles. No association between lipoprotein levels or their ratio quartiles and ischemic stroke was seen for either sex after adjusting for risk factors.
Conclusions: Our results indicated that the LDL-C/HDL-C ratio is an independent predictor for AMI, and the importance of better management of cardiovascular risks among people with high LDLC/HDLC ratios for the prevention of future cardiovascular disease.

J Atheroscler Thromb, 2011; 18:89-98.

Key words; Epidemiology, Acute myocardial infarction, Atherosclerosis, Risk factor, Cholesterol

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Accepted for publication: September 2, 2010

Introduction

According to the World Health Organization, cardiovascular disease was the most common cause of death worldwide in 2005, accounting for approximately 30% of all deaths[1]. Among individuals 60 years of age or older, the main cause of death was isch-

emic heart disease, followed by cerebrovascular disease[2]. Prevention of cardiovascular disease (CVD), which includes cardiovascular and cerebrovascular disorders, is emphasized in both developed and developing countries[1, 2].

Dyslipidemia is an independent risk factor that contributes to the increase of CVD and death[3, 4]. Epidemiological studies[5, 6] have conclusively linked high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) with CVD incidence and mortality. The positive association between the LDL-C level and risk has been confirmed in a lipid-lowering randomized trial[7]. Current guidelines for the prevention of atherosclerotic disorders recommend specific target levels of lipid profiles to determine CVD risk and to evaluate the effectiveness of lipid-lowering therapies[8, 9]. Accordingly, LDL-C and HDL-C measurements are included in the standard health check-up supported by the Japanese government.

In recent years, additional indicators of CVD based on standard serum lipid profiles have been introduced[5, 10]. For instance, the total cholesterol (TC)/HDLC ratio is a useful and simple index of CVD risk[11]. Furthermore, the LDL-C/HDL-C ratio more accurately predicts CVD risk than LDL-C or HDL-C levels[5, 12]. In a large-scale intervention trial, a change in this ratio was a better indicator of successful CVD risk reduction[13]. Although previous studies have investigated the association between levels and the ratios of various lipoproteins and CVD risk[10, 12-14], only a few reports have evaluated the clinical utility of various lipid measures to predict CVD in Japan.

The aims of our study were to examine and compare the relationships between levels of TC, HDL-C, LDL-C, ratios of TC/HDL-C and LDL-C/HDL-C, and future cardiovascular outcomes among rural Japanese residents.

Methods

Study Participants

This study was part of the large population-based prospective Iwate Kenpoku Cohort study (Iwate-KENCO study) and a government-sponsored, multiphase health check-up program in the northern part of the Japanese main island. Survey methods have been described in detail previously[15, 16].

The baseline survey was conducted from April 2002 to January 2005. Participants were recruited from the community-dwelling population living in the Ninohe, Kuji and Miyako districts of Iwate prefecture, which include 17 municipalities. During the survey period, individuals in these municipalities were invited to participate in multiphase health screening. A total of 31,318 residents (11,003 males and 20,315 females) aged 18 years or older participated in the annual health check-up. We obtained written informed consent from 26,469 of these residents. After excluding 1,903 participants due to a self-reported history of CVD, medical history of CVD confirmed by the Northern Iwate Heart Disease Registry Consortium (NIHDRC) database and the Iwate Stroke Registry (ISR) database[17], taking lipid-lowering medications, and missing data for lipid-related items, we included 24,566 (8,714 males and 15,852 females) in the present analysis.

The study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the Declaration of Helsinki[18].

Measurements

We measured height and weight, and calculated body mass index (BMI) using the following equation: BMI = body weight (kg)/height $(m)^2$. Blood pressure was measured twice in a sitting position after urination and a five-minute rest. Measurements were performed by well-trained staff using automatic devices, and the average of the two measurements was reported for systolic and diastolic blood pressures (SBP and DBP).

Self-administered questionnaires were used in the baseline survey to obtain demographic characteristics, history of cardiovascular disease, cerebrovascular disease, medication use, alcohol consumption, tobacco smoking and exercise habits.

