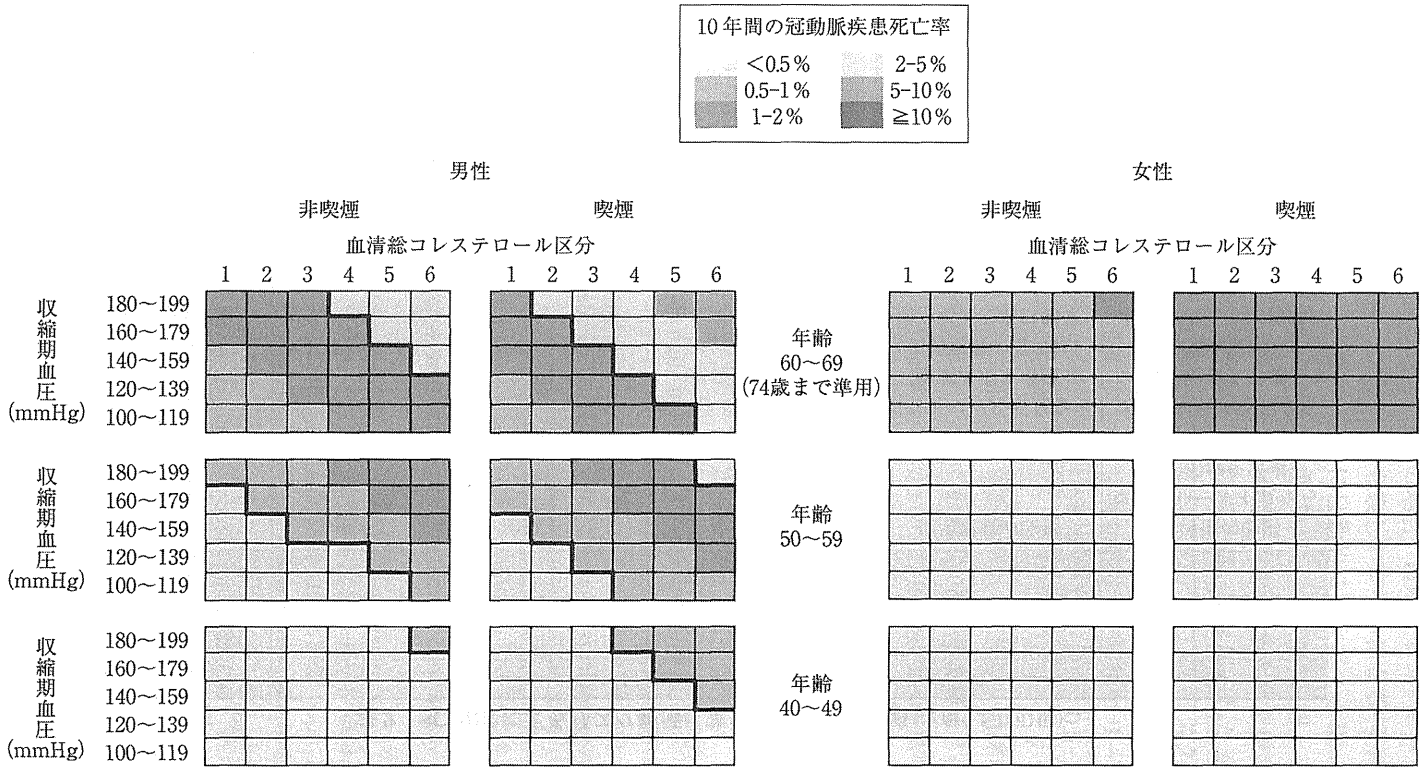
絶対リスクは危険因子の変化や加齢で変化するため少なくとも年に1回は絶対リスクの再評価を行うこと.



＊血清コレステロール区分：
総コレステロールの場合，1＝160～179，2＝180～199，3＝200～219，4＝220～239，5＝240～259，6＝260～279(mg/dL)

図2　冠動脈疾患絶対リスク評価チャート(一次予防)(文献[10]より引用)

表3 カテゴリー分類別脂質管理目標値(文献[10]より改変)

治療方針の原則	管理区分	脂質管理目標値(mg/dL)			
		LDL-C	HDL-C	TG	non-HDLC
一次予防 まず生活習慣の改善を行った後，薬物療法の適用を考慮する	カテゴリーI	<160	≧40	<150	<190
	カテゴリーII	<140			<170
	カテゴリーIII	<120			<150
二次予防 生活習慣の是正とともに薬物治療を考慮する	冠動脈疾患の既往	<100			<130

注釈(抜粋)
・これらの値はあくまでも到達努力目標値である.
・LDLコレステロールは20-30%の低下を目標とすることも考慮する.
・いずれのカテゴリーにおいても管理目標達成の基本はあくまでも生活習慣の改善である.
・カテゴリーIにおける薬物療法の適用を考慮するLDLコレステロールの基準は180 mg/dL以上とする.

危険因子に対する包括的な管理が必要であり，本来は関係学会が集まって統一ガイドラインを策定することが望ましい．ガイドライン2012ではその嚆矢として'包括的リスク管理'を示している.

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わが国の虚血性心疾患の疫学

Epidemiology of ischemic heart diseases in Japan

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◎わが国の虚血性心疾患の死亡率は諸外国と比較してもきわめて低く，年齢調整死亡率は1970年以降，男女ともに低下傾向が続いている．一方，虚血性心疾患の発症率も諸外国と比べれば低いものの，国内の観察研究において年齢調整発症率が増加傾向にあるという報告が散見されており，その傾向には男女差・地域差があることを示唆する結果となっている．また，虚血性心疾患の危険因子のなかで，高血圧・喫煙については改善あるいは不変である一方，脂質異常症・糖尿病・肥満の保有率が上昇しており，欧米型のリスクパターンに推移しつつあることが明らかになっている．危険因子への曝露から発症までにはタイムラグが生じることを加味すると，将来的に虚血性心疾患の発症率がさらに上昇することが懸念されるため，今後も虚血性疾患やその危険因子の推移を継続的に探索するとともに，発症予防に向けて，男女差・地域差を加味した危険因子対策の推進がよりいっそう必要であると思われる．

Key word：虚血性心疾患，死亡率，発症率，危険因子，疫学

日本をはじめとするアジア諸国では，循環器疾患のなかでも脳卒中のリスクが高く，心筋梗塞に代表される虚血性心疾患のリスクが低いことが特徴である．しかし，わが国では第二次世界大戦後に生活習慣の欧米化が進み，循環器疾患の疾病構造に変化が生じている．

本稿では，統計ならびに疫学研究の知見をもとに，虚血性心疾患の死亡率・発症率およびその危険因子に関するわが国の特徴について概説する．

死亡率

わが国における人口動態調査をもとにした心疾患の粗死亡率(人口10万人当り)の推移を図1に示す．心疾患全体としては，2011年のデータでは男性148.6，女性160.1と戦後増加傾向を示しているが，虚血性心疾患についてはデータの存在する1970年と比べると増加しているものの，2000年あたりからは男性は微増，女性は横ばいといった傾向が続いている(2011年データでは男性71.0，女性52.9)．また，虚血性心疾患のなかで心筋梗塞の傾向をみてみると，男女ともに2000年あたりから横ばいか，あるいは微減といった状況である．一方，人口高齢化の影響を加味した年齢調整死亡率をみてみると，心疾患全体では1970年ごろをピークに死亡率が減少している(図2)．また虚血性心疾患の推移をみてみると，データの存在する1970年から基本的にはつねに減少傾向にあるといえる．この傾向は心筋梗塞でも同様である．以上のように，わが国における虚血性心疾患による死亡はすくなくとも増加しておらず，高齢化を考慮に入れるとむしろ減少していると考えられる．この傾向の理由としては，一部地域を除き，全体としてはいまだ発症率が増えていないこと，医療技術の進歩や救急体制の整備によって死亡率が低下したことなどが理由としてあげられるであろう．

