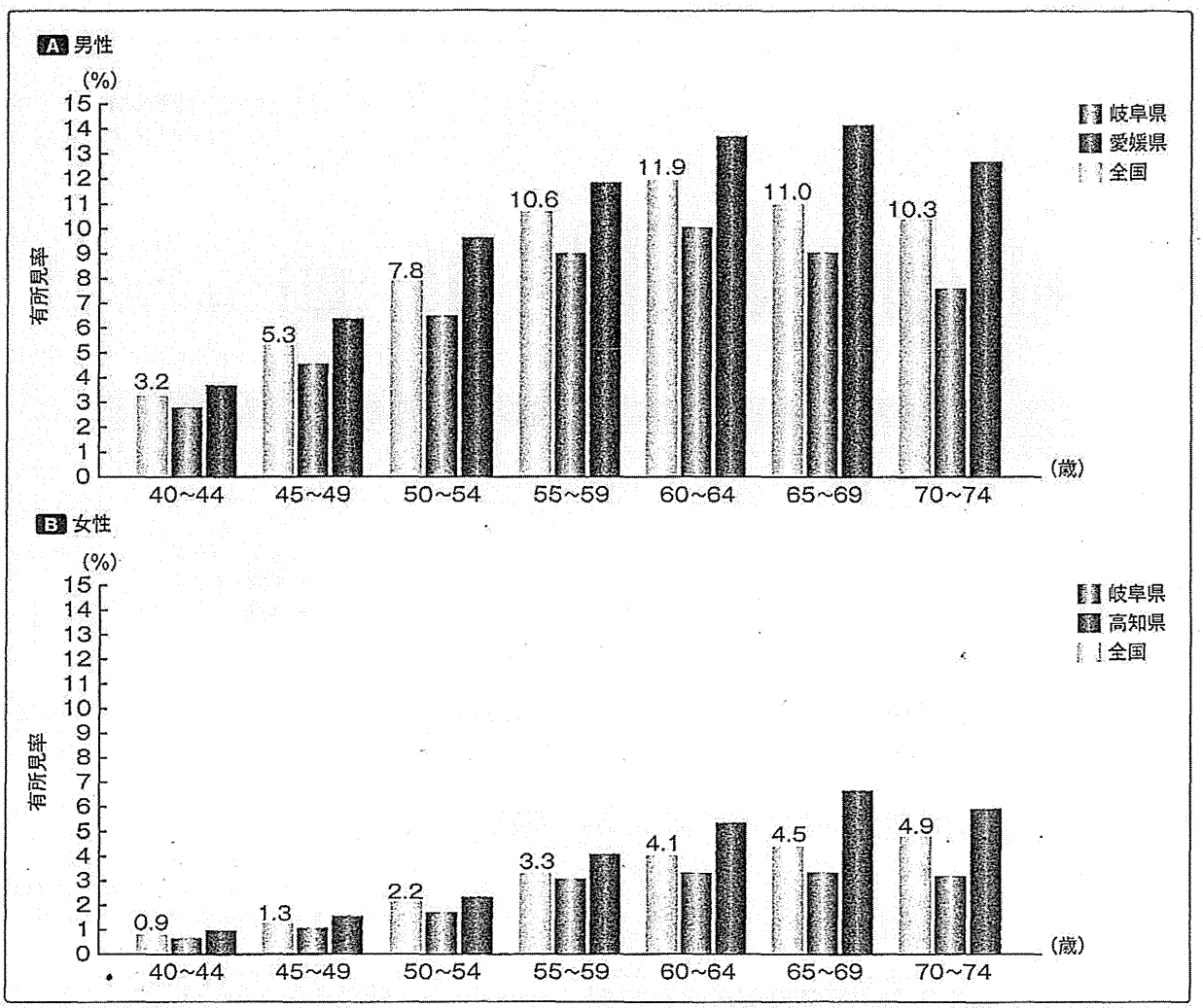

図7 特定健診ナショナルデータベースより分析した性別・年齢階級別の空腹時高血糖有所見率（全国・最大県・最小県の比較，特定健診2010年暫定データによる）

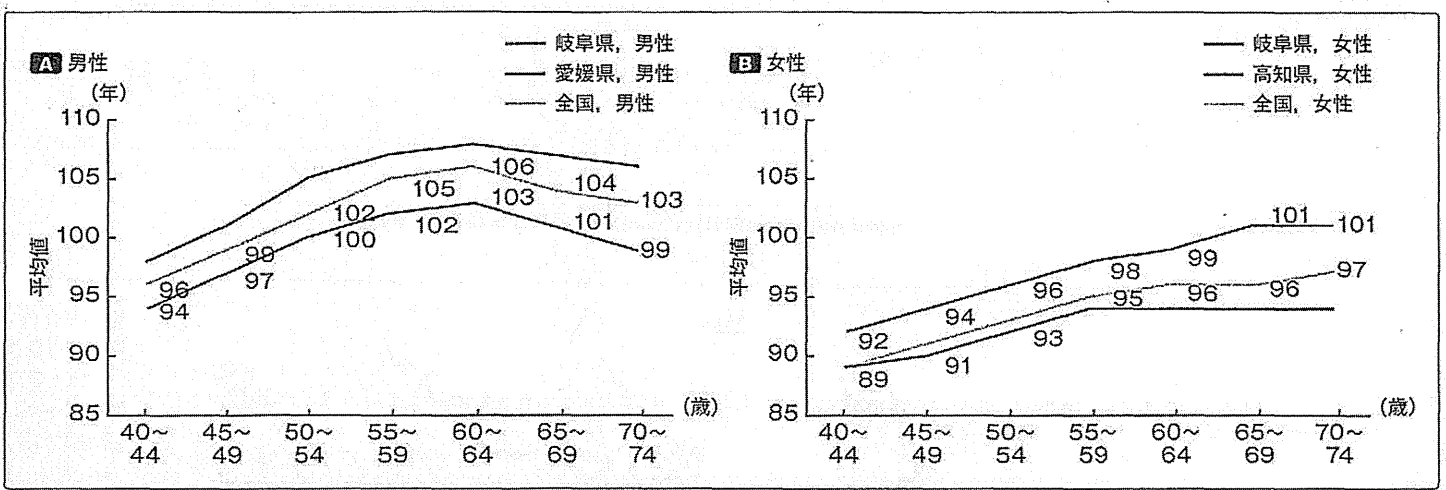

図8 特定健診ナショナルデータベースより分析した空腹時血糖値の性別・年齢階級別平均値（全国・最大県・最小県の比較）

県と低い県について，性別・年齢階級別の有所見率，平均値を図7，図8に示した．異常率の高い県ではすでに40歳代前半より高く，加齢による変化は全国値を＋2～3 mg/dl平行移動した状況で推移している．

さらに，愛知県の特定健診データベースを用い，糖尿病治療の有無とHbA1cの関連を検討した（図9）．平成22年度の特定健診受診者でHbA1cを測定した85万2千人のうち，HbA1c（JDS）8.0 %以上は1.2 %（10,285人），そのうち糖尿病治療中と回答したのは5,986人（58.2 %）であり，残りの4割は糖尿病の治療を受けていなかった．

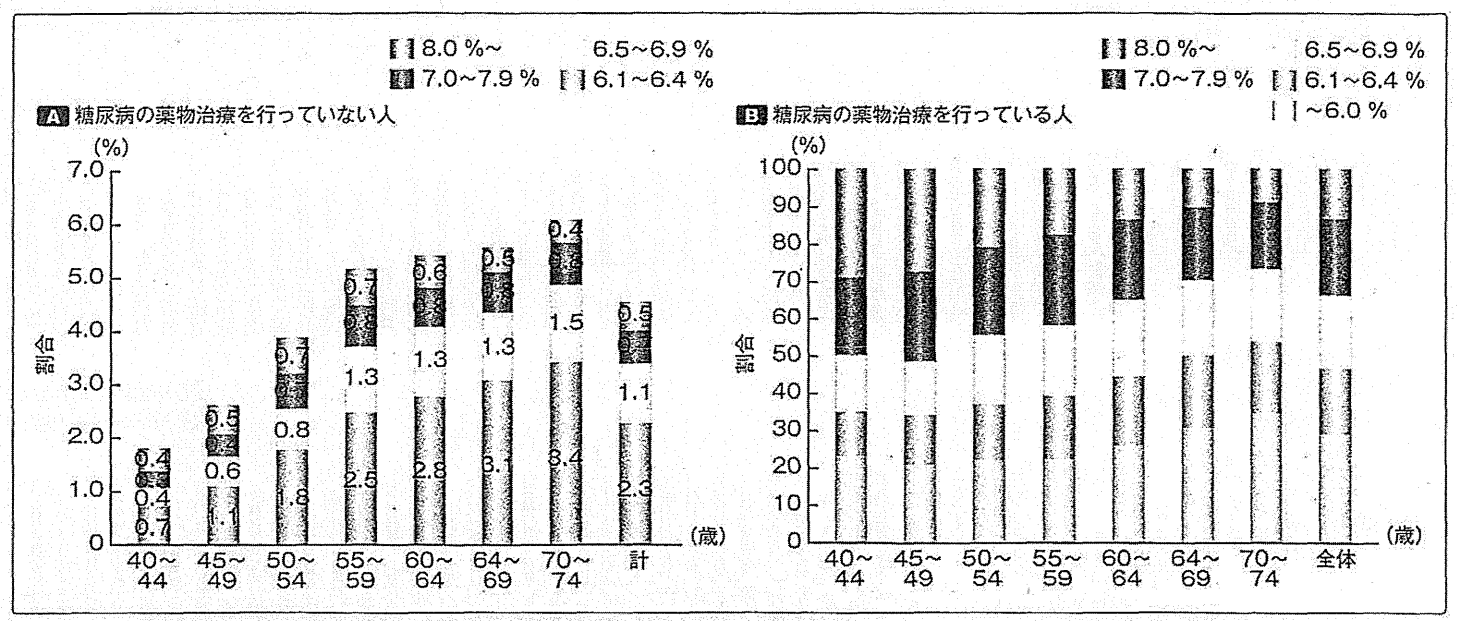

図9 糖尿病治療の有無別にみたHbA1c(JDS)の区分別割合(平成21年愛知県「特定健診・特定保健指導情報データ分析・評価」)