Biochemical Analysis

Fasting or casual blood samples were collected from the antecubital vein, transferred to a laboratory and analyzed the same day. Serum total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels were measured by enzymatic methods. Serum low-density lipoprotein cholesterol (LDL-C) was measured by the enzymatic homogenous assay, Cholestest-LDL (Daiichi Chemicals Co. Ltd, Tokyo, Japan). These lipid profiles were measured by Iwate Health Service Association. These measurements have been standardized by the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN) controlled by the CDC (Centers for Disease Control and Prevention, Atlanta, USA), and have met all criteria for both the precision and accuracy of lipid measurements.

We measured plasma glucose concentrations by the hexokinase ultraviolet method using an automated analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). Glycosylated hemoglobin A1c (HbA1c) levels were determined by high-performance liquid chromatography using an automated analyzer (Tosoh Corporation, Tokyo, Japan).

We determined serum levels of high-sensitivity C-reactive protein (hs-CRP) using the latex-enhanced immunonephelometric method (Dade Behring, Germany). The detection limit of the hs-CRP assay is 0.1 mg/L and results below the limit of detection were reported as 0.1 mg/L.

Outcome Measures

The primary endpoints of this study were the incidence of definitive acute myocardial infarction (AMI) or ischemic stroke, while cases of sudden death of unknown cause were not included as cardiovascular endpoints. Investigators reviewed the population register of each local government and confirmed dates of death and locations to which participants had relocated. Persons known to be alive at the end of follow-up and those who had moved away from the study areas were treated as censored cases[16]. We confirmed that approximately 99.9% of participants who were registered at the baseline were alive. Incidences of AMI among participants were confirmed by assessing the Northern Iwate Heart Disease Registry Consortium (NIHDRC) database, in which definitive AMI cases were determined based on the criteria of the MONICA study. Incidences of ischemic stroke were confirmed by accessing the Iwate Stroke Registry (ISR) database[17].

Statistical Analysis

For each sex, we determined the prevalence (for categorical variables) and mean and standard deviation (for continuous variables). Participants were categorized as follows: LDL-C/HDL-C ratio quartiles (Q1 <1.6, Q2 ≥ 1.6-<2.1, Q3 ≥ 2.1-<2.6, Q4 ≥ 2.6), TC level (mg/dL) quartiles (Q1 <180, Q2 ≥ 180-<200, Q3 ≥ 200-<220, Q4 ≥ 220), LDL-C level (mg/dL) quartiles (Q1 <100, Q2 ≥ 100-<120, Q3 ≥ 120-<140, Q4 ≥ 140), HDL-C level (mg/dL) quartiles (Q1 <50, Q2 ≥ 50-<60, Q3 ≥ 60-<70, Q4 ≥ 70) and TC/HDL-C ratio quartiles (Q1 <2.8, Q2 ≥ 2.8-<3.4, Q3 ≥ 3.4-<4.1, Q4 ≥ 4.1). Significance was estimated using the Kruskal-Wallis test for continuous items and the Chi-square test or Fisher's exact test for categorical items among quartiles.

Disease-free survival curves for AMI or ischemic stroke cases based on lipid profiles and their ratio quartiles were determined using Kaplan-Meier methods. Age- and multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were computed using Cox proportional hazard models. To estimate adjusted HR, we included age (10 years increase), current smoking status (yes or no), SBP, BMI, uric acid and HbA1c in the multivariate adjusted models from our previous report[15].

All significance tests were two-sided and p values <0.05 were considered significant. All data were analyzed using SPSS version 16 (SPSS Inc., Chicago, USA).

Table 1. Characteristics of participants at baseline

	N (%) or mean (SD)	
	Male (n=8,714)	Female (n=15,852)
Age (years)	63.7 (11.5)	60.7 (11.7)
Body mass index	23.9 (3.0)	24.0 (3.5)
Systolic blood pressure (mmHg)	130.6 (19.6)	125.0 (20.2)
Diastolic blood pressure (mmHg)	78.3 (11.1)	73.6 (11.2)
Total cholesterol (mg/dL)	190.7 (32.5)	204.3 (32.5)
Triglyceride (mg/dL)	124.8 (83.5)	111.1 (66.7)
HDL-C (mg/dL)	55.9 (15.2)	61.2 (14.3)
LDL-C (mg/dL)	113.3 (29.2)	122.9 (28.9)
HbA1c (%)	5.14 (0.73)	5.09 (0.64)
Hypertension (%)	2263 (26.0)	3875 (24.4)
Diabetes mellitus (%)	610 (7.0)	551 (3.5)
Current smoking (%)	2714 (31.1)	471 (3.0)
Regular alcohol consumption (%)	5276 (60.5)	1912 (12.1)