ちなみに，わが国の人口動態調査での死亡統計を解釈する際には2点注意が必要である．

1点目は，虚血性心疾患にあたる死因分類が“心筋梗塞”と“その他の虚血性心疾患”に大別されており，狭心症などの情報が“その他の虚血性心

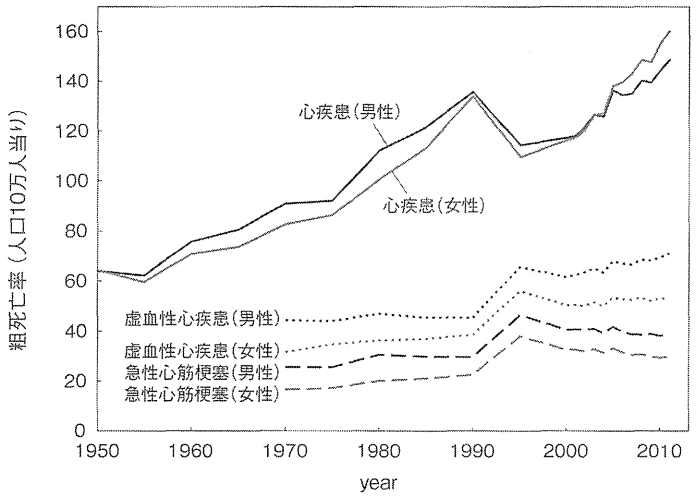

図 1　わが国の心疾患粗死亡率の推移（男女別，人口10万人当り）
2011 年度人口動態調査より作成．

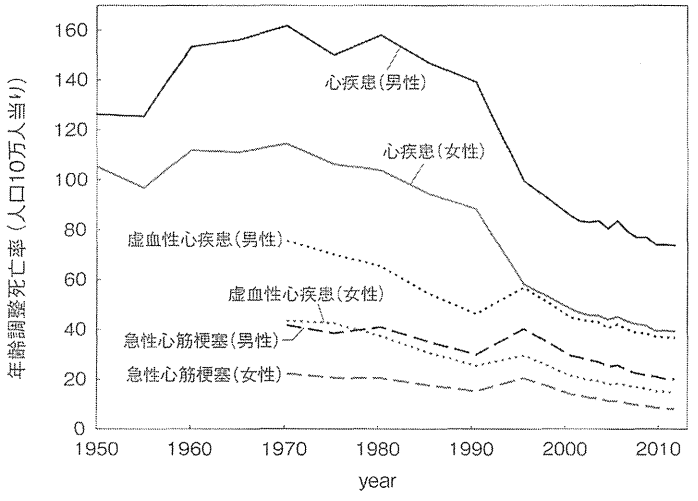

図 2　わが国の心疾患年齢調整死亡率の推移（男女別，人口10万人当り）
2011 年度人口動態調査より作成．

疾患”に集約されている点である．より正確にいうと，“その他の虚血性心疾患”には死因基本分類コードの I20 狭心症，I24 その他の急性虚血性心疾患（心筋梗塞に至らなかった冠状動脈血栓症など），I25 慢性虚血性心疾患（陳旧性心筋梗塞など）が含まれており，狭心症のみの死亡率を抽出するのは人口動態調査からは困難である．

2 点目は，死亡診断書の死因欄における心疾患の取扱いの変化である．わが国では原因にかかわらず急死例に“心不全”あるいは“急性心不全”と死亡診断書を記載する習慣があったが，1994 年に国際疾病分類が第 9 版から第 10 版に変更になる際，死亡診断書に「疾患の終末期の状態として心不全，呼吸不全などは書かないでください」という注意書きが添えられるとともに，遵守への周知がなされるようになった．その結果，1995 年の死亡統計では心疾患全体の死亡率が大きく減少する一方で，虚血性心疾患などによる死亡率が上昇しているが，実際に上昇したわけではなく，前述の死因欄記載ルールの変更に伴うみかけ上の変化と

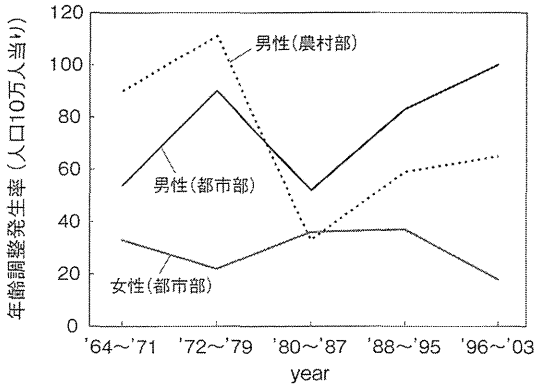

図 3　冠動脈疾患の年齢調整発生率（Akita-Osaka研究，人口10万人当り）[2]
冠動脈疾患は“心筋梗塞＋心突然死”で定義．
女性（農村部）は発生頻度が0あるいは1で年齢調整発生率の推定不能．

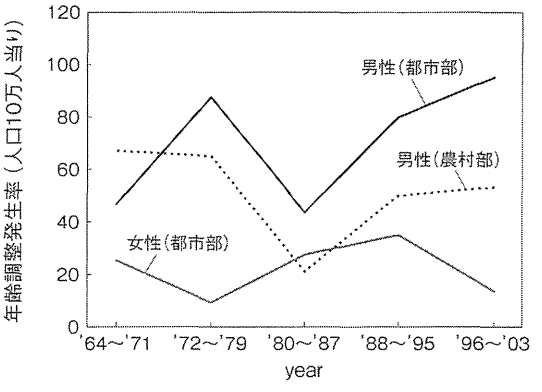

図 4　心筋梗塞の年齢調整発生率（Akita-Osaka研究，人口10万人当り）[1]
女性（農村部）は発生頻度が0あるいは1で年齢調整発生率の推定不能．

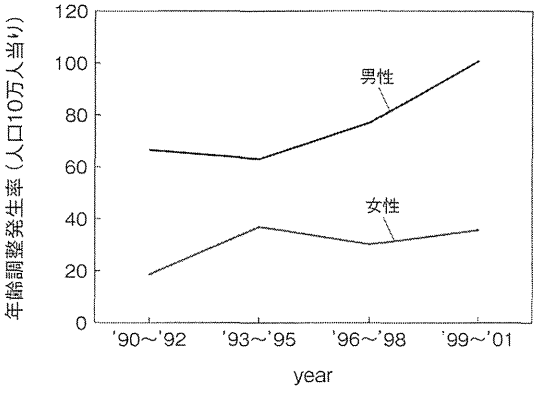

図 5　心筋梗塞の年齢調整発生率（Takashima AMI registry，人口10万人当り）[2]

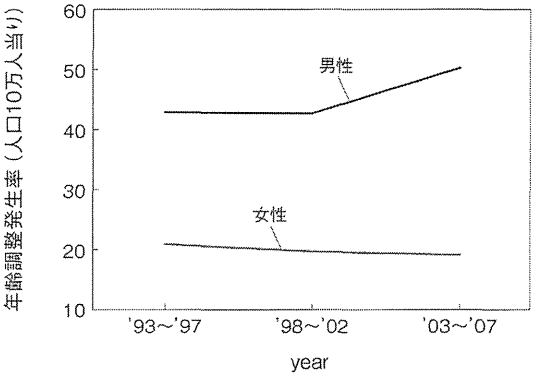

図 6　心筋梗塞の年齢調整発生率（Yamagata AMI registry，人口10万人当り）[3]

考えられる（図1，2参照）．

発症率

わが国では，虚血性心疾患発症率の推移について検討した疫学研究の報告は少ない．

都市部（大阪府八尾市）と農村部（秋田県井川町）における冠動脈疾患の年齢調整発生率について，1964年から2003年までの追跡を行ったAkita-Osaka研究[1]では，①都市部においては男女ともに1980～1987年の調査で冠動脈疾患の発症率に低下がみられたものの，その後ふたたび上昇に転じている，②農村部男性においては，発生率に若干の増減がみられるものの，総じて都市部よりも低い発生率となっている，③農村部女性では虚血性心疾患の発生がきわめてまれである，といった傾向がみられた（図3）．この傾向は心筋梗塞発症のみを対象とした場合でも同様であった（図4）．なお，Akita-Osaka研究では冠動脈疾患を“心筋梗塞＋心突然死”と定義しており，近年ではcoronary interventionもイベントとして評価している．

滋賀県の地方都市（高島市）を対象としたTakashima AMI registryでは，1990～1992年の急性心筋梗塞の年齢調整発症率は男性66.5，女性18.7であったが，1999～2001年の調査では男性100.7，女性35.7と男女ともに増加している[2]（図5）．