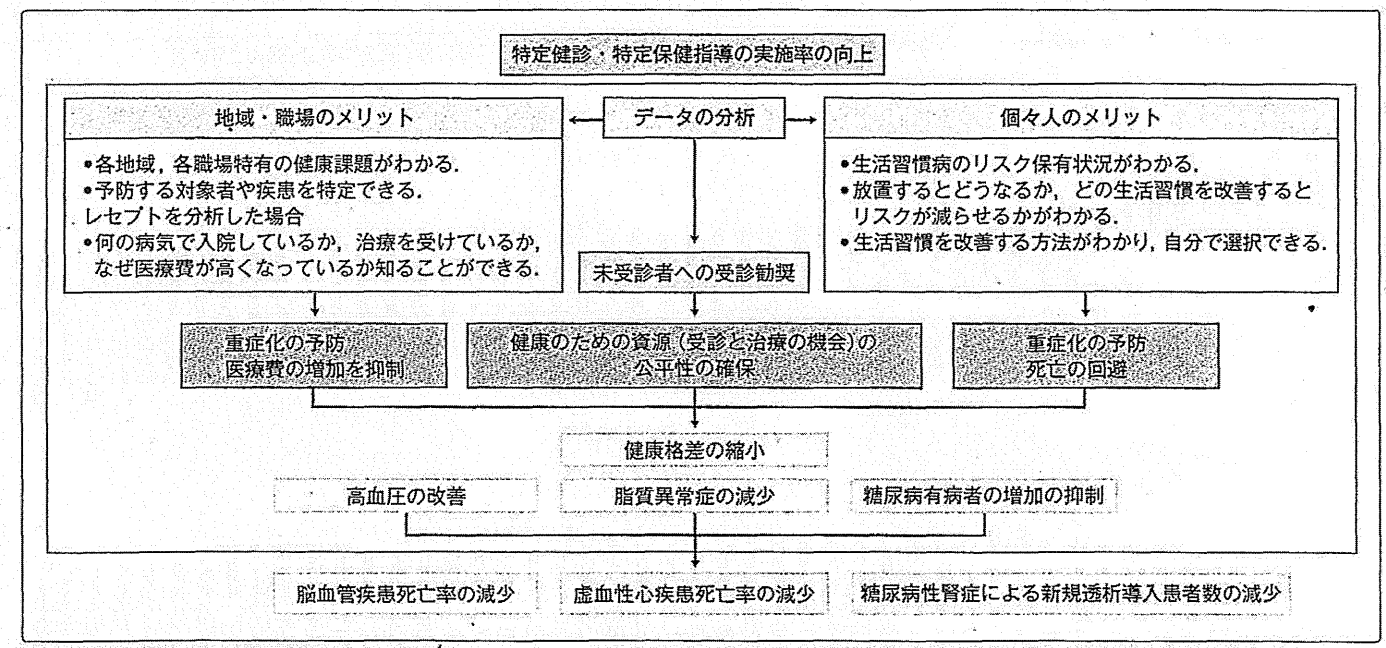

図10 特定健診・特定保健指導と健康日本21(第2次):特定健診・保健指導のメリットを活かして健康日本21(第2次)を着実に推進(文献13)

健診で高血糖を指摘されていても治療につながっていない状況があると考えられる．一方，糖尿病治療中と回答した約4万人のうち，34 %はHbA1c (JDS) が7.0 %以上であり，とくに40歳代のコントロールが不十分であることがわかった．

この結果から，糖尿病では治療につながっていない人が多く，健診の機会を通じて受診勧奨を積極的に進める必要があると考えられる．また治療中でもコントロール不良の場合，食事療法や運動療法などの履行が難しい，治療を中断しやすいなどの問題が考えられる．医療保険者と医療機関が連携した対応が必要であると考えられる．

おわりに：特定健診・保健指導を活用した今後の糖尿病対策

今年度発出された「標準的な健診・保健指導プログラム改訂版」では，「特定健診・特定保健指導の実施率の向上を図りつつ，分析に基づく取組を実施していくことは，健康日本21（第二次）を着実に推進し，ひいては社会保障制度を持続可能なものとするために重要である」としている（図10）[13]．特定健診データを分析することで，地方自治体の健康課題を把握できるため，健康日本21の推進

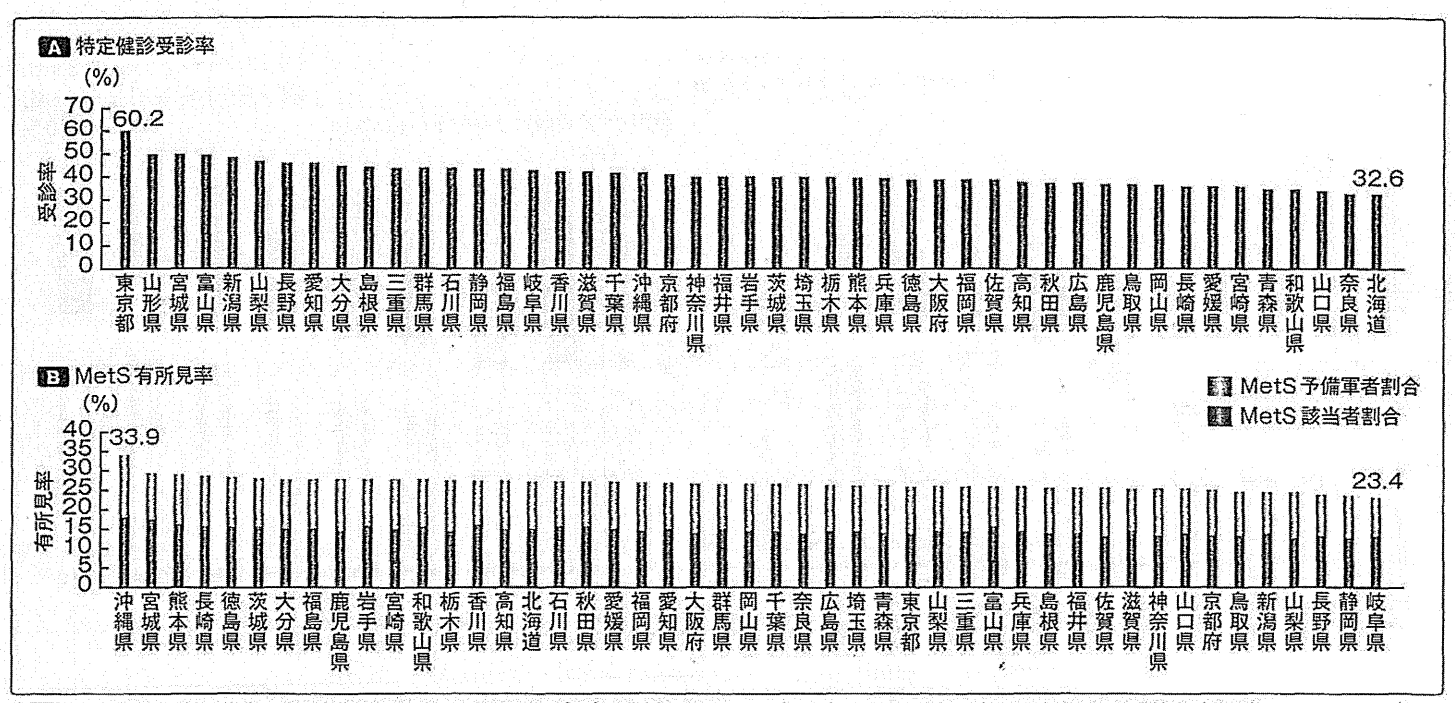

図11 平成22年度都道府県別特定健診受診率およびMetS有所見率(全国2223万人のデータをもとに厚生労働省NDB公表値より作成)

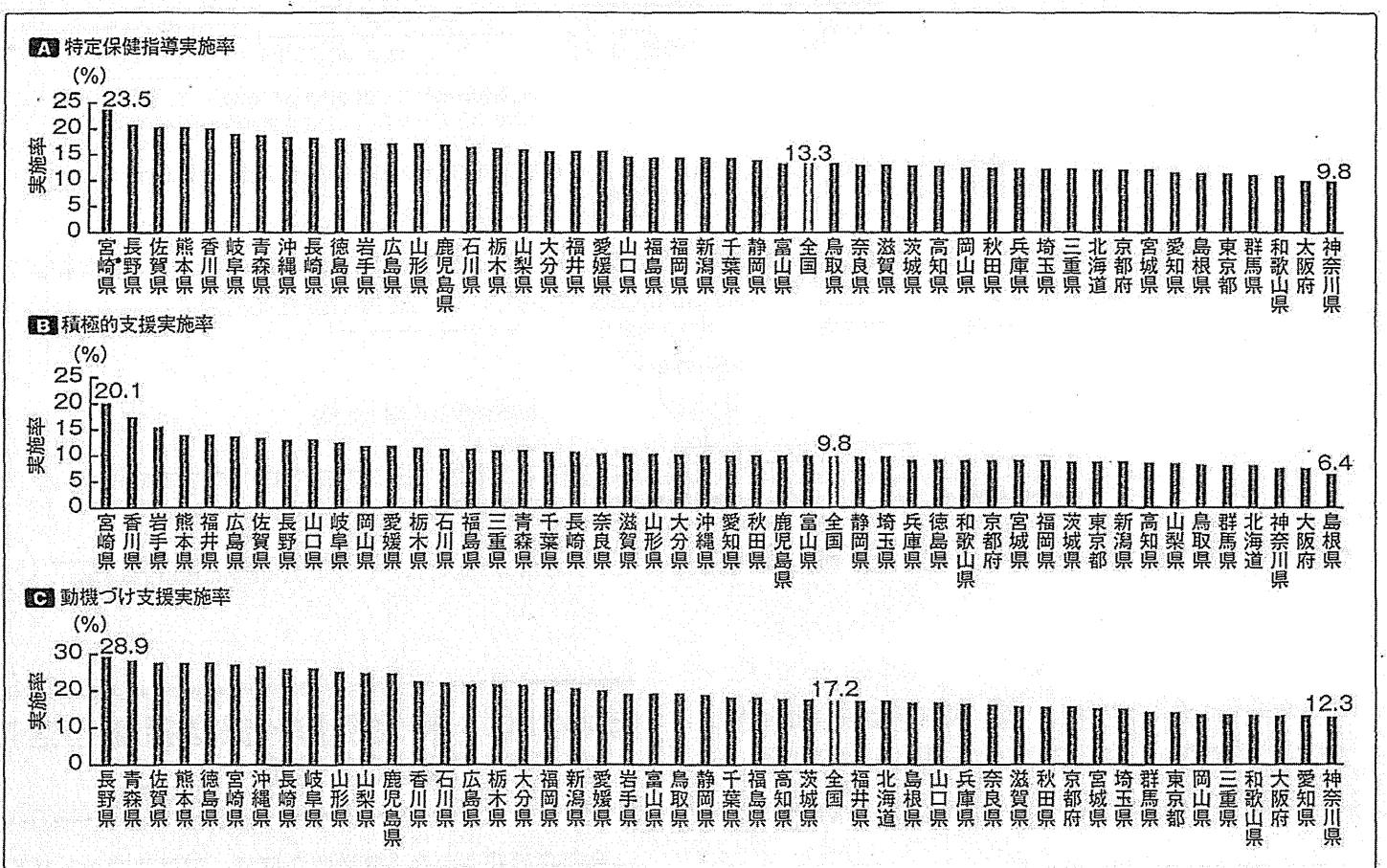

図12 全医療保険者総計：都道府県別保健指導実施率(平成22年度)

のために活用していくことが重要である.