Results

Table 1 shows the characteristics of study participants. Mean age was 63.7 years for males and 60.7 years for females. The proportions of hypertension were 26.0% for males and 24.4% for females, and 7.0% and 3.5% for diabetes mellitus. Mean follow-up period was 2.7 years. During the survey period, 35 males and 5 females suffered from AMI, and 114 males and 68 females suffered from ischemic stroke. We could not estimate a survival curve for AMI for females due to its low incidence.

The LDL-C/HDL-C ratio-specific characteristics at baseline among male participants are shown in **Table 2**. BMI, HbA1c, uric acid, TC, TG, LDL-C and hs-CRP were significantly correlated with higher LDL-C/HDL-C ratio quartiles. In contrast, the proportion of participants who regularly consumed alcohol and HDL-C seemed to be inversely correlated

Table 2. LDL-C/HDL-C ratio-specific characteristics among male participants at baseline (n=24566)

LDL-C/HDL-C ratio	N (%) or mean (SD)				p^a
	Q1 <1.6 (n=2277)	Q2 ≥1.6-<2.1 (n=2125)	Q3 ≥2.1-<2.6 (n=1818)	Q4 ≥2.6 (n=2494)	
Age (years)	63.7 (11.6)	64.1 (11.5)	63.6 (11.6)	63.5 (11.4)	0.13
Body mass index (kg/m^2)	22.7 (2.8)	23.6 (2.9)	24.3 (2.9)	25.0 (2.8)	<0.01
Current smoking	758 (33.3)	624 (29.4)	523 (28.8)	809 (32.4)	<0.01
Regular alcohol consumption	1774 (77.9)	1346 (63.3)	1065 (58.6)	1091 (43.7)	<0.01
Systolic blood pressure (mmHg)	131.0 (20.3)	130.3 (19.4)	130.3 (19.5)	130.8 (19.1)	0.53
Diastolic blood pressure (mmHg)	78.2 (11.5)	78.0 (11.0)	78.2 (10.8)	78.6 (11.0)	0.44
Antihypertensive medication	566 (24.9)	516 (24.3)	453 (24.9)	605 (24.3)	0.27
Hemoglobin A1c (%)	5.02 (0.64)	5.12 (0.70)	5.18 (0.80)	5.23 (0.76)	<0.01
Hypoglycemic medication	87 (3.8)	90 (4.2)	80 (4.4)	115 (4.6)	0.19
Uric acid (mg/dL)	5.6 (1.4)	5.7 (1.3)	5.7 (1.3)	6.0 (1.4)	<0.01
Total cholesterol (mg/dL)	174.8 (29.0)	184.8 (28.5)	192.9 (28.6)	208.7 (32.3)	<0.01
Triglyceride (mg/dL)	94.3 (67.2)	112.8 (81.7)	129.9 (78.7)	158.9 (88.7)	<0.01
LDL-C (mg/dL)	85.7 (19.4)	107.2 (18.5)	119.7 (19.8)	139.0 (25.5)	<0.01
HDL-C (mg/dL)	71.1 (15.5)	58.3 (10.1)	51.4 (8.7)	43.3 (7.9)	<0.01
hs-CRP (mg/dL)	0.13 (0.44)	0.14 (0.57)	0.14 (0.44)	0.16 (0.45)	<0.01

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; hs-CRP, high sensitivity C-reactive protein

[a]Significance was estimated using Kruskal-Wallis test for continuous items and Chi-square test or Fisher's exact test for categorical items.

with LDL-C/HDL-C ratio quartiles.

Fig. 1 shows disease-free survival curves for AMI among males based on LDL-C/HDL-C ratio quartiles. The disease-free survival rate for male participants with a LDL-C/HDL-C ratio of 2.6 or higher (fourth quartile) was significantly different from other quartiles. Multivariate-adjusted HR of Q4 was significantly higher than Q1 (p=0.03) (**Table 3-1**).