一方，高島市の研究とほぼ同時期に開始された山形県全域が対象となるYamagata AMI registryでは，1993～1997年の調査時点で急性心筋梗塞の

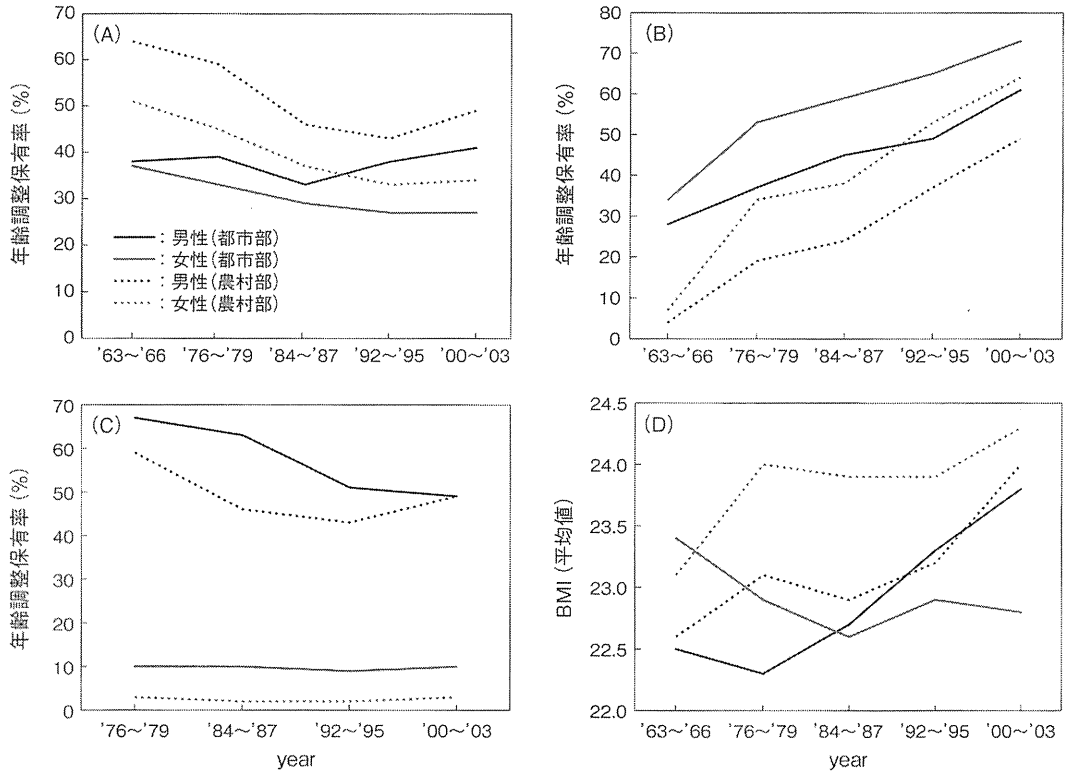

図 7　危険因子の年齢調整保有率の推移（Akita-Osaka研究）[1]

A：高血圧（収縮期 140 mmHg/拡張期 90 mmHg/降圧治療），B：高コレステロール血症（総コレステロール 200mmH/dL 以上/治療者），C：現在喫煙，D：BMI（平均値）．

年齢調整発症率が男性 42.7，女性 20.7 であったのに対し，2003～2007 年の調査では男性 50.1，女性 18.9 と，男性で増加がみられるのとは対照的に女性ではほぼ横ばいといった傾向を示した[3]（図6）．宮城県全域を対象とした MIYAGI-AMI registry でも，急性心筋梗塞の年齢調整発症率の推移は男性では有意な上昇がみられる一方，女性では調査開始時と比べて発症率は上昇しているものの統計学的に有意な傾向は見出せなかった[4]．

このように，虚血性心疾患のなかでも心筋梗塞の発症率については，わが国においては男女差・地域差が存在することが示唆されている．

危険因子

他の循環器疾患と同様，虚血性心疾患においてもさまざまな危険因子が明らかとなっている．

1．血圧

わが国において，血圧は脳卒中に関するもっとも重要な危険因子であるが，虚血性心疾患でも同様であり，死亡率・発症率ともに大きく寄与する危険因子である[5,6]．

前述の Akita-Osaka 研究における高血圧保有率の推移を図 7-A に示すが，都市部・農村部の男女ともに 1980 年代に一度低下傾向を示していたものの，男性では都市部・農村部ともに若干上昇傾向をみせている[1]．ちなみに，同研究にて 1980～1987 年調査時に都市部の冠動脈疾患発症率が一度低下したのは，高血圧保有率が低下したことが一因と考えられている．

また，2010 年度国民健康・栄養調査によると，収縮期血圧の平均値（男性 133.9 mmHg，女性 126.2 mmHg），拡張期血圧の平均値（男性 82.4 mmHg，女性 77.0 mmHg）ともに 2000 年と比べて変化がみられないのに対し，高血圧有病者の割合は男性 60.0%，女性 44.6%であり，2000 年に比べて男性では増加しているが，女性は変わらない．

平均値としての血圧は収縮期・拡張期ともに上昇はみられないものの，高血圧の有病率はいぜん

高く，虚血性心疾患予防対策の一環として高血圧の管理は非常に重要である．

2. 脂質異常症

脂質異常症が循環器疾患のなかでもとくに冠動脈疾患の危険因子であることはよく知られている．わが国のコホート研究を統合したメタアナリシスにおいても，高コレステロール血症が冠動脈疾患死亡や心筋梗塞の発症と有意な関連を示す結果となっている[7,8]．

日本人の総コレステロール値が年を経るに従って上昇していることも明らかとなっており，2010年国民健康・栄養調査での平均値は，男性203.0 mg/dL，女性210.9 mg/dLであり，2000年時に比べて男女とも上昇傾向にある(2000年度男性199.0 mg/dL，女性206.2 mg/dL)．また，同調査での脂質異常症が疑われる者の割合は，男性22.3%，女性17.7%であり，こちらも2000年に比べて男女ともに増加傾向にある(2000年度男性21.2%，女性15.2%)．ただし，同調査の血液検査は空腹時検査ではなく，また“脂質異常症が疑われる者”の定義は「HDL-Cが40 mg/dL未満，または，コレステロールを下げる薬を服用している者」となっているため，脂質異常症の定義として適切かどうかは疑問が残る．

一方，Akita-Osaka研究における高コレステロール血症の推移をみてみると，男女および都市部・農村部問わず高コレステロール血症保有率が上昇していることがわかる[1](図7-B)．同研究では高コレステロール血症者の定義は総コレステロール200 mg/dL以上あるいは脂質降下薬の服用者である．

調査・研究によって脂質異常症の定義が異なるという問題はあるものの，いずれのデータもわが国において脂質異常症が増加傾向にあるという結果は一貫している．

3. 喫煙

わが国における喫煙率はいぜんとして高い．1970年代では男性約80%，女性約15%程度であった喫煙率が，2010年度国民健康・栄養調査では男性32.2%，女性8.4%と減少傾向にある．喫煙人口の内訳をみると男女ともに30代の喫煙率がもっとも高く，喫煙率の低下は高齢者層における低下が影響していると思われる．

Akita-Osaka研究での年齢調整喫煙率の推移をみると，都市部男性では減少傾向にあるものの，女性では喫煙率自体が低いものの横ばい状態，農村部男性では一度低下した喫煙率がふたたび上昇する傾向にある[1](図7-C)．

わが国の疫学研究においても，NIPPON DATA80が虚血性心疾患死亡[9]，JPHCが冠動脈疾患発症[10]に対して喫煙によるリスク上昇を示しており，とくに若年者層をターゲットとした禁煙対策が重要である．

4. 糖尿病

糖尿病は欧米において冠動脈疾患の確立した危険因子であり，日本の疫学研究においても冠動脈疾患発症のリスク上昇と関連していることが示されている[11]．また，日本動脈硬化学会が作成した『動脈硬化性疾患予防ガイドライン2012年版』におけるLDLコレステロール管理目標設定の際にも，糖尿病がある場合には一次予防の管理区分としてもっとも厳しいカテゴリーⅢが自動的に適用される．

2010年度国民健康・栄養調査では，血糖値の平均値は男性103.8 mg/dL，女性100.9 mg/dLと2000年時と比べてあまり変化がない一方で，糖尿病が強く疑われる者(ヘモグロビンA1cが6.1%以上，または現在糖尿病の治療を受けている者)の割合は，男性17.4%，女性9.6%であり，男女とも増加している現状がある．

5. 肥満

肥満は前述の高血圧，脂質異常症，糖尿病やメタボリックシンドロームと密接にかかわる危険因子である．肥満自体は，これらの危険因子を介して虚血性疾患の危険因子となることが知られており，たとえば日本のJALS研究においても，BMI高値群(27.5 kg/m^{2}以上)は基準群(21 kg/m^{2}未満)と比べて心筋梗塞発症のリスクが有意に高いことが示されている[12]．

Akita-Osaka研究のBMI値の推移をみてみると(図7-D)，都市部女性を除きBMIが上昇傾向にあることがわかる[1]．一方，国民健康・栄養調査の推移をみると，20～60歳代の男性肥満者(BMI 25 kg/m^{2}以上)の割合は1995年時で24.3%

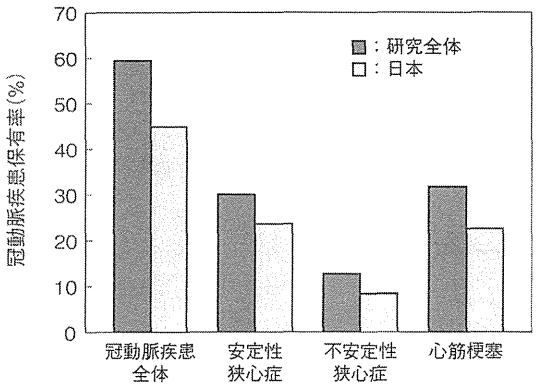

図 8　冠動脈疾患保有率(REACH registry)[13]

だったのが，2010 年時では 31.2%と上昇傾向にあるのに対し，とくに 40 歳以上の女性では 1995 年の 26%から 2010 年の 22.2%へと低下しており，全体の傾向としても減少傾向にある．