課題として指摘されることは特定健診，特定保健指導実施率の低さ，地域間格差，医療保険者間格差である．平成22年度特定健診受診率は43.2％であるが，全国で最も高い東京では60％，低い北海道では33％と2倍近い開きがある（図11）．保健指導実施率についても，図12と図13に示した通りであり，とくに低い地域での底上げが必要とされよう．保険者ごとに，また地域ごとに，より

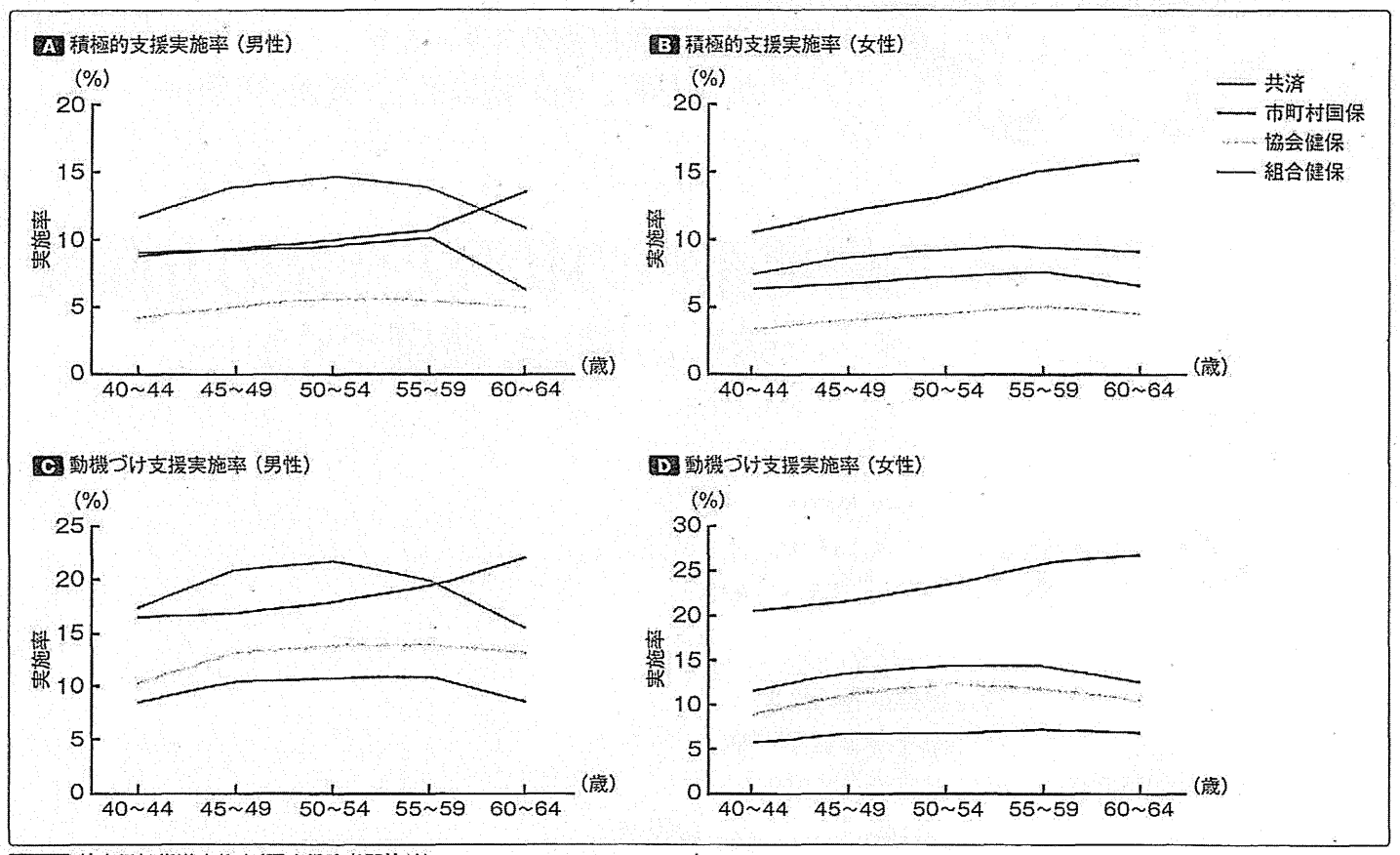

図13 特定保健指導実施率（医療保険者間比較）

実施率と効果性の高まる方法の研究と実践が必要とされる．

標準プログラムの普及，指導者の育成，電子システム構築などの実施体制の整備の段階を経て，ようやく軌道に乗りかけたところである．糖尿病の個人のコントロール改善には血糖値，HbA1cのモニタリングが重要であるように，集団においてもデータ分析結果を活用した対策の強化が期待される．

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Profile

津下一代（つした かずよ）
1983年 名古屋大学 医学部 医学科 卒業，国立名古屋病院 研修医
1985年 国立名古屋病院 内科
1989年 名古屋大学 第一内科 第5研究室（内分泌・代謝）
1992年 愛知県総合保健センター 総合診断部
2000年 あいち健康の森健康科学総合センター 勤務
2010年 同 センター長，現在に至る

MAIN THEME

特集
糖尿病と国家規模のスキーム
—わが国の糖尿病対策はどこへ向かうのか—

特定健診・特定保健指導の状況と今後の方向性
—ナショナルデータベースを活用した健康づくり—

村本あき子 ● *Muramoto, Akiko*（写真）
津下一代 ● *Tsushita, Kazuyo*
あいち健康の森健康科学総合センター

1 ● 第一期特定健診・特定保健指導の概要
2 ● 第一期特定健診・特定保健指導実施状況
3 ● 第一期特定健診・特定保健指導の成果
4 ● 第二期特定健診・特定保健指導の改訂点，着眼点

はじめに

糖尿病をはじめとする生活習慣病は，健康長寿の最大の阻害要因になるだけでなく，国民医療費にも多大な影響を与えている．その多くは不健康な生活の積み重ねによる内臓脂肪型肥満により引きおこされるが，身体活動の増加やバランスのとれた食事，禁煙といった生活習慣改善によって予防できる．

特定健診・特定保健指導制度開始から5年が経過した．当制度において，健診・保健指導にメタボリックシンドローム（MetS）の概念が導入され，健診は自らの健康状態や生活習慣の課題に気づかせ，生活習慣改善に向けて働きかける機会として位置づけられた[1,2]．これまでに，複数の厚生労働科学研究などにおいて特定保健指導の効果評価が行われ，生活習慣改善支援による生活習慣病予防・改善効果が示されている．

特定健診・特定保健指導制度には，医療保険者に健診・保健指導の実施を義務づけたこと，血液検査項目や問診項目，健診項目の判定基準や保健指導の方法を標準化し，電子的にデータを集約・評価するシステムを導入したことなどの特徴がある．当制度の導入によりナショナルデータベースの分析が可能になったことは，わが国の健康づくりを推進するうえで大きな成果といえよう．

本稿では，特定健診・特定保健指導制度の実施状況とこれまでに得られた成果，平成25年4月から始まった第二期特定健診・特定保健指導制度の方向性について述べる．

1 第一期特定健診・特定保健指導の概要（図1）[3]

特定健診では，各検査項目において「保健指導判定値」，「受診勧奨判定値」が設けられている．保健指導は健診受診者全員に対して行うが，健診結果および質問項目から生活習慣病の危険因子の数に応じて，「情報提供」のみ行うレベル，「情報提供」および「動機づけ支援」を行うレベル（主にMetS予備群該当者），「情報提供」および「積極的支援」を行うレベル（主にMetS該当者）の3種類に区分する．

「動機づけ支援」では，対象者自らが行動目標を立て，6カ月後に行動目標の達成状況や，身体状況・生活習慣に変化がみられたかについて評価

健診検査項目の判定値

項目		データ基準 保健指導判定値	受診勧奨判定値
収縮期血圧	(mmHg)	130	140
拡張期血圧	(mmHg)	85	90
中性脂肪	(mg/dl)	150	300
HDL-C	(mg/dl)	39	34
LDL-C	(mg/dl)	120	140
空腹時血糖	(mg/dl)	100	126
HbA1c(NGSP)	(%)	5.6	6.5
AST	(U/l)	31	61
ALT	(U/l)	31	61
γGTP	(U/l)	51	101

保健指導対象者の選定と階層化

ステップ1（内臓脂肪蓄積のリスク判定）

・腹囲　男性≧85cm，女性≧90cm　→（1）
・腹囲　男性<85cm，女性<90cm かつ BMI≧25　→（2）

ステップ2（追加リスク数の判定）

○ 検査結果，質問票より追加リスクをカウントする．
○ ①～③はメタボリックシンドロームの判定項目，④はその他の関連リスクとし，④喫煙歴については①から③のリスクが1つ以上の場合にのみカウントする．

①空腹時血糖≧100mg/dl または　HbA1c(NGSP)≧5.6%
　または　薬剤治療を受けている場合
②中性脂肪≧150mg/dl または　HDL-C <40mg/dl
　または　薬剤治療を受けている場合
③収縮期血圧≧130mmHg または　拡張期血圧≧85mmHg
　または　薬剤治療を受けている場合
④質問票　喫煙歴あり

ステップ3（保健指導レベルの分類）

○ ステップ1，2から保健指導対象者をグループ分け

（1）の場合
①～④のリスクのうち追加リスクが　2以上の対象者は　積極的支援レベル
　1の対象者は　動機づけ支援レベル
　0の対象者は　情報提供レベル

（2）の場合
①～④のリスクのうち追加リスクが　2以上の対象者は　積極的支援レベル
　1又は2の対象者は　動機づけ支援レベル
　0の対象者は　情報提供レベル

図1　第一期特定健診・特定保健指導の概要（文献3より）

する．「積極的支援」では，「動機づけ支援」に加えて3カ月以上，継続的に支援する．

2 第一期特定健診・特定保健指導実施状況

平成23年度特定健康診査・特定保健指導の実施状況（速報値）によると，平成23年度の特定健診対象者数は約5,250万人で，受診者数は約2,360万人，特定健診実施率は45.0%である[4]．

また，平成23年度に特定保健指導の対象者となった者は約420万人であり，うち特定保健指導終了者は約66.6万人（特定保健指導実施率：15.9%）であった．

制度が開始された平成20年度からの推移をみると，各保険者，健診・保健指導実施機関により制度の周知が図られたこと，実施しやすい体制が整いつつあることなどにより，特定健診実施率・保健指導実施率はともに徐々に高まってきている状況がみられる．だが，目標値である70%，45%にはいまだ開きがあり，引き続き実施率の向上が課題である．