Multivariate-adjusted HR of Q3 for TC levels (HR=2.44, p=0.04) and Q4 for LDL-C levels (HR=2.50, p=0.04) were significantly higher and that of Q3 for HDL-C levels (HR=0.20, p=0.03) was significantly lower than Q1; however, a linear and obvious relationship was not observed across all quartiles (**Table 3-1**).

Table 3-2 shows hazard ratios for ischemic stroke based on lipoprotein levels and their ratio quartiles among males. For the LDL-C/HDL-C ratio, no significant relationship was found between quartiles and the risk of ischemic stroke [multivariate-adjusted HR of Q4=0.86 (p=0.56)]. Furthermore, no relationship was found between quartiles of LDL-C levels, HDL-C levels and the TC/HDL-C ratio, and the risk of ischemic stroke [multivariate-adjusted HRs of Q4=0.73 (p=0.27) for LDL-C levels, 0.90 (p=0.73) for HDL-C levels and 0.81 (p=0.47) for TC/HDL-C ratio]. Although multivariate-adjusted HR of Q3 for TC levels was significantly lower than Q1 (HR=0.55, p=0.04), a linear and obvious relationship was not observed across quartiles.

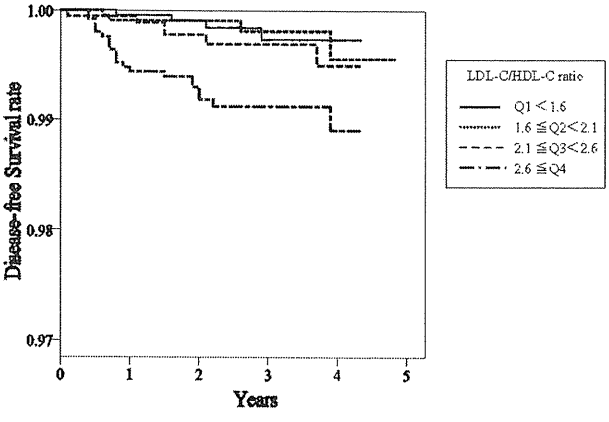

Fig. 1. Acute myocardial infarction-free rate for LDL-C/HDL-C ratio quartiles among male participants (n=8714, Cases=35).

Table 3-3 shows hazard ratios for ischemic stroke for lipoprotein levels or their ratio quartiles among females. We found no significant relationship between quartiles of LDL-C/HDL-C ratio and risk of ischemic stroke [multivariate-adjusted HR of Q4=1.17 (p=0.69)]. In addition, we observed no relationship between the other quartiles [multivariate-adjusted

Table 3-1. Hazard ratios for acute myocardial infarction according to lipid level quartiles among male participants (n=8714, Mean age=63.7±11.5, Mean follow-up years=2.7±0.9)