総じて，わが国ではとくに男性で肥満者の割合が増加している傾向にあるといえよう．

国際比較

公開されている WHO の死亡統計や OECD による死亡統計から各国の虚血性心疾患の年齢調整死亡率を比較すると，スロバキア，ハンガリー，フィンランドなどの東ヨーロッパ・北ヨーロッパの死亡率が上位を占め，ついで西ヨーロッパ・北アメリカ諸国が続いている．これに対し日本の死亡率は，東ヨーロッパ・北ヨーロッパの約 1/8～1/10，西ヨーロッパ・北アメリカの約 1/5 にとどまっており，世界的にみても低い死亡率であるといえる．なお，男女間で比較すると，いずれの国においても男性の死亡率が女性に比べ高く，前述のように日本においても同様の傾向である．

一方，虚血性心疾患の発症率について同一の診断基準を用いてわが国と他の国の一般集団における発症率を直接比較した報告はない．

しかし，アテローム血栓症高リスク例を対象にした国際的観察研究である REACH registry (REduction of Atherothrombosis for Continued Health registry)の結果から，わが国と諸外国との差異を類推することが可能である．なお，REACH registry の概要については「サイドメモ」も参照していただきたい．

図 8 は REACH registry エントリー時点のわが国の冠動脈疾患保有率を，研究全体の平均と比較したものである[13]．冠動脈疾患全体・心筋梗塞・安定および不安定狭心症いずれも日本の保有率は研究全体と比べて下まわっているのがわかる．また，表 1 はベースラインの危険因子保有率を参加地域別に比較したものであるが，日本は他地域と比較して脂質異常症・肥満の割合が低い一方で，現在喫煙率は高いという特色がある[13]．ただし，肥満については BMI 30 kg/m^{2}以上という定義であることに注意が必要である．

図 9 は冠動脈疾患既往のある対象者の追跡 1 年時点でのイベント発症率であるが，わが国の心血管死・非致死性心筋梗塞および脳梗塞・不安定狭心症いずれのイベントにおいても研究全体と比べて発生率が低い[13,14]．また，4 年時点の解析では，日本と他地域を比較した場合に心血管死に対する

サイドメモ　REACH registry

REACH registry(REduction of Atherothrombosis for Continued Health registry)は，心筋梗塞などの心血管疾患を引き起こすアテローム血栓症やそのハイリスク例における心血管疾患イベント発生率の調査，各国のリスク管理の評価を目的とした国際的観察研究である．対象はアテローム血栓症(冠動脈疾患，脳血管疾患，末梢血管疾患)の既往者あるいは危険因子〔糖尿病治療，糖尿病性腎症，足関節上腕血圧比＜0.9，頸動脈プラーク，無症候性頸動脈狭窄症(≧70%)，3 カ月の治療後も収縮期血圧≧150 mmHg，高コレステロール血症治療，1 日 15 本以上の喫煙，65 歳以上の男性，70 歳以上の女性〕を 3 つ以上有する 45 歳以上の外来患者．2003 年 12 月(日本は 2004 年 8 月)から登録が開始され，計 44 カ国，67,888 例が参加している．エンドポイントは心血管死および心筋梗塞・脳卒中・血行再建術などによる入院である．当初の予定追跡期間は約 2 年間であったが，4 年目の追跡調査も報告されている．世界の心血管疾患に関して系統的なデータが収集され，疾病構造や危険因子保有率・治療状況・予後といったさまざまな項目の地域間比較が可能となっており，重要な知見が多数公表されている．

表 1　危険因子保有率の国際比較(REACH registry)[13]

	糖尿病 (%)	高血圧 (%)	脂質異常症 (%)	肥満 (%)	過去喫煙 (%)	現在喫煙 (%)
研究全体	43.9	81.7	72.1	29.8	41.7	15.2
日本	45.8	70.9	46.4	4.0	45.2	16.9
北アメリカ	50.6	86.4	82.7	41.5	43.7	14.4
ラテンアメリカ	44.0	78.0	61.5	23.9	41.5	8.6
西ヨーロッパ	39.1	79.1	72.3	28.1	44.1	17.0
東ヨーロッパ	27.6	83.7	55.1	28.9	30.8	20.9
中東	52.4	80.7	82.4	29.9	31.2	14.8
アジア	47.4	79.0	61.0	8.2	29.3	12.8
オーストラリア	30.3	77.6	77.6	29.2	54.0	6.8

糖尿病：薬物治療中の場合あるいは既往歴のある場合，高血圧：降圧薬服用者，脂質異常症：薬物治療中，肥満：BMI 30 kg/m^{2}以上．

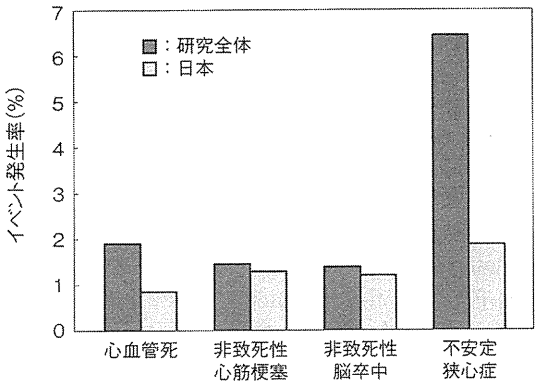

図 9　冠動脈疾患既往者の性・年齢調整1年後イベント発生率(REACH registry)[13,14]

ハザード比が0.70と，わが国の高リスク集団は他地域の高リスク集団と比べて予後が良好であることが示唆された[15]．

これらの結果から，わが国は諸外国よりも虚血性心疾患の発症率が低いことが類推され，その要因のひとつとして肥満・脂質異常症といった危険因子の保有率が低いことが考えられる．

おわりに

現在，わが国の虚血性心疾患の死亡率・発症率は諸外国と比べて低い水準にある．

しかし，死亡率については医療の進歩により減少傾向にあるものの，発症率については高齢化の影響を調整しても上昇傾向にあるという報告が散見されているとともに，その傾向には男女差・地域差があることを示唆する結果となっている．また脂質異常症・糖尿病・肥満といった危険因子の保有率が上昇し，欧米型のリスクパターンに近づきつつあることが明らかとなっており，危険因子への曝露から発症までにはタイムラグが生じることを加味すると，将来的には虚血性心疾患の発症率がさらに上昇することが懸念される．

したがって，虚血性心疾患やその危険因子の推移を継続的に探索するとともに，発症予防に向けて男女差・地域差を加味したより細やかな危険因子対策の推進が必要であると思われる．

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Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category
The Suita Study

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Background and Purpose—We aimed to clarify the association of chronic kidney disease (CKD) with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure categories in an urban general population.

Methods—We studied 3466 Japanese individuals (35–93 years old) in the Suita Study. Carotid atherosclerosis was expressed as the maximum carotid intima-media thickness and the presence of stenosis (>25%). The estimated glomerular filtration rate was calculated using the equations recommended by the Japanese Society of Nephrology. CKD was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Blood pressure categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—The multivariable-adjusted maximum carotid intima-media thickness and odds ratio for stenosis in subjects with estimated glomerular filtration rate <50 mL/min per 1.73 m^2 were greater than those in subjects with estimated glomerular filtration rate ≥90 mL/min per 1.73 m^2. When subjects were stratified according to blood pressure categories, the multivariable-adjusted maximum carotid intima-media thickness was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension. Similarly, the impact of CKD on stenosis was evident only in subjects with hypertension (multivariable-adjusted odds ratios for stenosis [95% confidence interval] were 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension compared with non-CKD/optimal blood pressure).

Conclusions—In a general population, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension. (***Stroke*. 2013;44:3537-3539.)**

Key Words: carotid artery diseases ■ carotid intima-media thickness ■ hypertension ■ renal insufficiency, chronic

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease in general populations.[1] Recently, we have shown that even slight renal dysfunction, with an estimated glomerular filtration rate (eGFR) of 50 to 59 mL/min per 1.73 m^2, results in an increased risk of cardiovascular disease in an urban general population.[2]

One possible explanation for the association of CKD with cardiovascular disease is that CKD-related nontraditional risk factors accelerate atherosclerosis independent of traditional vascular risk factors.[3] However, there is controversy as to whether CKD is independently associated with carotid intima-media thickness (IMT).[4] This may be because the impact of CKD, especially mild kidney disease, on carotid atherosclerosis is somewhat limited. CKD seems to increase the risk of carotid atherosclerosis when hypertension and impaired glucose metabolism are present.[5] We hypothesized that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant cardiovascular risk factors. Thus, we aimed to clarify the association of CKD with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure (BP) categories in an urban general population.