3 第一期特定健診・特定保健指導の成果

1）ナショナルデータベースの構築と活用

本制度開始以前の健診データは国全体として統一されておらず，実施機関が異なると比較が不可

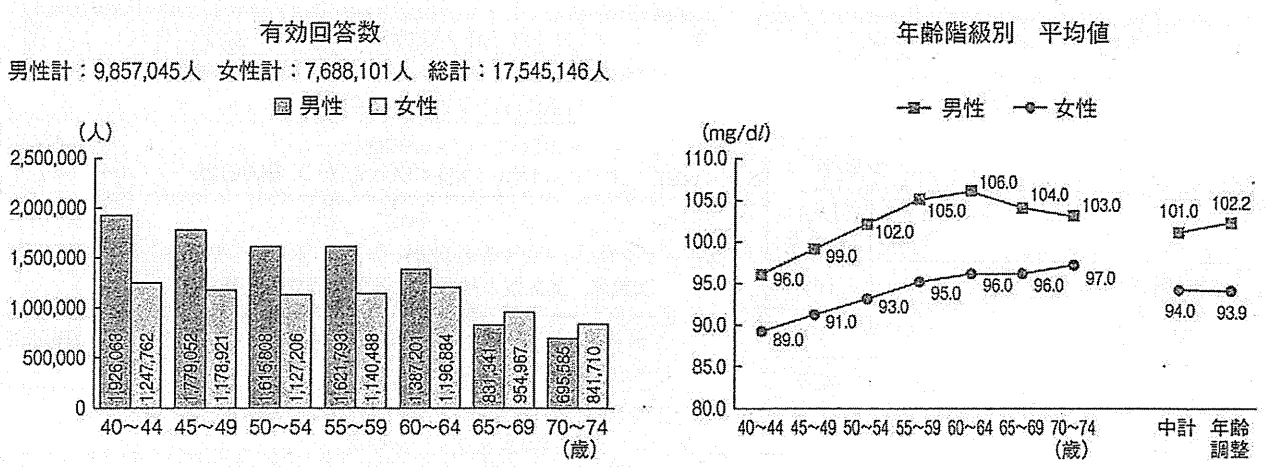

図2　全国の空腹時血糖の状況（2010年）（文献5より）

能であった．特定健診の結果を基に，標準化された生活習慣問診や臨床検査値，生活習慣病治療者の割合とコントロール状況，予備群や未治療者の割合などの記録が電子化され国に集約されたことにより，ナショナルデータベースが構築され，分析が可能になったことは当制度の大きな成果である．

厚生労働科学研究において，特定健診データを活用して効果的な健康施策を展開するための手引きも作成・公表されており，全国や他地域との比較，保険者間比較，データの経年変化などの評価にも活用が期待できる[5]．

たとえば全国の空腹時血糖の状況（図2）をみると，男性では女性より40歳代から一貫して高く，50歳代の平均値が正常高値を超えているが，60歳代後半から70歳代にかけてやや低下がみられることがわかる．また，血糖高値（空腹時血糖126 mg/dl以上）の割合は都道府県別に格差が存在することがわかる（図3）．

2）特定保健指導の効果検証

これまでに複数の厚生労働科学研究において，健診データなどを用いて特定保健指導の効果評価が行われている．ここでは津下班において実施した，多施設共同研究による保健指導効果の検証について述べる．

(1) 特定保健指導による検査値の改善

積極的支援実施群において，翌年の健診時までに体重は1.7±3.4 kg減（体重減少率：2.2%），臨床検査値では収縮期血圧（SBP），拡張期血圧（DBP），トリグリセライド（TG），HDLコレステロール（HDL-C），LDLコレステロール（LDL-C），空腹時血糖（FPG），HbA1c，AST，ALT，γ-GTPの有意な改善がみられた[6]．

MetS該当者は42.5%から21.9%へ減少（減少率：48.5%），MetS該当者とMetS予備群該当者の合計は92.3%から55.3%へと減少した．血圧，脂質などについては保健指導判定値，受診勧奨判定値に該当する例の減少がみられた（図4）．

積極的支援レベルに該当したが特定保健指導を実施せず翌年の特定健診を受診した例を対照群として，積極的支援実施群と1年後健診時の検査値変化量を比較したところ，積極的支援実施群では，体重，腹囲，血圧，脂質，血糖などの改善が有意に大きかった．