	Number of events	Incidence rate[a]	Age-adjusted hazard ratios	95% CI	p	Multivariate- adjusted hazard ratios[b]	95% CI	p
LDL-C/HDL-C ratio								
Q1 <1.6	4/2277	0.28	1.00 (Reference)			1.00 (Reference)		
Q2 ≥1.6-<2.1	4/2125	0.32	1.08	0.27-4.33	0.91	0.99	0.25-3.96	0.98
Q3 ≥2.1-<2.6	6/1818	0.67	1.88	0.53-6.67	0.33	1.51	0.42-5.46	0.53
Q4 ≥2.6	21/2494	1.24	5.02	1.72-14.62	<0.01	3.50	1.15-10.64	0.03
TC levels (mg/dL)								
Q1 <180	12/3292	0.41	1.00 (Reference)			1.00 (Reference)		
Q2 ≥180-<200	6/2183	0.46	0.75	0.28-1.99	0.56	0.82	0.34-2.52	0.88
Q3 ≥200-<220	10/1651	1.33	1.63	0.71-3.78	0.25	2.44	1.01-5.91	0.04
Q4 ≥220	7/1588	1.00	1.17	0.46-2.98	0.74	1.81	0.68-4.77	0.23
LDL-C levels (mg/dL)								
Q1 <100	8/2884	0.36	1.00 (Reference)			1.00 (Reference)		
Q2 ≥100-<120	5/2427	0.31	0.72	0.23-2.19	0.56	0.64	0.21-1.96	0.43
Q3 ≥120-<140	9/1813	1.00	1.82	0.70-4.71	0.22	1.30	0.48-3.51	0.60
Q4 ≥140	13/1590	1.85	3.20	1.32-7.72	0.01	2.50	1.02-6.09	0.04
HDL-C levels (mg/dL)								
Q1 <50	24/3253	0.85	1.00 (Reference)			1.00 (Reference)		
Q2 ≥50-<60	7/2346	0.47	0.41	0.18-0.95	0.04	0.48	0.21-1.13	0.09
Q3 ≥60-<70	2/1647	0.27	0.16	0.04-0.67	0.01	0.20	0.05-0.86	0.03
Q4 ≥70	2/1468	0.33	0.19	0.05-0.81	0.02	0.27	0.06-1.19	0.08
TC/HDL-C ratio								
Q1 <2.8	4/2003	0.37	1.00 (Reference)			1.00 (Reference)		
Q2 ≥2.8-<3.4	3/2148	0.24	0.69	0.15-3.08	0.63	0.60	0.13-2.72	0.51
Q3 ≥3.4-<4.1	9/2066	0.77	2.18	0.67-7.07	0.20	1.52	0.45-5.19	0.50
Q4 ≥4.1	19/2497	1.13	4.05	1.38-11.90	0.01	2.82	0.91-8.72	0.07

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol
[a]Unadjusted incidence rate per 1,000,000 per year. [b]Age (10-year increase), current smoking, systolic blood pressure, body mass index, uric acid, and hemoglobin A1c were included in the Cox regression analysis.

HRs of Q4=0.73 (p=0.44) for TC levels, 0.68 (p=0.34) for LDL-C levels, 0.59 (p=0.19) for HDL-C levels and 1.43 (p=0.39) for TC/HDL-C ratio].

Discussion

This community-based, prospective cohort study conducted in a Japanese rural area showed that the LDL-C/HDL-C ratio at baseline was an independent predictor for future AMI among male participants, with a ratio of 2.6 or higher suggesting a risk of disease. Although an association between LDL-C and TC quartiles and the risk was observed, it may be weaker than LDL-C/HDL-C. On the other hand, we observed no obvious association between any lipoprotein level or their ratio quartiles and the risk of ischemic stroke in either sex. To the best of our knowledge, this is the first report to prospectively examine the association between the lipoprotein level or ratio quartiles and cardiovascular events, and to clarify the relationship between the LDL-C/HDL-C ratio and AMI among males in a rural Japanese community.

Several epidemiological studies have reported the LDL-C/HDL-C ratio to be an excellent predictor of coronary heart disease (CHD) risk[10, 12-14, 19]. In the Helsinki Heart Study[12], the LDL-C/HDL-C ratio was a strong predictor of CHD risk among participants with high triglyceride levels during 5-year follow up. Furthermore, the PROSPER study[13], which was a prospective cohort study that examined about 5,800 elderly participants over 3.7 years, suggested that increased CHD risk is associated with an elevated LDL-C/HDL-C ratio. In contrast, the Quebec Cardiovascular Study[11] showed that ratios of LDL-C/HDL-C and TC/HDL-C were associated with ischemic heart disease, and indicated that the TC/HDL-C

Table 3-2. Hazard ratios for ischemic stroke according to lipid level quartiles among male participants (n=8714, Mean age=63.7±11.5, Mean follow-up years=2.7±0.9)