Patients and Methods

We sequentially enrolled 3,446 individuals (1,844 women and 1,602 men, 35–93 years old [62±11 years]) who underwent regular health checkups and carotid ultrasonography between April 2002 and March 2004 from the participants in the Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases. Each index of

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This article encompasses the doctoral dissertation of Dr Ohara.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002957/-/DC1.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.002957**

Table 1. Adjusted Max-IMT According to eGFR Category

	eGFR, mL/min per 1.73 m²				*P* Value for Trend
	≥90	60–89	50–59	<50	
Men	236	1106	174	86	
Age adjusted	1.44±0.04	1.47±0.02	1.52±0.05	1.64±0.07*	0.078
Multivariable adjusted	1.43±0.04	1.48±0.02	1.51±0.05	1.63±0.07*	0.134
Women	436	1214	137	57	
Age adjusted	1.21±0.02	1.20±0.01	1.22±0.03	1.38±0.05†	0.014
Multivariable adjusted	1.21±0.02	1.20±0.01	1.21±0.03	1.34±0.05*	0.079

Means±SD (mm). eGFR indicates estimated glomerular filtration rate; and max-IMT, maximum carotid intima-media thickness.
*P<0.05 and †P<0.01 vs eGFR≥90.

carotid atherosclerosis was defined as follows. Max-IMT was defined as the maximum IMT in the entire scanned area. Stenosis was defined as the presence of a stenotic area ≥25% on a cross-sectional scan. The eGFR was calculated using equations recommended by the Japanese Society of Nephrology.[6] The subjects were categorized into 4 groups (eGFR ≥90, 60–89, 50–59, and <50 mL/min per 1.73 m²) as in our previous study.[2] CKD was defined as an eGFR <60 mL/min per 1.73 m². BP categories (optimal, normal, high-normal BP, and hypertension) were based on the European Society of Hypertension and European Society of Cardiology 2007 criteria.[7] The association of eGFR category with carotid atherosclerosis and the association of CKD with carotid atherosclerosis according to BP categories were examined using analysis of covariance and logistic regression analysis, after adjusting for cardiovascular risk factors as covariates (see Methods in the online-only Data Supplement).

Results

CKD was identified in 16.2% (eGFR=50–59: 10.9%; eGFR<50: 5.3%) of men and in 10.5% (7.4%, 3.1%) of women (see Table I in the online-only Data Supplement.). The multivariable-adjusted max-IMT and odds ratio for stenosis in subjects with eGFR<50 were significantly greater than those in subjects with eGFR≥90; however, the max-IMT and odds ratio in subjects with eGFR=50 to 59 were not significantly different from those in subjects with eGFR≥90 (Tables 1 and 2). Consequently, the max-IMT and odds ratio for stenosis in the whole CKD sample were not significantly greater than those in the eGFR≥90 group.

When subjects were stratified according to BP categories, the multivariable-adjusted max-IMT in the hypertension category was significantly greater in both sexes. The max-IMT was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension (Figure [A]). The prevalence of stenosis was higher in subjects with high-normal BP and hypertension in all subjects. The impact of CKD on the prevalence of stenosis was more pronounced in subjects with hypertension (multivariable-adjusted odds ratio [95% confidence interval], 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension; Figure [B]). Similar trends were found in the analysis of stenosis in men.

Discussion

In our study, CKD was independently associated with carotid atherosclerosis in subjects with hypertension, but not in nonhypertensive subjects. This is the first study to show the combined impact of CKD and hypertension on carotid atherosclerosis in an urban general population.

In previous studies in general populations, only one study reported that reduced kidney function was a strong predictor of greater carotid IMT at baseline and progression of carotid atherosclerosis independent of vascular risk factors.[8] Another study found no independent association of eGFR with carotid IMT.[9] In our study, eGFR <50 mL/min per 1.73 m²

Table 2. Adjusted Odds Ratios (95% CI) for Stenosis According to eGFR Category

	eGFR, mL/min per 1.73 m²				Odds Ratio/10 mL per min eGFR Increase
	≥90	60–89	50–59	<50	
Men and women	672	2320	311	143	
Cases of stenosis	47	318	69	48	
Age adjusted	1	1.09 (0.78–1.53)	1.34 (0.87–2.06)	1.91 (1.16–3.14)	0.94 (0.88–1.01)
Multivariable adjusted	1	1.17 (0.83–1.66)	1.37 (0.88–2.13)	1.79 (1.07–2.98)	0.94 (0.88–1.01)
Men	236	1106	174	86	
Cases of stenosis	22	226	51	32	
Age adjusted	1	1.37 (0.84–2.23)	1.71 (0.96–3.04)	1.86 (0.96–3.04)	0.95 (0.87–1.03)
Multivariable adjusted	1	1.56 (0.94–2.57)	1.85 (1.02–3.36)	1.81 (0.91–3.59)	0.95 (0.87–1.04)
Women	436	1214	137	57	
Cases of stenosis	25	92	18	16	
Age adjusted	1	0.85 (0.52–1.37)	0.99 (0.50–1.96)	2.38 (1.12–5.06)	0.93 (0.84–1.04)
Multivariable adjusted	1	0.84 (0.51–1.38)	0.91 (0.45–1.84)	2.04 (0.93–4.47)	0.95 (0.85–1.06)

CI indicates confidence interval; and eGFR, estimated glomerular filtration rate.

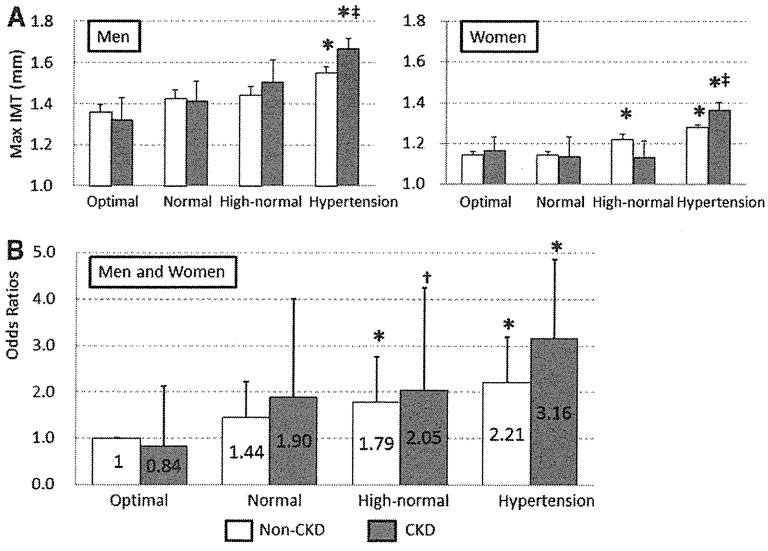

Figure. Multivariable-adjusted maximum carotid intima-media thickness (max-IMT; **A**) and odds ratios for stenosis (**B**) according to blood pressure (BP) category in subjects with and without chronic kidney disease (CKD). *P<0.05; †P=0.053 vs non-CKD/optimal BP; ‡P<0.05 vs non-CKD subjects in the same BP category.

was independently associated with carotid atherosclerosis, whereas CKD was not. The inconsistent results of these studies might be attributable in part to different eligibility criteria, background, or methods for evaluating renal function. An alternative explanation is that the association of CKD with carotid atherosclerosis may be somewhat limited.

In a recent Japanese study, CKD was associated with increased IMT only in subjects with hypertension.[5] Similarly, we showed that CKD was independently associated with carotid atherosclerosis in subjects with hypertension, whereas there was no significant impact of CKD in nonhypertensive subjects. Our results suggest that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant vascular risk factors. CKD may not directly contribute to early carotid atherosclerosis but may rather accelerate the development of atherosclerosis in the setting of progressive endothelial dysfunction in those with hypertension.

We could not demonstrate a causal relationship between CKD, hypertension, and carotid atherosclerosis because of the cross-sectional design of our study. However, carotid atherosclerosis reflects the cumulative effects of cardiovascular risk factors that are present over many years. In the future, we plan to determine whether the coexistence of CKD and hypertension increases the risk of carotid atherosclerosis in a prospective study.

In conclusion, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension in an urban general population. Our results suggest that the presence of hypertension should be considered for risk stratification of CKD for improved stroke prevention.

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Disclosures

None.

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High-density Lipoprotein Subclasses and Risk of Stroke and its Subtypes in Japanese Population

The Circulatory Risk in Communities Study

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Background and Purpose—High-density lipoprotein (HDL) cholesterol is an established protective factor for ischemic stroke. However, the contribution of HDL subclasses to stroke risk and its subtypes is uncertain.

Methods—A prospective nested case–control study of 40- to 85-year-old Japanese was undertaken using frozen serum samples collected from 5280 men and 7524 women. They participated in cardiovascular risk surveys from 1985 to 1999 (1 community) and 1989 to 1998 (2 communities) under Circulatory Risk in Communities Study. HDL cholesterol subclasses were classified by high-performance liquid chromatography into 3 subgroups: S-HDL (very small or small HDL), M-HDL (medium HDL), and L-HDL (large or very large HDL) cholesterol. One control subject per case was matched by sex, age, community, serum storage year, and fasting status.