動機づけ支援実施群では，翌年の健診時までに体重は1.5 ± 3.2kg減，臨床検査値においても血圧，脂質，血糖，肝機能に有意な改善がみられた．

以上の結果より，短期間のデータ分析ではある

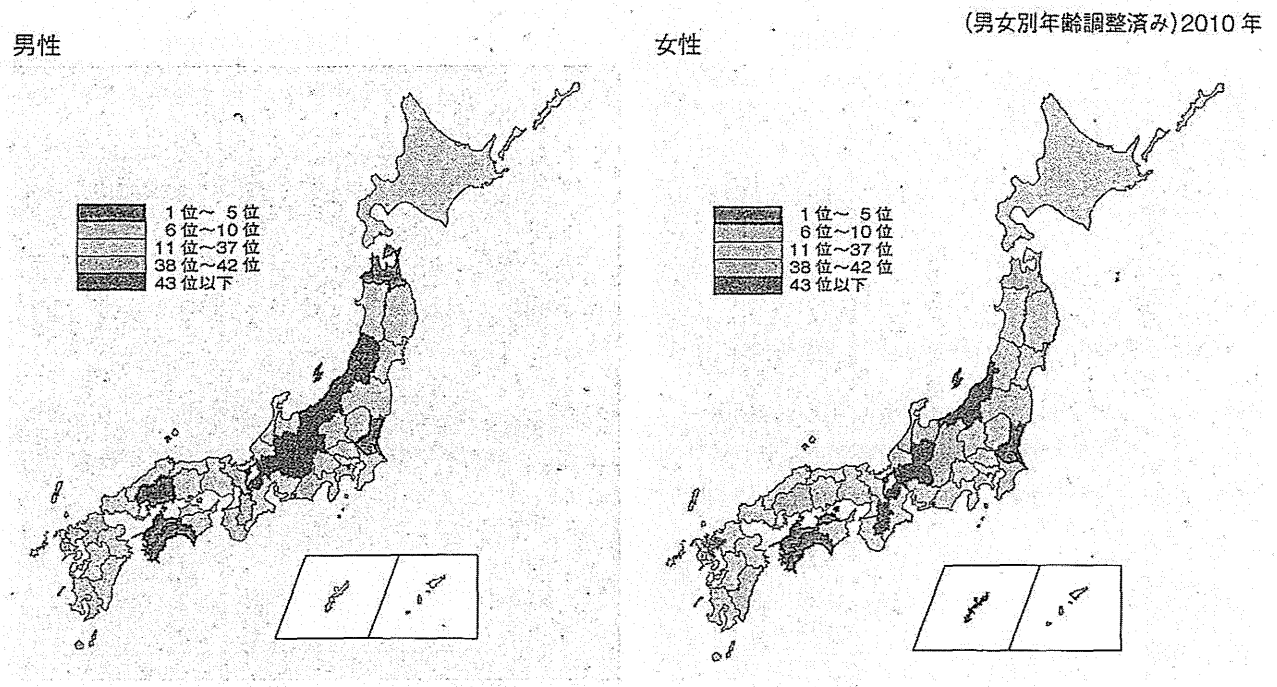

図3　都道府県別血糖高値（空腹時血糖 126 mg/dl 以上）の割合（文献5より）

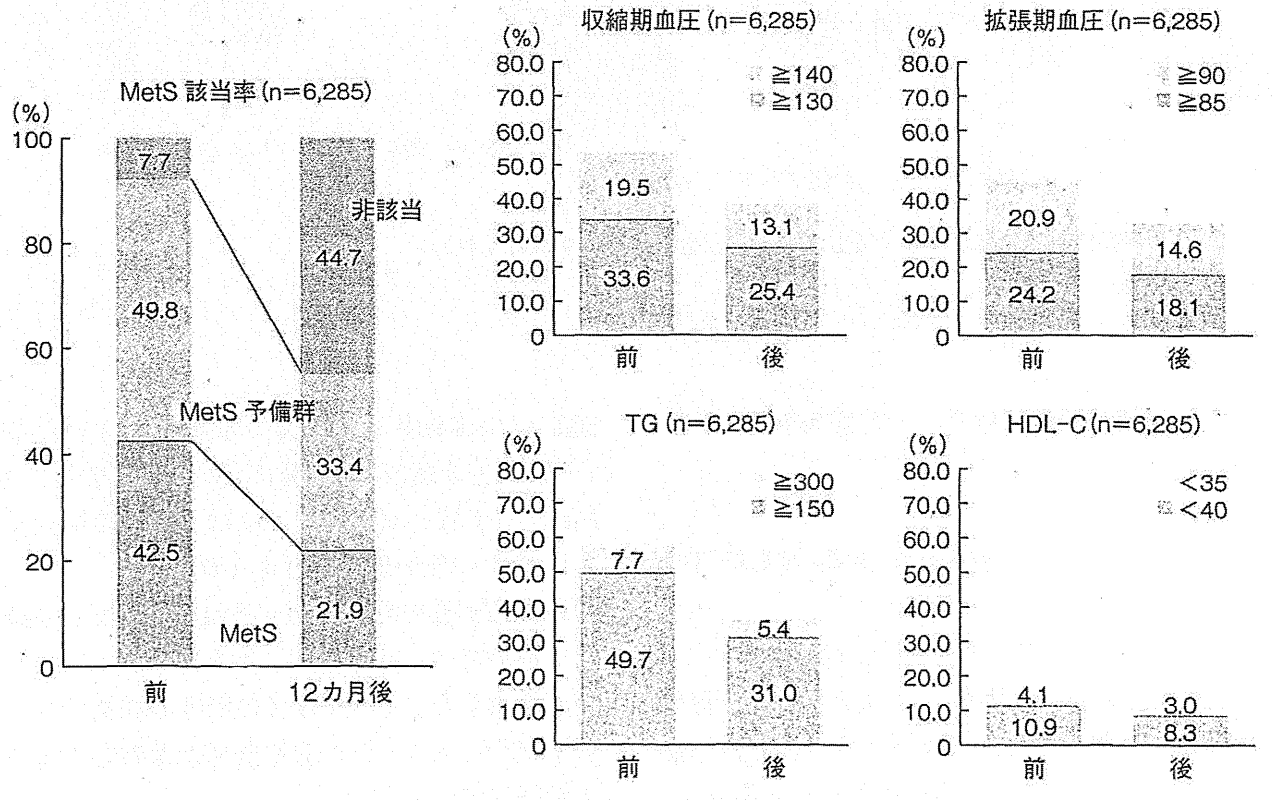

図4　積極的支援による1年後のメタボリックシンドローム（MetS）該当率，有所見率の変化（文献6より）

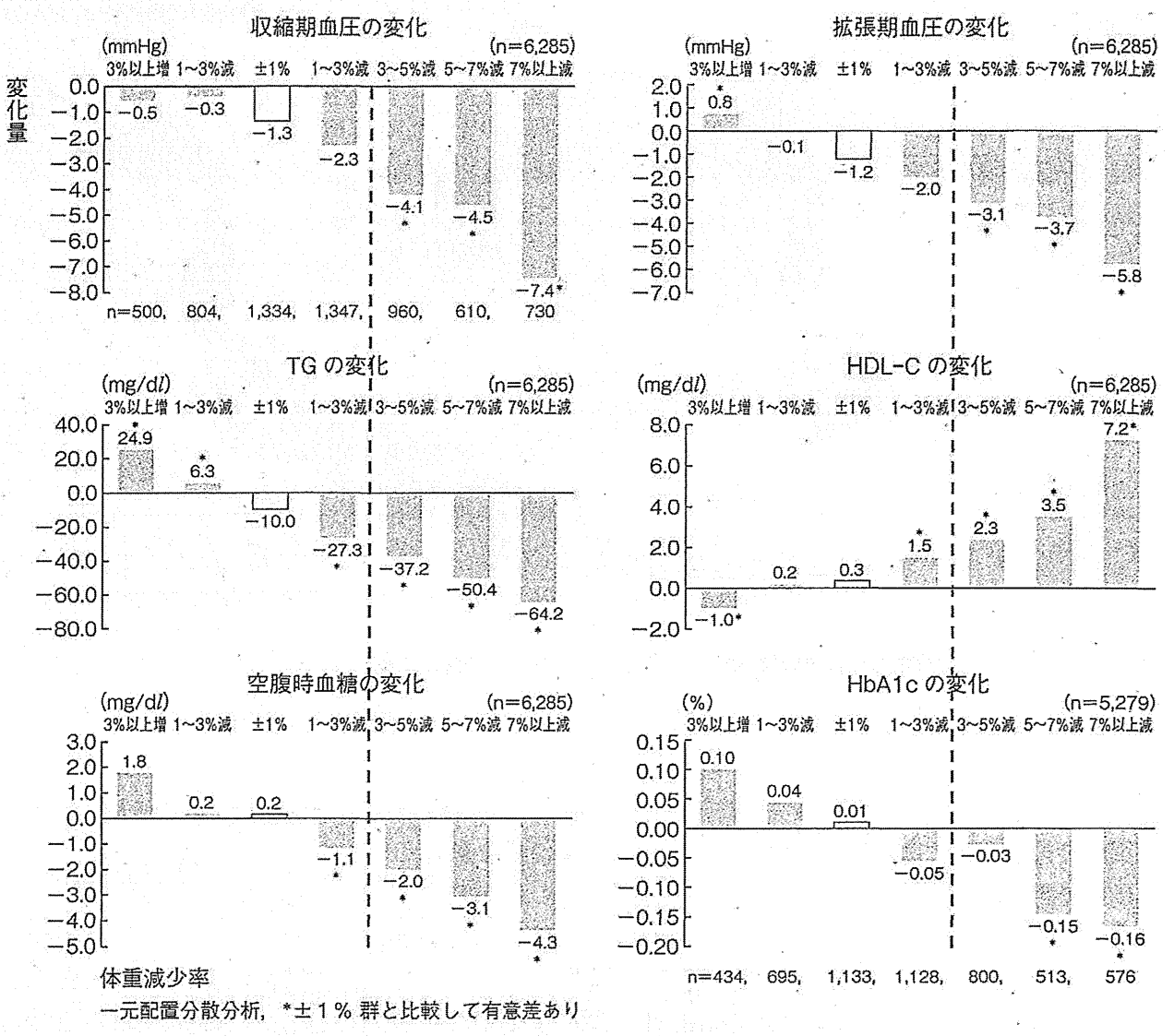

図5　1年間の体重変化率と検査値変化（積極的支援実施群）（文献6より）

が，特定保健指導における生活習慣病予防・改善効果が示唆された．

(2) 体重減少率と検査値変化の関連，減量の目安（図5）[6]

積極的支援実施群を対象とした検討において，1年後の体重減少率が大きくなるほど血圧，脂質，血糖などの改善は明らかとなり，翌年までの体重変化が±1%未満であった群を対照とした場合に，3%以上の減量群において各項目に有意な改善がみられた．2%減量は全体の47.0%，3%減量は36.6%，4%減量は28.6%で達成されていたことから，減量達成の実現可能性を考慮しても，MetSの予防・改善のためには1年後の減量目標として2~4%が妥当と考えられた．

積極的支援を実施した一部の男性事例を対象とした検討では，支援開始1年後にアディポネクチンが増加した．2~4%程度の軽度の減量でも，アディポサイトカインの分泌動態が改善しうることを示唆している[7]．

減量指導の現場では，具体的な数値目標，つまり2~4%というわずかな減量による血液検査結

果の改善を示すことによって，対象者の生活習慣改善に対するモチベーションを上げる効果が期待できる．

(3) 特定保健指導の3年後効果

長期的な保健指導効果を分析する目的で，2つの健康保険組合において平成20年度から23年度までに4年連続した健診データ登録があり，初年度に服薬（降圧薬，血糖降下薬，脂質代謝改善薬）がなく，積極的支援レベルに該当した男性を対象に，3年間に1回以上積極的支援を実施した群と一度もなんの支援も実施しなかった群を比較した．

3年後の生活習慣病薬服用率を比較すると，支援無群で19.5%であったのに対し，積極的支援実施群では13.7%と有意な抑制効果を認めた．特に，初年度に受診勧奨判定値以上のリスクをもつ対象者では，3年後の服薬率が支援無群で35.9%であるのに対し積極的支援実施群では21.6%と，支援効果が大きい結果となった．生活習慣改善により服薬開始を抑制あるいは先延ばしにすることができれば医療経済面においてもメリットがある．

また，初年度のFPGにより分類（<100 mg/dl，100≦<110 mg/dl，110≦<126 mg/dl）し3年間の支援実施の有無による3年後の糖尿病発症状況の相違を検討したところ，初年度のFPGが100≦<110 mg/dlの群について，3年後に「糖尿病が強く疑われる例（糖尿病薬服用あるいはFPG≧126 mg/dlまたはHbA1c≧6.5%に該当する例）」の割合は，支援実施群で7.8%であり，支援無群10.7%よりも有意に低くなった．このことから，血糖が「正常高値」の対象者に対して保健指導を実施することにより，3年後の糖尿病発症抑制効果を期待できると考えられた．

4 第二期特定健診・特定保健指導の改訂点，着眼点

1) 特定保健指導対象者ではない人への対応

健診受診者に対する「情報提供」には，単に健診結果を示すだけではなく，健診結果に基づいて生活習慣改善についての意識づけを行う，医療機関への受診・継続治療が必要な対象者には受診や服薬の重要性を認識してもらう，健診受診者全員に対して継続的に健診を受診する必要性を理解してもらうなどの目的がある[8]．

特に非肥満者（腹囲，BMI非該当）についてはMetSに対する保健指導のように標準化したプログラムが現段階では存在しないが，個別のリスクに応じて適切なフィードバックを行うことが重要である．

「標準的な健診・保健指導プログラム【改訂版】」には，健診結果とその他必要な情報の提供（フィードバック）文例集が掲載されている（図6）[3]．たとえば，非肥満で糖尿病治療中，空腹時血糖あるいはHbA1cが受診勧奨判定値を超える場合については，「今回の健診では，空腹時血糖は（　）mg/dl，HbA1cは（　）%でした．糖尿病の合併症を予防するためには，良好な血糖コントロールの状態を維持することが大切ですので治療を継続してください．もしあなたのHbA1cの値が7.0%以上であった場合は，糖尿病の血糖コントロールが良好ではない状態ですので，かかりつけの医師とよくご相談されるか，必要に応じて糖尿病の治療が受けられる医療機関にご相談され，治療を継続してください」といった具体的な文例があり，臨床現場でも活用可能であろう．

2) HbA1cの表記

日常臨床の現場においては，HbA1cの結果表記が平成24年度からJDS値からNGSP値へ変更になった．特定健診では，第一期中はJDS値のままであったが，第二期では日常臨床での普及状況などを勘案してNGSP値となった．

3) 特定保健指導の実施方法

より多くの対象者に保健指導が実施できるよう，ポイント制，保健指導実施者（初回と評価者），健診当日保健指導等が見直された．

【健診判定と対応の分類】

健診判定				対応			
		空腹時血糖 (mg/dl)	HbA1c (NGSP) (%)	肥満者の場合		非肥満者の場合	
				糖尿病治療 (+)	糖尿病治療 (−)	糖尿病治療 (+)	糖尿病治療 (−)
異常	受診勧奨判定値を超えるレベル	126〜	6.5〜	①肥満の改善と血糖コントロールの確認や改善が必要	②すぐに医療機関受診を	③血糖コントロールの確認や改善が必要	②すぐに医療機関受診を
	保健指導判定値を超えるレベル	110〜125	6.0〜6.4	④血糖コントロールは良好だが，肥満を改善する必要あり	⑤特定保健指導の積極的な活用と生活習慣の改善を	⑥血糖コントロールは良好，現在のコントロール継続	⑦運動／食生活等の改善を，ぜひ精密検査を
		100〜109	5.6〜5.9				⑧生活習慣の改善を，リスクの重複等あれば精密検査を
正常	基準範囲内	〜99	〜5.5		⑨肥満改善と健診継続を		⑩今後も継続して健診受診を

図6　血糖高値に関するフィードバック文例集（文献3より）

(1) ポイント制の続行と「支援B」の扱い

第一期特定保健指導の「積極的支援」における継続的支援ではポイント制が導入されており，「支援A（積極的関与タイプ）で160ポイント以上，支援B（励ましタイプ）で20ポイント以上の合計180ポイント以上の支援を行うこと」が必須とされていた．保健指導投入量と体重4%減量達成率の関連を調べた研究では，ポイント量に依存して効果が出ていることなども報告され[9]，ポイント制の効果について引き続きデータを蓄積し検証が行われることとなった．

ただし，第二期においては支援Bを必須とする条件が外れ，「支援Aを160ポイント以上，合計180ポイント以上」が新たな要件となった．すなわち，支援Aのみで180ポイント以上，または支援A（最低160ポイント以上）と支援Bの合計で180ポイント以上の支援を実施するものとなっている．

(2) 初回面接者と6カ月後評価者の同一性

第一期の特定保健指導では，初回面接と6カ月後評価を同一者が行うこととしていたが，第二期では，同一機関内において保健指導の記録やカンファレンスなどで指導者同士が情報を共有化できる環境にある場合にかぎり，同一者が行わなくてもよいこととなった．保健指導の現場では，組織内での職員の異動などの事情もあり，効率性の面においてもより現実に即したものになった．

(3) 健診当日の保健指導

保険者と健診機関の個別契約において，「階層化された保健指導対象者のすべてに保健指導を実施する」という契約がなされており，健診当日にすべての結果が出そろって特定保健指導対象者を決定できる場合には，健診当日に保健指導初回面接を実施できることになった．

4）禁煙・減酒の保健指導

「標準的な健診・保健指導プログラム【改訂版】」には，「保健指導のための禁煙支援簡易マニュアル」と「保健指導におけるアルコール使用障害スクリーニング（AUDIT）とその評価結果に基づく減酒支援（ブリーフインターベンション）の手引き」が掲載されている．

禁煙・減酒の保健指導は，本人が自分の問題と自覚し実現可能な目標を立て，記録しながら実践していく点で減量と共通の手法である．これらのスキルを身につけ，効果的な情報提供と保健指導に生かしたい．

5）2回目以降の対象者（リピーター）への支援

動機づけ支援や積極的支援を実施しても保健指導の支援レベルが改善せず，保健指導対象者から離脱できない場合がある．2回目以降の対象者に対する支援としては，前年度の目標や達成状況，前年度からの体重や検査データの変化，前年度の保健指導終了後からの取り組み状況，2回続けての保健指導利用に対する期待や不安などの確認が求められる．

6）健康日本21（第二次）との連動

国民の健康づくり運動である健康日本21（第二次）も，第二期特定健診・特定保健指導と同様に，平成25年度から開始された．「生活習慣病の発症予防と重症化予防の徹底」はその主要な柱であり，特定健診・特定保健指導と目指す方向は同じである．

全国の特定健診対象者という大きなデータベースを基に健康格差および生活習慣の違いなどを分析することにより，地域の健康課題を見える化でき，個別の生活習慣改善のみならず健康状態向上につながる環境整備にも役立つと考えられる．

おわりに

第一期特定健診・特定保健指導制度の状況と，第二期特定健診・特定保健指導の改訂点・着眼点について概説した．特定健診・特定保健指導制度は開始から5年間かけて定着し，多数の国民の健康情報が集積するシステムから，さまざまなエビデンスを生み出し始めたところである．

よりよい予防システムにしていくため，特に被扶養者の実施率向上，事業主健診データ活用のための関係者間の連携，地域・職域の連携，保健指導と医療機関の連携などが課題である．

特定保健指導の効果検証については，性別，年代別，職種別，保有リスク別などのきめの細かい分析や，糖尿病をはじめとする生活習慣病発症の予防効果の長期的検証，医療費適正化効果に関する評価が必要と考えられる．

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Associations Between Diabetes, Leanness, and the Risk of Death in the Japanese General Population

The Jichi Medical School Cohort Study

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OBJECTIVE—To examine the BMI-stratified associations between diabetes and the risks of all-cause death, cardiovascular disease (CVD) death, and cancer death.