	Number of events	Incidence rate[a]	Age-adjusted hazard ratios	95% CI	p	Multivariate- adjusted hazard ratios[b]	95% CI	p
LDL-C/HDL-C ratio								
Q1 <1.6	33/2277	2.36	1.00 (Reference)			1.00 (Reference)		
Q2 ≥1.6-<2.1	29/2125	2.36	0.93	0.57-1.53	0.78	1.02	0.61-1.71	0.94
Q3 ≥2.1-<2.6	21/1818	2.35	0.79	0.46-1.36	0.39	0.81	0.46-1.44	0.47
Q4 ≥2.6	31/2494	1.84	0.88	0.54-1.43	0.60	0.86	0.50-1.46	0.56
TC levels (mg/dL)								
Q1 <180	53/3292	1.84	1.00 (Reference)			1.00 (Reference)		
Q2 ≥180-<200	25/2183	1.94	0.69	0.43-1.12	0.13	0.69	0.42-1.13	0.15
Q3 ≥200-<220	16/1651	2.13	0.57	0.33-1.00	0.05	0.55	0.31-0.99	0.04
Q4 ≥220	20/1588	2.87	0.74	0.44-1.23	0.25	0.83	0.49-1.42	0.83
LDL-C levels (mg/dL)								
Q1 <100	45/2884	2.04	1.00 (Reference)			1.00 (Reference)		
Q2 ≥100-<120	32/2427	2.00	0.81	0.52-1.28	0.37	0.83	0.52-1.32	0.43
Q3 ≥120-<140	19/1813	2.11	0.66	0.39-1.13	0.13	0.65	0.37-1.12	0.12
Q4 ≥140	18/1590	2.57	0.76	0.44-1.31	0.32	0.73	0.42-1.27	0.27
HDL-C levels (mg/dL)								
Q1 <50	41/3253	1.45	1.00 (Reference)			1.00 (Reference)		
Q2 ≥50-<60	34/2346	2.28	1.17	0.74-1.84	0.51	1.18	0.74-1.87	0.49
Q3 ≥60-<70	23/1647	3.10	1.08	0.65-1.81	0.76	1.12	0.66-1.89	0.69
Q4 ≥70	16/1468	2.70	0.89	0.50-1.58	0.68	0.90	0.49-1.66	0.73
TC/HDL-C ratio								
Q1 <2.8	29/2003	2.68	1.00 (Reference)			1.00 (Reference)		
Q2 ≥2.8-<3.4	32/2148	2.55	0.99	0.60-1.64	0.97	0.99	0.59-1.67	0.97
Q3 ≥3.4-<4.1	22/2066	1.90	0.72	0.41-1.25	0.25	0.70	0.39-1.26	0.23
Q4 ≥4.1	31/2497	1.84	0.89	0.54-1.48	0.65	0.81	0.47-1.42	0.47

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol
[a]Unadjusted incidence rate per 1,000,000 per year. [b]Age (10-year increase), current smoking, systolic blood pressure, body mass index, uric acid, and hemoglobin A1c were included in the Cox regression analysis.

ratio might be a better indicator than the LDL-C/HDL-C ratio in males; however, a population-based cohort study from Framingham, Massachusetts reported that ratios of TC/HDL-C and LDL-C/HDL-C were positively associated with coronary heart disease risk in both sexes[5]. In the present study, multivariate-adjusted analysis showed that while the incidence of AMI was significantly associated with the LDL-C/HDL-C ratio, the magnitude of HR was almost identical in each quartile group of LDL-C/HDL-C and TC/HDL-C. Long-term observation may be needed to reveal an association between the LDL-C/HDL-C ratio or TC/HDL-C ratio and risk of future cardiovascular events.

We also observed a positive association between LDL-C levels and AMI. LDL-C is well known as an important risk factor for CVD. In the Suita study[20], which analyzed about 4,700 participants over a 11.9 years, the risk of myocardial infarction in the highest quartile of LDL-C (≥3.91 mmol/L) was 3.73 times higher than in the lowest quartile (<2.54 mmol/L) in males. Likewise, we showed that the highest quartile of LDL-C was significantly associated with the incidence of AMI. Upon additional analysis, no significant association was found between the LDL-C/HDL-C ratio and AMI after stratifying with the LDL-C median level [multivariate-adjusted HR of Q4 in high LDL-C=3.00 (p=0.56) and in low LDL-C=0.70 (p=0.66)]. The predictive value of LDL-C/HDL-C for AMI incidence may be evident with relatively high serum LDL-C (≥120 mg/L); however, LDL-C quartiles did not show a clear and linear trend compared to the LDL-C/HDL-C ratio. Moreover, TC quartiles did not show a liner a association in this study, although the third quartile of TC levels was significantly associated with the incidence; therefore, the

Table 3-3. Hazard ratios for ischemic stroke according to lipid level quartiles among female participants (n=15852, Mean age=60.7±11.7, Mean follow-up years=2.7±0.9)