Results—In 2005, we identified 241 strokes (155 ischemic and 86 hemorrhagic). S-HDL and M-HDL cholesterol levels were inversely associated with total stroke risk, ischemic stroke, specifically lacunar infarction, and hemorrhagic stroke. After adjustment for cardiovascular risk factors, these associations remained statistically significant. Multivariable conditional odds ratios (95% confidence interval) for 1 SD (0.12 mmol/L) increment of S-HDL cholesterol levels were 0.34 (0.23–0.52) for total stroke, 0.38 (0.23–0.63) for ischemic stroke, 0.33 (0.18–0.61) for lacunar infarction, 0.30 (0.14–0.65) for hemorrhagic stroke, and 0.30 (0.12–0.77) for intraparenchymal hemorrhage. The respective multivariable odds ratios for 1SD (0.10 mmol/L) increment of M-HDL cholesterol levels were 0.56 (0.41–0.75), 0.63 (0.45–0.88), 0.59 (0.40–0.87), 0.41 (0.21–0.80), and 0.38 (0.16–0.90). No associations were found between L-HDL cholesterol levels and risk of total stroke and its subtypes.

Conclusions—Small- to medium-sized HDL, not large HDL, cholesterol levels were inversely associated with total stroke risk. **(*Stroke*. 2013;44:327-333.)**

Key Words: high-density lipoprotein cholesterol ■ Japanese ■ nested case-control study ■ particle size ■ stroke

High-density lipoprotein (HDL) particles are heterogeneous in structure, having differential effect on their antiatherogenic properties.[1] Small, dense HDL particles display higher cholesterol efflux capacity,[2] potent protection for low-density lipoprotein (LDL) oxidation[3,4], and possess stronger anti-inflammatory properties than large HDL particles.[5]

Lipoprotein subclasses were quantified by gradient gel electrophoresis and nuclear magnetic resonance methods, the findings on the associations of HDL subclasses and cardiovascular disease have been inconsistent. Case–control studies using the gradient gel electrophoresis method reported that small HDL particles were inversely associated with the progression of coronary atherosclerosis[6] and risk of coronary heart disease,[7,8] and other studies showed opposite trends with prevalence of carotid atherosclerosis[9] and ischemic stroke risk.[10] In addition, studies using nuclear magnetic resonance observed that only large HDL particles, not small HDL or medium HDL particles, were inversely associated with risk of cardiovascular disease,[11] whereas another study with the nuclear magnetic resonance method showed that larger HDL particles were inversely associated, and smaller HDL particles

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were positively associated with the prevalence of coronary artery disease.[12]

High-performance liquid chromatography (HPLC) with gel permeation columns is an alternative method for classifying and quantifying lipoproteins according to particle sizes.[13] This method can provide cholesterol levels of major lipoproteins and their subclasses using a small amount of serum or plasma and measure simultaneously cholesterol levels in each lipoprotein fraction and lipoprotein particle size distribution. The HPLC defines 5 HDL subclasses based on HDL particle diameter size, which is similar to gradient gel electrophoresis and nuclear magnetic resonance methods.[13,14] Advantages of the HPLC method include its direct cholesterol determination in HDL and HDL subclasses within 16 minutes by using a small amount of plasma (<10 μL).[13,15]

In the present study, a prospective nested case–control study of men and women was conducted in 3 Japanese communities of the Circulatory Risk in Communities Study (CIRCS) using stored serum samples. We applied the HPLC method to assess HDL subclasses and to seek their associations with risk of stroke and its subtypes.

Methods

Surveyed Populations

The present study was an ancillary study of the CIRCS.[16] CIRCS is a dynamic cohort of Japanese men and women aged ≥30 years in 5 communities across Japan, overseen by a research team from the Osaka Medical Center for Health Science and Promotion, Osaka University and the University of Tsukuba. The surveyed populations comprised 13 314 men and women aged 40 to 85 years, who participated in cardiovascular risk surveys between 1985 and 2000 in a mideastern rural community (Kyowa; participants and census population for 40–85 years; n=6829 and n=8557, respectively) and between 1989 and 1998 in northeastern rural community (Ikawa; n=2570 and n=2981, respectively) and a southwest rural community (Noichi; n=3915 and n=7169, respectively). The participation rate in cardiovascular risk surveys among men and women aged 40 to 85 years was 80% in Kyowa, 86% in Ikawa, 55% in Noichi, and 71% for the total population. A 1.0- to 2.0-mL serum sample obtained from each participant was stored at −80°C for 1 to 20 years (median, 10.5 years). Participants with a history of stroke or coronary heart disease (n=510) were excluded from the analyses. The participants were followed up to determine the incidence of stroke occurring by the end of 2005. The Ethics Committee of Osaka University, The University of Tsukuba and the Osaka Medical Center for Health Science and Promotion approved this study.

Surveillance of Stroke and Classification of Stroke Subtypes

Susceptible cases of stroke were ascertained from national insurance claims, ambulance records, death certificates (cases with stroke as the underlying cause of death [International Classification of Diseases, 9th revision: 430–438] were selected), reports by local physicians, and reports by public health nurses and volunteers. To confirm the diagnosis of stroke, we called, visited, or invited the susceptible subjects to participate in annual cardiovascular risk surveys to obtain clinical histories. In addition, physicians obtained medical histories and reviewed medical records, including computed tomograpy/magnetic resonance imaging from local clinics and hospitals. In the case of deaths, histories were obtained from families, and medical records were reviewed.

The diagnosis of stroke was made according to the criteria of the National Survey of Stroke,[17] which requires a constellation of neurological deficits of sudden or rapid onset lasting ≥24 hours or until death. Strokes were classified as intraparenchymal hemorrhage, subarachnoid hemorrhage, or ischemic stroke (lacunar infarction, large-artery occlusive infarction, and embolic infarction) by computed tomograpy/magnetic resonance imaging using standardized criteria.[18] Strokes with negative findings on imaging studies and unclassified strokes were excluded. For each new case of stroke, 1 control subject was selected randomly from the participants with no incident stroke, matched for sex, age (±2 years), community, year of serum storage, and fasting status at serum collection (<8 and ≥8 hours).

Determination of HDL Particle Size

Nonfasting venous blood was collected in 7- to 10-mL plain tubes and allowed to stand for 30 minutes for serum separation. The serum samples were aliquoted immediately and placed on dry ice at survey sites and then stored at −80°C.

Serum lipoprotein analyses were performed by HPLC with gel permeation columns (LipoSEARCH; Skylight-Biotec, Inc., Akita, Japan).[15] By this method, HDL was classified by particle size into 5 subgroups: 13.5 to 15.0 nm (very large HDL), 12.1 nm (large HDL), 10.9 nm (medium HDL), 9.8 nm (small HDL), and 7.6 to 8.8 nm (very small HDL).[13] To simplify data analysis, we grouped these HDL subclasses as follows: S-HDL (very small or small HDL), M-HDL (medium HDL), and L-HDL (large or very large HDL).

Statistical Analysis

The odds ratios and 95% confidence intervals for total stroke and stroke subtype were estimated according to quartiles and 1SD increment of total HDL, S-HDL, M-HDL, and L-HDL cholesterol levels with conditional logistic regression models. Adjustment was made for hypertension status (normal, borderline, and hypertension), body mass index (kg/m^2), current alcohol intake (g/d), cigarette smoking status (never, ex-smoker, and current), cholesterol-lowering medication (yes/no), log-transformed triglycerides levels (mmol/L), and serum glucose category (normal, impaired glucose tolerance, and diabetes mellitus). SAS version 9.1.3 was used for the statistical analyses (2-tailed).

Results

Age-adjusted baseline characteristics of the controls according to quartiles of HDL subclasses are shown in Table 1. Body mass index was inversely associated with total HDL cholesterol and L-HDL, and the prevalence of current smokers was lower with the higher quartiles of L-HDL cholesterol levels. Total HDL cholesterol levels were positively associated with S-HDL, M-HDL, and L-HDL cholesterol levels, whereas triglycerides were inversely associated with total HDL cholesterol, S-HDL, M-HDL, and L-HDL cholesterol levels. Mean blood pressure, mean ethanol intake, and prevalence of hypertensive and glucose abnormality did not vary according to total HDL cholesterol, S-HDL, M-HDL, and L-HDL cholesterol levels. The prevalence of diabetes mellitus was lower with the higher quartiles of total HDL and L-HDL cholesterol levels.

During the follow-up period, we identified 241 incident strokes comprising 155 ischemic strokes (116 lacunar infarctions, 35 large-artery occlusive infarctions, and 11 embolic infarctions) and 86 hemorrhagic strokes (64 intraparenchymal hemorrhages and 22 subarachnoid hemorrhages).