RESEARCH DESIGN AND METHODS—Using a prospective study with 12 rural Japanese general populations (n = 3,641, mean age, 53.7 years; 33.5% men), we examined the associations between diabetes and the risk of all-cause death, CVD death, and cancer death. We also examined the effects of BMI and age on such associations.

RESULTS—During an average duration of 10.2 years (37,278 person-years), 240 deaths occurred (54 deaths from CVD, 101 from cancer, and 85 from other causes). Cox regression analysis showed leanness (defined as the lowest quartile of entire BMI; mean, 19.5 kg/m^2), but not obesity (BMI ≥25 kg/m^2), and diabetes were independently associated with an increased risk of all-cause death (hazard ratio [HR] 1.70 and 1.65, respectively; both $P < 0.01$.). Stratification with cause-specific deaths showed that leanness and obesity were associated with CVD death (HR 3.77 and 2.94, respectively), whereas diabetes was associated with cancer death (HR 1.87; all $P < 0.05$). The increased risk of all-cause death in diabetes was substantially higher in lean subjects aged <65 years (HR 3.4) or those aged ≥65 years (HR 4.2), whereas the risk in obese diabetes patients was significant only in subjects aged <65 years (HR 2.32; all $P < 0.05$).

CONCLUSIONS—Among the Japanese general population, diabetes confers an increased risk of all-cause death. Particular attention must be paid to the pronounced high mortality in diabetes accompanied with leanness, regardless of age.

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Diabetes is one of the fastest-growing public health problems in the world. Its prevalence is particularly advancing in Asia-Pacific regions, where more than half of diabetes patients reside and where nearly half of all deaths from cardiovascular disease (CVD) occur worldwide (1–4).

Diabetes increases the risk of premature death in the general population. Some studies have reported that the effect of diabetes on death can be augmented by obesity (5,6), whereas other studies have reported that the association is augmented by leanness (7–9). These data, however, have been derived from Western populations, and thus little evidence is available about the effects of BMI on the associations between diabetes and all-cause death in Asians.

Several distinctive features are apparent among the pathogenetic factors for diabetes and its complication in Asian populations compared with Western populations (2,3). Although most patients with diabetes are overweight or obese in Western populations, diabetes in lean patients is highly prevalent in Asian countries, where more than half of diabetic patients are considered normal weight (BMI <25 kg/m^2). Moreover, in contrast to Western populations, in which obesity has been shown to have an adverse effect on mortality (10,11), a recent large pooled analysis of 19 cohorts in Asia showed that leanness (i.e., underweight), rather than obesity, was associated with a substantially increased risk of death in Asian populations (12). Accordingly, precise estimates of the association between diabetes and the risk of death in Japan, including data on whether the association is augmented by obesity and/or leanness, are a critical prerequisite for informed decisions about strategies for the prevention and control of diabetes-related mortality.

Accordingly, we used a 10-year prospective study among 12 rural Japanese general populations to examine the associations between diabetes and the risks of all-cause death, CVD death, and cancer death. We also examined the effects of BMI and age on the associations between the diabetes and these risks.

RESEARCH DESIGN AND METHODS

—The Jichi Medical School (JMS) Cohort Study is a prospective, population-based study aimed at exploring the risk factors for CVD in 12 communities in Japan. Details regarding the JMS Cohort Study design and additional descriptive data are available in the Supplementary Data or in our previous reports (13–15). Enrollment into the JMS

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Cohort Study and baseline data collection were performed between April 1992 and November 1993. A total of 12,490 subjects (39.3% male [n = 4,911]), who were a mean ± SD age of 55.3 ± 11.6 years, participated in the current study. Of these, 12,393 (99.2%) gave us written informed consent to be prospectively followed up for study purposes and complete follow-up was achieved for 12,388 (99.9%).

Glucose parameters (i.e., plasma glucose levels and hemoglobin A_{1c} [HbA_{1c}]) and responses to a self-administered questionnaire documenting their medical history of diabetes were available for 3,727 subjects (33.2% male [n = 1,240]), who were a mean age of 53.8 ± 12.0 years. We excluded 86 participants who had insufficient data for at least one clinical parameter of age, sex, BMI, systolic or diastolic blood pressure (BP), habitual smoking, information on medical history of hypertension, myocardial infarction, stroke, and cancer, or data of circulating lipid parameters. Ultimately, data from 3,641 subjects were analyzed in the current study (Supplementary Fig. 1). The 3,641 subjects who were included in the present analysis were showed a younger age (53.7 ± 12.1 vs. 55.9 ± 11.4 years; $P < 0.001$) and a lower prevalence of men (33.5% [n = 1,220] vs. 41.7% [n = 3,649]; $P < 0.001$) compared with the 8,747 who were excluded from the analysis.

Measurements of baseline variables

To synchronize the methods of data collection, we established a central committee composed of the chief medical officers from the participating districts. This committee developed a detailed manual for data collection. Information about lifestyle and medical history was gathered by means of a written questionnaire. In some subjects, information about physical activity (n = 3,615 [99%]), educational level (n = 3,601 [99%]), and marital status (n = 3,616 [99%]) were also obtained (Supplementary Data). BMI was calculated as weight (kg)/height (m^2). Systolic and diastolic BP were measured with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Komaki, Japan), which was placed on the right arm of a subject who had rested in a sitting position for 5 min before measurement. Hypertension was defined as systolic BP/diastolic BP ≥140/90 mmHg or self-reported usage of antihypertensive medication.

Blood samples were drawn from the antecubital vein of seated subjects, with minimal tourniquet use (details are described in the Supplementary Data). Blood samples of 1,344 subjects (36.9%) were drawn after overnight fasting. Total cholesterol and triglycerides were measured using an enzymatic method (Wako; interassay coefficient of variation [CV], 1.5% for total cholesterol and 1.7% for triglyceride). HDL cholesterol was measured using the phosphotungstate precipitation method (Wako; interassay CV, 1.9%). Blood glucose was measured via an enzymatic method (Kanto Chemistry; interassay CV, 1.9%), and the value for HbA_{1c} was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following formula (16): HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) + 0.4%. These laboratory data were measured concurrent with sample collection.

Definition of leanness, obesity, and diabetes

The Japan Society for the Study of Obesity defines obesity as a BMI ≥25 kg/m^2 and leanness as a BMI <18.5 kg/m^2 (2,17) therefore, in the current study, we defined obesity as BMI ≥25 kg/m^2 (mean 27.0 ± 2.4 kg/m^2; n = 1,196). However, if we had defined leanness as BMI <18.5 kg/m^2, only 160 subjects (4% of total patients) would qualify. Thus, in the current study, we defined leanness as the lowest quartile of BMI (range 14.2–21.1; mean 19.5 ± 1.2 kg/m^2; n = 910). As a consequence, we defined normal BMI as BMI ranging from the second quartile of BMI to 25 kg/m^2 (mean 22.7 ± 1.0 kg/m^2; n = 1,535).

Diabetes was defined in accordance with the American Diabetes Association guidelines (18) as a fasting glucose concentration of 126 mg/dL or higher, casual blood glucose concentration of 200 mg/dL or higher, HbA_{1c} of 6.5% or higher, or self-reported use of antihyperglycemic drugs.

End point

As described in previous reports (13–15), mortality data from the date of entry to 31 December 2002 were collected from the Cause-of-Death Register at public health centers in each community with the permission of the Agency of General Affairs and the Ministry of Health, Labor, and Welfare. The follow-up period was 10.2 ± 2.1 years (37,278 person-years). Information on the cause of death was coded for participants who died using ICD-10 codes. Causes of death were classified as follows: *1*) CVD death: heart disease including sudden death (I21–I23, I46, I48–I50, Q20–Q28), CVD (I60, I61, I63, I69), and other CVD (I71); 2) cancer death (C02, C10, C14–C20, C22–C26, C30, C34, C41, C50, C53, C54, C61, C64, C65, C71, C74, C76, C81–C85, C90–C93); and 3) other causes, such as infection and suicide (A41, B15–19, D65, G12, G21, G93, J10–J18, J43, J84, J96, K72, M62, N00–N08, R57, R54, R64, S06, T58, X60–X84, Y85–Y87, W75–W84).

Statistical analysis

All statistical analyses were performed with SPSS 18.0J software (SPSS Inc, Chicago, IL). Clinical parameters in subjects with or without death were compared using the unpaired t test, and categorical parameters were compared with the χ^2 test. Next, we used Cox regression analysis to examine the independent effects of diabetes or BMI on the risk of all-cause death. After adjusting for significant covariates, such as age, sex, current smoking status, and systolic BP values, the hazard ratios (HR) and 95% CIs were calculated for all-cause death, CVD death, or cancer death in subjects with diabetes or leanness (obesity).

Finally, our population was subdivided into six categories according to BMI (leanness, normal BMI, and obesity) and the presence of diabetes, and the HR (95% CI) of all-cause deaths in each of the six categories was calculated. In that analysis, to examine whether the association among the six categories and all-cause death differed between middle-aged/younger individuals and older individuals, we used a Cox regression analysis separately in subjects aged <65 and ≥65 years. This analysis included significant covariates for adjusted variables, such as sex, current smoking status, systolic BP values, and pre-existing myocardial infarction, stroke, or cancer. We then performed additional adjustments for each of the following possible confounders: physical activity (n = 3,615), educational level (n = 3,601), and marital status (n = 3,616). Finally, using a Cox regression analysis, we examined whether there were any interactions between diabetes and BMI in the risk of all-cause death separately in those aged <65 years and those ≥65 years. A 2-sided P value <0.05 was defined as statistically significant.

RESULTS

Baseline clinical characteristics

The mean ± SD age of the 3,641 subjects was 53.7 ± 12.1 years, and 1,220 (33.5%) were men. At the time of study recruitment, there were 507 patients (13.9%) defined as having diabetes, 1,277 (35.1%) with hypertension, 58 (1.6%) with a pre-existing myocardial infarction or stroke, and 43 (1.2%) with a pre-existing cancer.