	Number of events	Incidence rate[a]	Age-adjusted hazard ratios	95% CI	p	Multivariate-adjusted hazard ratios[b]	95% CI	p
LDL-C/HDL-C ratio								
Q1 <1.6	11/4025	0.26	1.00 (Reference)			1.00 (Reference)		
Q2 ≥1.6-<2.1	18/4408	0.35	1.25	0.59-2.65	0.56	1.13	0.53-2.42	0.76
Q3 ≥2.1-<2.6	16/3599	0.46	1.24	0.58-2.68	0.58	0.92	0.41-2.05	0.83
Q4 ≥2.6	23/3820	0.58	1.66	0.81-3.41	0.17	1.17	0.54-2.49	0.69
TC levels (mg/dL)								
Q1 <180	12/3484	0.38	1.00 (Reference)			1.00 (Reference)		
Q2 ≥180-<200	20/3638	0.56	1.55	0.76-3.17	0.23	1.39	0.66-2.94	0.39
Q3 ≥200-<220	19/3896	0.47	1.38	0.67-2.85	0.38	1.15	0.54-2.48	0.72
Q4 ≥220	17/4834	0.27	0.97	0.46-2.03	0.93	0.73	0.32-1.63	0.44
LDL-C levels (mg/dL)								
Q1 <100	12/3291	0.43	1.00 (Reference)			1.00 (Reference)		
Q2 ≥100-<120	21/4066	0.48	1.15	0.56-2.33	0.71	1.15	0.55-2.42	0.71
Q3 ≥120-<140	16/4301	0.32	0.78	0.37-1.66	0.52	0.74	0.34-1.61	0.45
Q4 ≥140	19/4194	0.39	0.94	0.45-1.94	0.86	0.68	0.31-1.49	0.34
HDL-C levels (mg/dL)								
Q1 <50	22/3345	0.74	1.00 (Reference)			1.00 (Reference)		
Q2 ≥50-<60	21/4453	0.39	0.79	0.43-1.43	0.43	0.85	0.45-1.59	0.61
Q3 ≥60-<70	15/3993	0.35	0.66	0.34-1.28	0.22	0.78	0.39-1.55	0.47
Q4 ≥70	10/4061	0.23	0.46	0.22-0.97	0.04	0.59	0.27-1.29	0.19
TC/HDL-C ratio								
Q1 <2.8	9/3728	0.24	1.00 (Reference)			1.00 (Reference)		
Q2 ≥2.8-<3.4	16/4559	0.29	1.20	0.53-2.73	0.66	1.10	0.48-2.54	0.82
Q3 ≥3.4-<4.1	19/3997	0.44	1.44	0.65-3.19	0.37	1.12	0.49-2.57	0.78
Q4 ≥4.1	24/3568	0.70	2.03	0.94-4.39	0.07	1.43	0.64-3.22	0.39

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol
[a]Unadjusted incidence rate per 1,000,000 per year. [b]Age (10-year increase), current smoking, systolic blood pressure, body mass index, uric acid, and hemoglobin A1c were included in the Cox regression analysis.

LDL-C/HDL-C ratio may have greater clinical potential as a predictor of AMI than LDL-C or TC levels.

HDL-C is a well-known protective factor against CVD, and its levels are inversely associated with CHD[21]. We did not observe a clear association in the present study, which may have been due to the shorter follow-up period. Nevertheless, the LDL-C/HDL-C ratio at baseline was independently associated with future AMI, suggesting that the LDL-C/HDL-C ratio may better predict the outcome than HDL-C alone.

Interestingly, our results showed that the hazard ratio in male participants with a LDL-C/HDL-C ratio of 2.6 or higher was significantly higher than other quartiles. The Munster Heart Study (PROCAM)[14], which included middle-aged German men, showed a continuous and graded relationship between the LDL-C/HDL-C ratio and CHD mortality, with an increase in CHD deaths when the ratio was between 3.7 and 4.3. A clinical study of Japanese patients with suspected ischemic coronary disease evaluated the relationship between plaque formation and lipoprotein levels in coronary arteries using intravascular ultrasonography and found that the mean plaque area was significantly higher if the LDL-C/HDL-C ratio was at least 2.5[22]. It is possible that a LDL-C/HDL-C ratio of 2.6 or higher is a risk factor for AMI among Japanese males, and our results suggest that it is important to maintain an LDL-C/HDL-C ratio lower than 2.6 for primary prevention of AMI.