Table 2 shows odd ratios and 95% confidence intervals for total stroke and stroke subtypes according to the quartiles and 1SD increment of total HDL, S-HDL, M-HDL, and L-HDL cholesterol levels. We did not show the results for large-artery occlusive infarction, embolic infarctions, and subarachnoid hemorrhage because of small incidence numbers. Total HDL cholesterol levels were inversely associated

Table 1. Age-adjusted Baseline Characteristics of Control Subjects According to Quartiles of High-density Lipoprotein Cholesterol Levels by High-density Lipoprotein Subclass

	Total HDL cholesterol, mg/dL					L-HDL, mg/dL					M-HDL, mg/dL					S-HDL, mg/dL				
	13.1–36.0	36.5–44.9	45.0–53.7	54.0–87.8	*P* for trend	5.1–12.1	12.1–17.1	17.1–24.2	24.3–51.6	*P* for trend	1.9–9.1	9.2–11.6	11.9–14.4	14.4–21.5	*P* for trend	3.9–11.7	11.7–14.6	14.7–17.9	17.9–39.6	*P* for trend
No. of controls	51	58	67	65		65	53	66	57		52	54	66	69		45	57	68	71	
Age, y	66	67	65	66	0.56	66	67	65	65	0.56	67	68	65	64	0.03	67	65	66	66	0.87
Men, %	55	52	47	51	0.74	57	50	44	54	0.58	47	51	57	48	0.78	40	56	56	49	0.61
Systolic BP, mm Hg	135	137	134	132	0.25	135	138	133	132	0.21	132	135	138	133	0.54	134	136	134	134	0.83
Diastolic BP, mm Hg	79	79	78	77	0.34	80	78	76	79	0.36	78	77	80	77	0.84	77	80	79	78	0.80
Hypertension, %	39	42	34	37	0.71	41	44	34	32	0.33	37	37	36	41	0.64	35	39	35	41	0.91
Body mass index, kg/m^2	23.9	23.8	23.0	22.8	0.03	24.2	24.0	23.3	21.6	<0.001	22.8	22.9	23.7	23.6	0.07	23.0	23.1	22.9	24.0	0.12
Ethanol intake, g/d	13.2	11.7	11.3	14.7	0.73	16.1	9.7	10.9	13.9	0.64	10.7	11.3	10.7	17.4	0.10	9.6	13.1	11.0	16.1	0.15
Current smokers, %	38	30	19	23	0.07	48	20	24	12	0.001	28	25	27	26	0.94	6	18	16	18	0.57
Cholesterol-lowering medication, %	4	3	5	0	0.23	5	6	2	0	0.96	2	2	5	3	0.78	2	2	4	3	0.85
Total HDL cholesterol, mmol/L	0.74	1.05	1.26	1.61	<0.001	0.90	1.05	1.32	1.51	<0.001	0.84	1.08	1.24	1.51	<0.001	0.85	1.15	1.25	1.38	<0.001
L-HDL, mmol/L	0.26	0.36	0.53	0.71	<0.002	0.23	0.37	0.52	0.81	<0.002	0.39	0.45	0.49	0.56	<0.002	0.43	0.52	0.50	0.44	0.91
M-HDL, mmol/L	0.20	0.30	0.33	0.41	<0.003	0.27	0.29	0.37	0.33	<0.003	0.18	0.26	0.34	0.44	<0.003	0.19	0.29	0.34	0.40	<0.001
S-HDL, mmol/L	0.29	0.39	0.40	0.48	<0.004	0.40	0.38	0.43	0.38	0.79	0.27	0.36	0.42	0.51	<0.004	0.23	0.34	0.41	0.54	<0.002
Triglycerides, mmol/L	1.77	1.52	1.13	1.00	<0.005	1.77	1.4	1.13	0.98	<0.001	1.47	1.40	1.29	1.10	0.001	1.50	1.31	1.23	1.21	0.02
Impaired glucose tolerance, %	12	12	14	9	0.64	14	12	14	7	0.97	9	11	15	11	0.32	16	9	12	12	0.87
Diabetes mellitus, %	14	7	5	6	0.04	11	10	5	5	0.04	12	5	9	5	0.23	9	7	9	6	0.84

Triglycerides are expressed as geometric mean

BP indicates blood pressure; HDL, high-density lipoprotein; L-HDL, large high-density lipoprotein; M-HDL, medium high-density lipoprotein; and S-HDL, small high-density lipoprotein.

Table 2. Odds Ratios (95% Confidence Interval) of Stroke and Subtypes According to High-density Lipoprotein Cholesterol Levels by High-density Lipoprotein Subclass

	Total HDL cholesterol					L-HDL quartiles				
	1	2	3	4	OR per 1 SD increment	1	2	3	4	OR per 1 SD increment
Total stroke										
No of cases	70	62	54	55		55	67	56	63	
No of controls	51	58	67	65		65	53	66	57	
Age-, sex-, and community-matched OR	1.00	0.67 (0.39–1.17)	0.46 (0.25–0.84)*	0.47 (0.26–0.88)*	0.85 (0.69–1.06)	1.00	1.54 (0.91–2.62)	1.04 (0.62–1.76)	1.38 (0.78–2.41)	1.09 (0.89–1.32)
Multivariable OR[a]	1.00	0.60 (0.33–1.10)	0.41 (0.21–0.81)*	0.40 (0.19–0.80)†	0.79 (0.61–1.02)	1.00	1.78 (1.00–3.16)	1.25 (0.70–2.23)	1.57 (0.81–3.05)	1.13 (0.89–1.44)
Ischemic stroke										
No of cases	49	43	28	35		38	42	37	38	
No of controls	38	39	39	39		44	38	40	33	
Age-, sex-, and community-matched OR	1.00	0.77 (0.41–1.44)	0.46 (0.22–0.96)*	0.57 (0.27–1.18)	0.89 (0.69–1.15)	1.00	1.30 (0.70–2.44)	1.11 (0.58–2.11)	1.40 (0.69–2.83)	1.11 (0.87–1.41)
Multivariable OR[a]	1.00	0.66 (0.33–1.35)	0.37 (0.15–0.87)*	0.47 (0.20–1.12)	0.85 (0.62–1.16)	1.00	1.70 (0.83–3.48)	1.35 (0.65–2.80)	1.80 (0.76–4.24)	1.19 (0.87–1.62)
Lacunar infarction										
No of cases	40	30	21	25		31	34	21	30	
No of controls	23	31	30	32		30	26	33	27	
Age-, sex-, and community-matched OR	1.00	0.50 (0.23–1.07)	0.29 (0.12–0.72)†	0.33 (0.14–0.79)*	0.82 (0.61–1.10)	1.00	1.25 (0.60–2.61)	0.58 (0.26–1.30)	1.00 (0.44–2.25)	1.02 (0.78–1.34)
Multivariable OR[a]	1.00	0.52 (0.22–1.21)	0.23 (0.08–0.67)†	0.27 (0.10–0.75)*	0.75 (0.53–1.06)	1.00	1.77 (0.75–4.16)	0.62 (0.24–1.60)	0.97 (0.35–2.69)	1.02 (0.72–1.44)
Hemorrhagic stroke										
No of cases	21	19	26	20		17	25	19	25	
No of controls	13	19	28	26		21	15	26	24	
Age-, sex-, and community-matched OR	1.00	0.46 (0.14–1.47)	0.39 (0.13–1.20)	0.30 (0.09–1.00)	0.75 (0.50–1.13)	1.00	2.24 (0.83–6.06)	1.00 (0.40–2.51)	1.46 (0.56–3.84)	1.04 (0.74–1.46)
Multivariable OR[a]	1.00	0.46 (0.13–1.64)	0.44 (0.12–1.62)	0.35 (0.09–1.35)	0.79 (0.49–1.29)	1.00	2.71 (0.83–8.84)	1.43 (0.45–4.56)	1.87 (0.57–6.13)	1.17 (0.76–1.80)
Intraparenchymal hemorrhage										
No of cases	13	18	17	16		12	18	16	18	
No of controls	9	14	21	20		17	10	17	20	
Age-, sex-, and community-matched OR	1.00	0.66 (0.15–2.99)	0.36 (0.08–1.57)	0.33 (0.07–1.52)	0.74 (0.45–1.22)	1.00	2.85 (0.86–9.47)	1.49 (0.49–4.54)	1.45 (0.44–4.81)	1.08 (0.72–1.62)
Multivariable OR[a]	1.00	0.80 (0.13–4.95)	0.52 (0.07–3.89)	0.32 (0.05–2.16)	0.68 (0.37–1.28)	1.00	4.06 (0.74–22.2)	3.71 (0.61–2.60)	1.60 (0.25–10.4)	1.06 (0.60–1.87)

BMI indicates body mass index; HDL, high-density lipoprotein; L-HDL, large high-density lipoprotein; M-HDL, medium high-density lipoprotein; OR, odds ratio; and S-HDL, small high-density lipoprotein.

*P<0.05, †P<0.01, ‡P<0.001.