Leanness, diabetes, and all-cause deaths

During an average duration of 10.2 ± 2.1 years (37,278 person-years), 240 deaths occurred (6.4 events/1,000 person-years), including 54 CVD deaths, 101 cancer deaths, and 85 other-cause deaths (e.g., infection, suicide, accident). The baseline clinical characteristics according to the incidence of all-cause death are reported in Table 1. The prevalence of leanness or diabetes was higher in subjects with death than in those without death. The crude incidence rate of all-cause death was 13.0 events/1,000 person-years for diabetes and 5.4 events/1,000 person-years for nondiabetes. By comparison, the crude incidence rate per 1,000 person-years of all-cause death was 8.4 events in lean subjects, 5.2 events in subjects with normal BMI, and 6.5 events in obese subjects. The prevalence of cause-specific death subdivided by the presence of diabetes or BMI is reported in Supplementary Tables 1 and 2. Kaplan-Meier curves showing cumulative all-cause death according to the presence of diabetes or the classification of BMI are shown in Fig. 1*A* and *B*. There was no significant difference in the rate of all-cause death among the subjects subdivided by the presence of diabetes or BMI in the first 5-year period, whereas the differences were significant for the second 5-year period (both $P < 0.05$ by log-rank test).

Next, the HR (95% CI) of all-cause death associated with leanness (obesity) or diabetes was calculated using Cox regression analysis (Table 2). The HR (95% CI) of all-cause death in subjects with leanness, but not obesity, and diabetes were significant, even after adjustment for significant covariates. Stratification with cause-specific deaths showed that leanness and obesity were both associated with an increased risk of CVD death, whereas diabetes was associated with an increased risk of cancer death. When we defined obesity as the highest quartile of BMI (≥25.3 kg/m^2; mean 27.7 kg/m^2, n = 910) instead of BMI ≥25 kg/m^2, the risk of CVD death in obesity remained unchanged (data not shown). Furthermore, when we examined the male-to-female differences in the risk of all-cause death as well as cancer death in diabetes, we found that this conclusion remained unchanged (Supplementary Tables 3 and 4).

The increased risk of all-cause death in leanness or diabetes (Table 2) did not change when the 66 subjects who died within 2 years of follow-up were excluded (data not shown). After exclusion of 58 subjects with a pre-existing myocardial infarction or stroke and 43 with cancer at baseline, associations of leanness or diabetes with all-cause death remained significant (data not shown). When we adjusted for various confounding factors, such as physical activity, educational level, and marital status in the associations between diabetes or leanness and all-cause death, the risk of diabetes or leanness remained unchanged (data not shown).

Table 1—*Baseline clinical characteristics of the study population according to the occurrence of death*

	No death (n = 3,401)	Death (n = 240)	P value
Patient characteristics			
Age (years)	53.1 ± 12.1	62.2 ± 7.3	<0.001
Male	1,090 (32.0)	130 (54.2)	<0.001
BMI (kg/m^2)	23.4 ± 3.3	23.2 ± 3.9	0.56
BMI classification			
Leanness	834 (24.5)	76 (31.7)	0.02
Normal BMI	1,452 (42.7)	83 (34.6)	
Obesity	1,115 (32.8)	81 (33.8)	
Current smoker	698 (20.5)	81 (33.8)	<0.001
Comorbidity			
Diabetes	442 (13.0)	65 (27.1)	<0.001
Hypertension	1,154 (33.9)	123 (51.2)	<0.001
Pre-existing			
Myocardial infarction or stroke	46 (1.4)	12 (5.0)	<0.001
Cancer	36 (1.1)	7 (2.9)	0.02
BP measurements (mmHg)			
Systolic	125 ± 21	132 ± 23	<0.001
Diastolic	76 ± 13	80 ± 14	<0.001
Pulse pressure	49 ± 12	52 ± 13	<0.001
Laboratory data			
Fasting glucose (mg/dL)	105.0 ± 27.4	115.4 ± 35.2	<0.001
Hemoglobin A_{1c} (%)	5.9 ± 0.7	6.0 ± 0.8	0.001
Total cholesterol (mg/dL)	189.7 ± 34.4	186.2 ± 36.4	0.13
Triglycerides (mg/dL)	114.7 ± 73.5	124.2 ± 76.4	0.053
HDL (mg/dL)	53.3 ± 13.2	51.8 ± 15.4	0.10

Continuous data are expressed as means ± SD and categorical data as n (%). P values are calculated by unpaired t test or χ^2 test. Statistical significance is defined as $P < 0.05$. Leanness is defined as the lowest quartile of BMI (range 14.2–21.1; mean 19.5 kg/m^2), and obesity is defined as BMI ≥5 kg/m^2.

Effects of BMI or age on the associations between diabetes and all-cause death

Among 2,866 subjects aged <65 years, the risk of all-cause death conferred by diabetes, compared with nondiabetes with normal BMI (reference), increased when diabetes was accompanied by leanness or obesity (Fig. 2*A*). In contrast, among the 775 subjects aged ≥65 years, the risk of all-cause death conferred by diabetes, compared with nondiabetes with normal BMI, increased when the diabetes was accompanied by leanness but not by obesity (Fig. 2*B*). We repeated the analysis after excluding subjects who died within the initial 2 years of follow-up or those who had a pre-existing myocardial infarction, stroke, or cancer at baseline, and the conclusions remained unchanged (data not shown). Furthermore, we performed additional adjustments for each of the following possible confounders in Fig. 2: physical activity, educational level, and

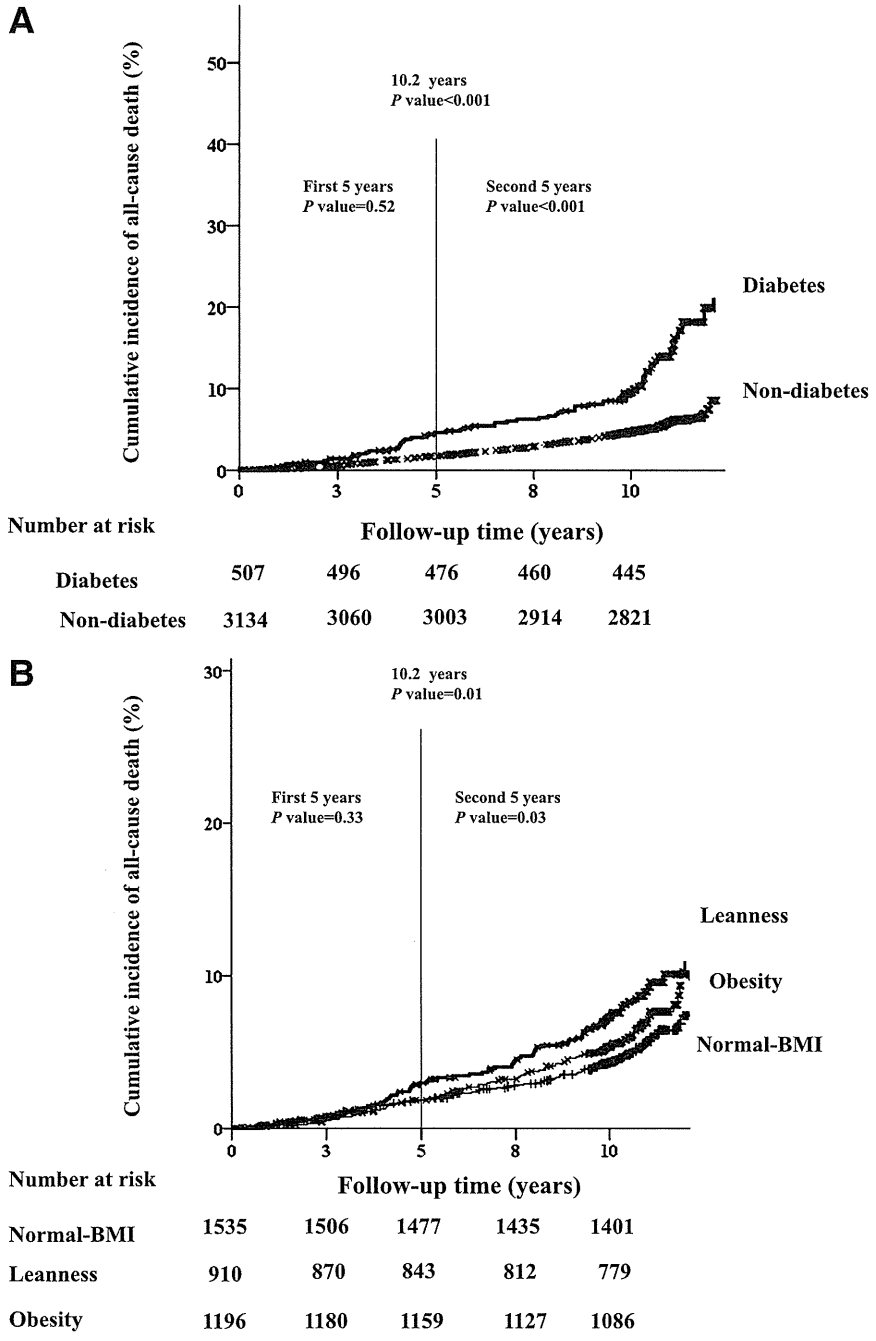

Figure 1—*Kaplan-Meier curves show the cumulative incidence of all-cause death by the presence of diabetes vs. nondiabetes* (A)*, or the classification of BMI by leanness or obesity vs. normal BMI* (B)*. P values were calculated using log-rank test.*

marital status. The conclusions remained unchanged (data not shown).

Finally, using a Cox regression analysis (including sex, current smoking status, systolic BP values, and pre-existing myocardial infarction, stroke, or cancer), we examined whether there was an interaction between diabetes and BMI in the risk of all-cause death separately in those aged <65 years and those ≥65 years. As a result, we found a significant interaction between diabetes and leanness only in subjects aged <65 years (P = 0.047).

CONCLUSIONS—In the present 10-year prospective study in a rural Japanese general population, we have demonstrated for the first time the associations between diabetes, BMI, and the risk of death. The main findings of the current study are that *1*) leanness, but not obesity, and diabetes were independently associated with an increased risk of all-cause death; 2) leanness and obesity were both associated with an increased risk of CVD death, whereas diabetes was associated with cancer death; and 3) lean diabetic subjects had a substantially high risk of all-cause death regardless of age, whereas obese diabetic subjects showed increased risk only in those aged <65 years. These findings provide opportunities for a careful evaluation of the risks accompanying diabetes that can be modified by BMI or age.

Excess mortality in diabetes

Most of the literature regarding diabetes and excess mortality has been derived from Western populations (19,20), and there are few prospective studies on mortality and cause of death from diabetes in Japan. The recent substantial increase in rates of diabetes in Asian countries (2,3) highlights the need to better understand the mortality related to diabetes and to identify high-risk subjects in order to prevent excess mortality from diabetes within each Asian country. In the current study, diabetes almost doubled the incidence of all-cause death compared with nondiabetes, and diabetes increased the risk of all-cause deaths by 65%, even after adjustment for significant covariates (Table 2).

Contrary to previous reports from Western populations (21,22), we observed that CVD mortality was not significantly greater in diabetes than nondiabetes. Because the number of CVD death was small, this issue merits further analysis. Nevertheless, a direct comparison between diabetes in Japanese in Caucasians showed that the CVD mortality is threefold higher in Caucasians (23). Moreover, a World Health Organization multinational study demonstrated that Japanese cohorts showed a very low excess mortality from CVD death compared with Western populations (24). These findings indicate that the association of diabetes with CVD mortality may differ between Japanese and Western populations; further studies on a large cohort from a Japanese general population will be required to clarify that issue.