We did not find an association between the LDL-C/HDL-C ratio and ischemic stroke. Furthermore, there were mostly non-significant associations between other lipid profiles or their indices and ischemic stroke. The Cardiovascular Health study[23] reported a positive association between LDL-C and the risk of ischemic stroke, and the Oyabe study[24]

demonstrated an inverse relationship between HDL-C levels and ischemic stroke incidence; however, the Framingham study[25] and Hisayama study[26] did not report a clear association between the LDL-C level and the risk of ischemic stroke, and HDL-C levels were not associated with the risk of ischemic stroke in the Women's Health study[27]. Furthermore, LDL-C and HDL-C were not associated with ischemic stroke in the Atherosclerosis Risk in Community study[28]. Also, the NIPPON DATA 80[29, 30] reported that there was no relationship between ischemic stroke and TC levels. We propose three possible explanations for these discrepancies. First, these associations were heterogeneous across ischemic stroke subtypes, and lacunar infarction and cardioembolic infarction seem to be less associated with elevated LDL-C levels than atherothrombotic infarction[26]. It is probable that including these subtypes in the analysis masks the true association; therefore, the LDL-C/HDL-C ratio may not be clearly associated with the risk of total ischemic stroke in the present study. Ischemic stroke subtype-specific analysis may be needed to assess the potential relationship with the LDL-C/HDL-C ratio. Second, the follow-up period in our study was relatively short compared to previous studies. Long-term observation may reveal an association between the LDL-C/HDL-C ratio and risk of ischemic stroke. Finally, adjustment for confounding factors, especially blood pressure levels, might be insufficient in multivariate analysis. Ischemic stroke is likely to be influenced by blood pressure levels compared to AMI, and insufficient adjustment for blood pressure levels may mask the true association. To improve the accuracy of our findings, additional analysis stratified by blood pressure levels may be needed.

We found that the LDL-C/HDL-C ratio was associated with cardiovascular risk factors in both sexes. The Hisayama study[26] reported that LDL-C levels were linearly correlated with BMI, fasting blood glucose levels, and systolic and diastolic blood pressures, while HDL-C levels were inversely correlated with LDL-C levels. These factors are components of metabolic syndrome (MetS), which has received considerable attention because it is known to be a condition associated with a high risk for ischemic heart disease[31]. Furthermore, the LDL-C/HDL-C ratio was significantly correlated with hs-CRP levels, which is a circulatory inflammatory marker and well-known predictor of atherosclerotic disorders[32]; therefore, it is probable that the LDL-C/HDL-C ratio can assess the inflammation of blood vessels.

Our study has several limitations. The first is selection bias. Participants were selected from those who attended the annual health check-up, and they may have greater health awareness than the general population. Second, the follow-up period was relatively short (2.7 years) compared to previous cohort studies that observed outcomes for more than five years. Long-term observational studies may be needed to access causal associations between the LDL-C/HDL-C ratio and cardiovascular outcomes. Third, unknown sudden deaths were excluded from analysis, and it is possible that incidences were underestimated. Fourth, the present study investigated the outcome of total ischemic stroke. Ischemic stroke subtype-specific analysis may be needed in the future. Finally, we used LDL-C levels directly measured by a homogeneous assay in this study. It is possible that directly measured LDL-C levels are not as accurate as calculated LDL-C levels.

Conclusions

The LDL-C/HDL-C ratio at baseline was an independent predictor of future AMI among Japanese males. A ratio of 2.6 or higher may indicate non-fatal AMI risk, and might have the potential to assess the inflammation of blood vessels. In addition to other lipid profiles and ratios, our results indicate the utility of the LDL-C/HDL-C ratio as a predictor of AMI among men and the importance of lifestyle modification and better management of cardiovascular risks among people with high LDLC/HDLC ratios for primary prevention of future cardiovascular disease; however, given the relatively short follow-up period of this study, long-term studies may be needed to confirm our findings.

Conflict of Interest

The authors report no conflicts of interest.

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