[a]Adjusted for hypertension status BMI, current alcohol intake, cigarette smoking status, cholesterol-lowering medication, log-transformed triglyceride levels, serum glucose category, and matching for sex, age, community, year of serum stored, and fasting status.

with risk of total stroke and lacunar infarction but not of hemorrhagic stroke. S-HDL cholesterol levels were strongly and inversely associated with risk of total stroke, ischemic stroke, particularly lacunar infarction, and hemorrhagic stroke, specifically intraparenchymal hemorrhage. These associations remained statistically significant after further adjustment for cardiovascular risk factors. Moderate inverse associations were observed between M-HDL cholesterol levels and risk of total stroke and its subtypes. No associations were found between L-HDL cholesterol levels and risk of total stroke or its subtypes.

Discussion

The present study is the first study to show that higher cholesterol levels in small HDL and medium HDL particles were associated with lower risk of total stroke, either ischemic or hemorrhagic stroke even after adjustment for known cardiovascular risk factors and matching variables of age, sex, years of serum

M-HDL quartiles					S-HDL quartiles				
1	2	3	4	OR per 1 SD increment	1	2	3	4	OR per 1 SD increment
68	67	55	51		75	64	53	49	
52	54	66	69		45	57	68	71	
1.00	0.77 (0.42–1.39)	0.41 (0.21–0.80)†	0.35 (0.17–0.69)†	0.64 (0.49–0.83)‡	1.00	0.36 (0.18–0.73)†	0.14 (0.06–0.33)‡	0.08 (0.03–0.21) ‡	0.39 (0.27–0.57)‡
1.00	0.66 (0.34–1.28)	0.31 (0.15–0.64)†	0.23 (0.11–0.51)‡	0.56 (0.41–0.75)‡	1.00	0.37 (0.17–0.78)†	0.18 (0.06–0.34)‡	0.05 (0.02–0.15) ‡	0.34 (0.23–0.52) ‡
46	41	35	33		50	40	32	33	
37	33	41	44		31	36	42	46	
1.00	0.84 (0.41–1.73)	0.51 (0.24–1.10)	0.44 (0.12–0.97)*	0.72 (0.54–0.96)*	1.00	0.33 (0.13–0.85)*	0.14 (0.05–0.42)‡	0.09 (0.03–0.30) ‡	0.44 (0.28–0.69) ‡
1.00	0.72 (0.33–1.61)	0.39 (0.17–0.90)*	0.30 (0.12–0.76)*	0.63 (0.45–0.88)†	1.00	0.34 (0.13–0.89)*	0.14 (0.05–0.44)‡	0.07 (0.02–0.25)‡	0.38 (0.23–0.63)‡
33	32	26	25		36	30	26	24	
26	23	33	34		20	30	30	36	
1.00	0.92 (0.40–2.15)	0.45 (0.18–1.12)	0.40 (0.16–1.01)	0.68 (0.49–0.95)*	1.00	0.26 (0.09–0.79)*	0.13 (0.04–0.47))†	0.08 (0.02–0.31)‡	0.36 (0.21–0.63)‡
1.00	0.70 (0.27–1.80)	0.35 (0.13–0.94)*	0.30 (0.11–0.86)*	0.59 (0.40–0.87)†	1.00	0.29 (0.09–0.93)*	0.15 (0.04–0.57)†	0.07 (0.02–0.32)‡	0.33 (0.18–0.61)‡
22	26	20	18		25	24	21	16	
15	21	25	25		14	21	26	25	
1.00	0.58 (0.19–1.74)	0.21 (0.05–0.83)*	0.17 (0.04–0.72)*	0.43 (0.24–0.78)†	1.00	0.40 (0.14–1.13)	0.12 (0.03–0.52)†	0.04 (0.01–0.28)‡	0.30 (0.15–0.61)‡
1.00	0.30 (0.07–1.34)	0.11 (0.02–0.62)*	0.09 (0.02–0.53)†	0.41 (0.21–0.80)†	1.00	0.45 (0.13–1.54)	0.12 (0.02–0.66)*	0.02 (0.002–0.20)‡	0.30 (0.14–0.65)‡
14	23	17	10		17	21	16	10	
10	19	17	18		9	18	20	17	
1.00	0.64 (0.19–2.22)	0.31 (0.06–1.58)	0.14 (0.03–0.82)*	0.36 (0.17–0.75)†	1.00	0.42 (0.13–1.36)	0.15 (0.03–0.68)*	0.04 (0.005–0.35)†	0.29 (0.13–0.66)†
1.00	0.25 (0.04–1.72)	0.18 (0.02–1.60)	0.06 (0.005–0.62)*	0.38 (0.16–0.90)*	1.00	0.46 (0.11–2.00)	0.16 (0.03–1.02)	0.02 (0.001–0.29)†	0.30 (0.12–0.77)*

storage, fasting status, and community. There was no association between L-HDL cholesterol levels and risk of total stroke and its subtypes. Risk of total stroke was ≈90% lower among persons at the highest quartile of S-HDL cholesterol levels or M-HDL cholesterol levels than among those at the lowest quartile. S-HDL and M-HDL cholesterol levels were not associated with age, sex, blood pressure levels, body mass index, smoking, and diabetes mellitus. Taken together, higher cholesterol levels in S-HDL and M-HDL are suggested to reduce risk of stroke beyond the effects of other conventional risk factors. Small HDL and medium HDL cholesterol levels can be increased by increasing dietary intake of carbohydrate[19] and use of fenofibrate.[20] These nonpharmacological and pharmacological interventions may increase hepatic triglyceride lipase activity that promotes the conversion of large HDL particles into small HDL particles via cholesteryl ester transfer protein.[21,22]

Mechanisms for HDL subpopulation in protection against cardiovascular disease are complex and not fully understood. The ATP-binding cassette transporter A1 (ABCA1) mediates the efflux of cellular cholesterol and phospholipids to lipid-poor apolipoproteins.[23,24] Because smaller HDL particles contained phospholipid and more apoA-1 compared with large HDL particles, they have a larger capacity to remove cholesterol from membranes of peripheral cells, particularly macrophages and form cells.[2] Our result is in line with this mechanism, supporting those subjects with higher cholesterol levels in small HDL or medium HDL particle subclasses may protect against atherosclerosis and atherosclerotic cardiovascular disease. The inverse association between cholesterol levels in smaller HDL particles and risk of cardiovascular disease was observed in the Epic-Norfolk prospective population study,[8] Lopid Coronary Angiography Trial Study[6], and Caerphilly Study.[7] The ATP-binding cassette transporter G1 (ABCG1) stimulates the cholesterol efflux to larger HDL particles[25] because larger HDL particles are the preferred acceptor of ABCG1-mediated cholesterol efflux.[26] This may explain findings of a previous study that large HDL particles were inversely associated with risk of cardiovascular disease, including myocardial infarction and ischemic stroke in women.[11] ABCA1 mediates cholesterol and phospholipid efflux to lipid-poor apoA-I but not to mature HDL. ABCG1 mediates macrophage cholesterol efflux to mature HDL, which might explain mechanism of the relationship of HDL to atherosclerosis risk.[25] However, a study with mice suggested that both ABCA1 and ABCG1 contribute to macrophage reverse cholesterol transport. That study showed a greater decrease in macrophage reverse cholesterol transport from cells where both ABCA1 and ABCG1 expressions were knocked down than from ABCG1-knockdown cells.[27] Another study also indicated that ABCA1 may lipidate lipid-poor apoA-I to generate nascent HDL, which can then act as acceptor for ABCG1-mediated cholesterol efflux.[28]

The present study first showed that cholesterol levels in smaller HDL particles were inversely associated with risk of lacunar infarction. The mechanism for a protective effect of small HDL particles on lacunar infarction is unknown. Anti-inflammatory effects of smaller HDL particles[5,29] may reduce risk of lacunar infarction by inhibiting angionecrosis[30,31] or microatheroma formation[32] in cerebral vessels.

An inverse association was found between smaller HDL cholesterol levels and risk of hemorrhagic stroke, primarily intraparenchymal hemorrhage. One mechanism to explain the protective effect of smaller HDL particles might be their enriched apolipoprotein and enzymes with antioxidative activities.[4] Reduced LDL oxidation may contribute to inhibition of microatheroma formation in small cerebral vessels.[31,33,34]

The strength of the present study is the large number of strokes confirmed by imaging studies, which allowed investigation of the association between S-HDL, M-HDL, and L-HDL cholesterol levels and risk of total stroke and its subtypes. There are several limitations. First, we used frozen serum to estimate HDL cholesterol levels and did not examine long-term changes in HDL cholesterol levels in stored serum samples. A previous study on frozen storage (−70°C) of serum samples for up to 7 years showed no significant change in HDL cholesterol.[35] Second, the frozen serum samples used in the present study had been thawed once. However, a previous study reported that freezing and thawing of HDL have no effect on HDL particle size.[36]

In conclusion, the present study showed that cholesterol levels in small HDL and medium HDL particles were inversely associated with risks of total stroke, either ischemic or hemorrhagic stroke, whereas those in large HDL particles were not associated with risk of total stroke or any subtypes.

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Disclosure

None.

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Ⅵ　脂質異常症・動脈硬化の検査・診断

LDLコレステロール直接法の現在の課題

三井田　孝　　西村邦宏