Diabetes and cancer are common conditions, and their codiagnosis in the same individual is not infrequent (25). In a previous Japanese cohort study, diabetes was associated with an increase in the risk of total cancer incidence of 27%

Table 2—*Cox regression analysis for all-cause death, CVD death, and cancer death in the total population* (n = *3,641*)

Variable	All-cause death (*n* = 240) HR (95% CI)	CVD death (*n* = 54) HR (95% CI)	Cancer death (*n* = 101) HR (95% CI)
Age (+12 years)	3.32 (2.63–4.19)‡	4.88 (2.67–8.90)‡	3.20 (2.25–4.55)‡
Sex (0: women; 1: men)	1.87 (1.38–2.54)‡	1.71 (0.93–3.17)	2.02 (1.24–3.28)†
BMI classification			
Normal BMI	1 (Reference)	1 (Reference)	1 (Reference)
Leanness (0: no; 1: yes)	1.70 (1.24–2.33)†	3.77 (1.74–8.16)†	1.50 (0.92–2.43)
Obesity (0: no; 1: yes)	1.24 (0.91–1.70)	2.94 (1.40–6.17)†	1.18 (0.73–1.90)
Current smoking (0: no; 1: yes)	1.69 (1.22–2.34)†	0.98 (0.46–2.10)	2.14 (1.31–3.48)†
Systolic BP, +21 mmHg	1.05 (0.93–1.19)	1.14 (0.88–1.48)	1.01 (0.83–1.23)
Diabetes (0: no; 1: yes)	1.65 (1.23–2.21)†	1.27 (0.66–2.42)	1.87 (1.21–2.89)†

HR (95% CI) for all-cause death, CVD death, and cancer death are shown. Leanness was defined as the lowest quartile of BMI (range 14.2–21.1; mean 19.5 kg/m^2), normal BMI was defined as BMI ranging from the 2nd quartile of BMI to 25 kg/m^2 (mean 22.7 kg/m^2), and obesity was defined as BMI ≥25 kg/m^2 (mean 27.0 kg/m^2). Statistical significance was defined as $P < 0.05$. †$P < 0.01$; ‡$P < 0.001$.

in men and 21% in women (26). We also demonstrated that cancer death was higher in diabetes compared with nondiabetes without sex differences (Supplementary Tables 3 and 4). It is not easy to differentiate whether diabetes causes cancer or whether risk factors for diabetes, such as obesity and physical inactivity, are associated with cancer. However, our data showed that an increased risk of cancer mortality in diabetes remained unchanged even after adjustment for significant covariates, including obesity or physical activity. By site, emerging data support higher risks of death from cancers of the liver, pancreas, and colon among adults with diabetes, whereas the evidence with other malignancies is equivocal (25–27). There were not enough cancer deaths in the current study to analyze the association between diabetes and cancer death by tumor site (Supplementary Tables 1 and 2).

The biological plausibility of the associations between diabetes and cancer has tended to be site-specific but may partly be the result of diabetic metabolic and hormonal alternations as well as their underlying common biological mechanisms such as hyperinsulinemia, abnormal production of adipocytokines and growth factors, and epigenetic changes (25). Because our data showed only cancer deaths, but not cancer incidences, we cannot exclude the possibility that a diagnosis of diabetes or poor glycemic control can lead to poor outcomes among subjects who developed cancer during the follow-up period (28). Further studies are warranted to quantify the specific impact of diabetes on cancer incidence versus cancer survival.

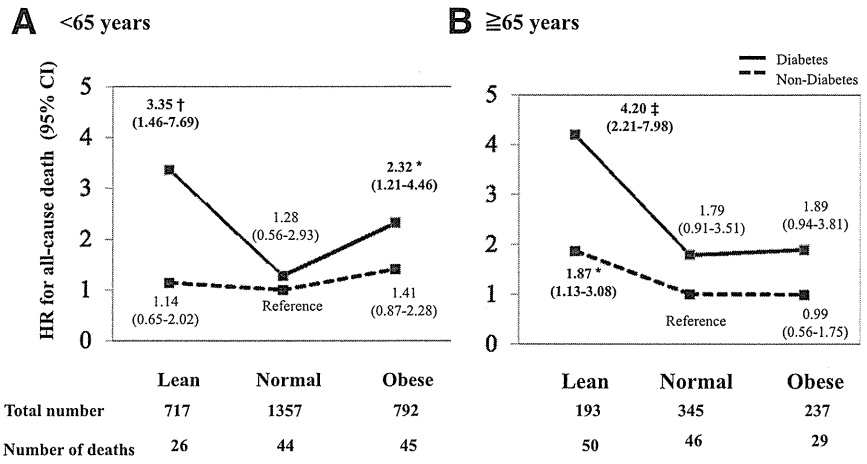

Figure 2—*Cox regression analysis of all-cause death separately by BMI or age. The HR (95% CI) of all-cause deaths according to the presence of diabetes and BMI are shown separately in those aged <65 years (A) and those ≥65 years (B). The analysis was adjusted for sex, current smoking status, systolic BP values, and pre-existing myocardial infarction, stroke, or cancer. The reference group was defined as nondiabetes with normal BMI. Statistical significance was defined as* P < *0.05. *P < 0.05 vs. reference group, †P < 0.01 vs. reference group, and ‡P < 0.001 vs. reference group.*

Effects of age and BMI on the association between diabetes and all-cause death

A recent meta-analysis from Western populations demonstrated the "obesity paradox" in diabetes and the importance of assessing nonobese (BMI <25 kg/m^2) diabetes as being high-mortality cases (9). We demonstrated that, compared with nondiabetes with normal BMI, lean diabetes showed a substantially higher risk of all-cause death in subjects aged <65 years and also those aged ≥65 years. Especially in subjects aged <65 years, a significant interaction was found between diabetes and leanness in the risk of all-cause death. Obese diabetes, by contrast, showed an elevated risk only in subjects aged <65 years (Fig. 2), a finding similar to the previous findings of Nilsson et al. (29) that obese diabetes in older persons (all subjects were 75 years old) presented no mortality risk. This may be partly explained by a survival bias; that is, the detrimental effects of obesity-related metabolic abnormalities are generally less prominent among older subjects than they are in middle-aged individuals (30,31).

The reasons for pronounced mortality in lean diabetes in the current study are not clear. The pathophysiology of lean diabetes is heterogeneous, including impaired insulin secretion, increased endogenous glucose production, high inflammatory state, and higher perceived stress hormones (32,33). The contrasting general clinical phenotypes of lean diabetes compared with obese diabetes have recently been discussed (32,33), although we cannot contribute to that discussion. Incomplete control for confounding or reverse causation bias could also explain the substantial risk in lean diabetes. In an effort to control for reverse causation, we repeated the analysis after excluding subjects who died within the initial 2 years of follow-up and those who had a preexisting myocardial infarction, stroke, or

cancer at baseline; the conclusions remained unchanged. However, that the leanness associated with higher mortality during the follow-up period was a result of occult diseases involving muscle or fat wasting cannot be excluded.

The strengths of the current study include *1*) this is a population-based study in an Asian (Japanese) population where there are limited data available addressing the association between diabetes, leanness, and mortality; and 2) complete follow-up was achieved in almost the entire cohort. There were also several limitations, however. A number of people from the original cohort (13–15) were excluded (71%); thus, there is a potential bias in the study participants chosen for the study analysis. Data on diabetes type, duration (i.e., no distinction between subjects with new-onset diabetes and those with longer-duration diabetes), disease severity, and the presence of diabetes complications at baseline would have been informative and would have extended the knowledge achieved in the current study. Second, we could not separate diabetes into type 1 or type 2 diabetes, although the incidence of type 1 diabetes is extremely low (approximately 2 cases/year/100,000 individuals) in Japan (34). Lastly, information regarding BMI and glucose values was available only at baseline, making it impossible to evaluate the effects of changes during the follow-up period in either or both of these factors.

In conclusion, among the Japanese general population, a diagnosis of diabetes confers an increased risk of all-cause death. Particular attention must be paid to the pronounced high mortality for lean diabetes. Taken together with the evidence of a rapidly increasing number of diabetes cases in Asia, the findings from the current study suggest that an integrated strategy combining preventive actions against diabetes, improvement of care for diabetes that includes early detection of diabetes complications as well as undiagnosed chronic disease, and multidisciplinary care programs is needed.

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Y.Y. designed the study, collected and analyzed the data, and wrote the manuscript. K.Kar. analyzed the data and wrote the manuscript. S.I., T.O., T.G., K.Kay., A.T., K.S., Y.N., and E.K. designed and supervised the study, collected the data, and revised the manuscript. S.I. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ORIGINAL ARTICLES

Fasting insulin and risk of cerebral infarction in a Japanese general population: The Jichi Medical School Cohort Study

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Abstract

Objective: We investigated the relation between fasting insulin (FI) and risk of cerebral infarction in a Japanese general population. *Methods:* The subjects were 2,610 men and women without past history of stroke or myocardial infarction and under treatment for diabetes, examined between 1992 and 1995 as part of the Jichi Medical School Cohort Study. The FI level was measured once at the baseline. Subjects were divided into quintiles by FI levels, and Cox's proportional hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cerebral infarction. *Results:* During an average of 11.1 years of follow-up, 87 participants developed cerebral infarction. Crude incidence rates of FI quintiles 1-5 were 4.69, 2.35, 1.85, 2.77 and 3.30 per 1,000 person-years, respectively. The multivariate-adjusted HRs for cerebral infarction were 2.33 (95% CI, 1.10 – 4.96) in quintile 1 (Q1), 1.25 (95% CI, 0.55 – 2.84) in Q2, 1.68 (95% CI, 0.76 – 3.70) in Q4 and 2.06 (95% CI, 0.94 – 4.47) in Q5, using Q3 as the reference.
Conclusions: The lowest FI level was associated with increased risk of cerebral infarction and the association between FI and risk of cerebral infarction appeared to be a U-shaped relationship.

INTRODUCTION

Insulin resistance is defined as a state of subnormal biologic response to a given concentration of insulin, and it is well established that insulin resistance is independently associated with risk of stroke.[1-6] To assess insulin resistance, several indices have been used, such as the homeostasis model assessment[1,3-5], but it is rare to use fasting insulin (FI) solely. The relation between FI and stroke was investigated in several prospective studies, but this relation is controversial.[3,7,8] In addition, little is known about the relationship between FI and the risk of cerebral infarction in a Japanese general population.[3] The purpose of this study was to examine the relationship between insulin resistance measured by FI and cerebral infarction in a Japanese general population in a prospective study.

METHODS

Subjects

The Jichi Medical School (JMS) Cohort Study is a prospective study that began in 1992 with the aim of investigating risk for cardiovascular disease in a Japanese population. Details of the JMS Cohort Study design and some descriptive data have been published previously.[9,10] The baseline data of this cohort study were obtained between April 1992 and July 1995. In this study, participants were 12,490 Japanese men and women who underwent mass screening programs in 12 communities across Japan. At least one JMS alumnus worked as a physician in each community. Mass screening for cardiovascular disease has been conducted in Japan since 1983 in accordance with the health and medical service law for the

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