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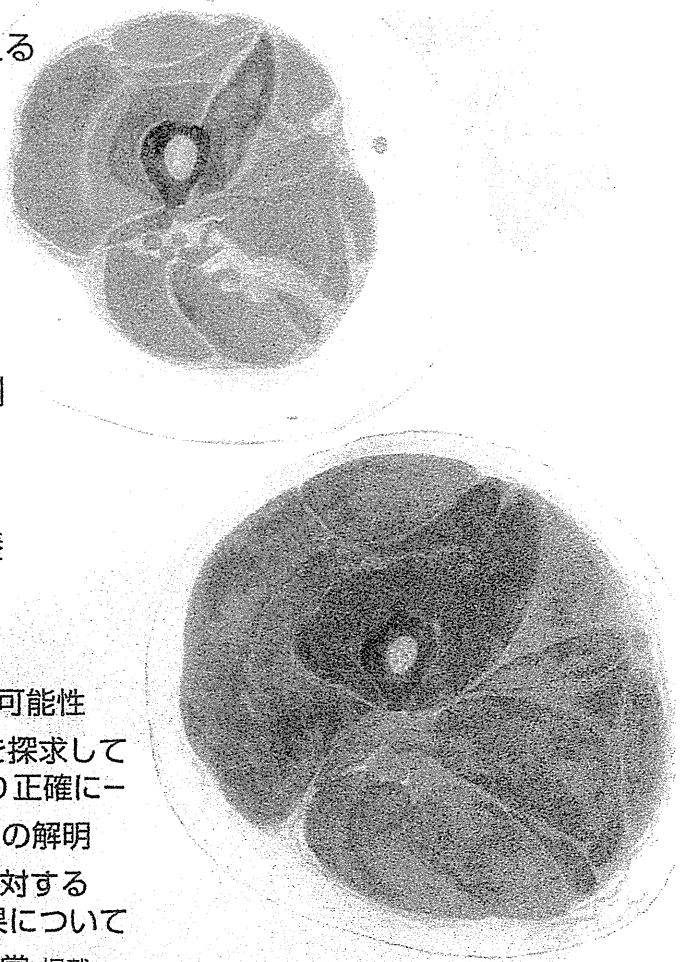
# 特集 サルコペニアの基礎と臨床

葛谷 雅文 企画

《座談会》介護予防ならびにロコモティブシンドロームとサルコペニア

《特集》





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# サルコペニアの疫学 II

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## 要　旨

無作為抽出された地域住民を対象とするコホート研究である「国立長寿医療研究センター 老化に関する長期縦断疫学研究（NILS-LSA）」での調査から，日本人高齢者全体で筋量減少者は850万人，筋力低下者は1,000万人，身体機能低下者は350万人を超えると推計された．また Asian Working Group for Sarcopenia のサルコペニア判定のアルゴリズムを用いてサルコペニアの有病者数の推計を行った結果，男性が132万人，女性が139万人と推計された．


## はじめに

現在の日本は4人に1人が65歳以上の高齢者であり，今後も高齢化率はさらなる上昇が見込まれる状況を考慮すると，日常生活における障害や寝たきりを引き起こすサルコペニアへの対策は喫緊の課題である．サルコペニアの予防，治療戦略を構築するうえで我が国のサルコペニアの実態の把握が不可欠であるが，サルコペニアに関する疫学研究は諸外国と比較しても少ないのが現状である．

本稿では，無作為抽出された地域在住の中高齢者を対象とする大規模コホートデータをもとに，日本人高齢者のサルコペニアの実態について概説する．

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キーワード：地域住民，NILS-LSA，
Asian Working Group for Sarcopenia，
有病率

## 地域住民におけるデータの収集

一般の地域住民を対象とするコホート研究である「国立長寿医療研究センター 老化に関する長期縦断疫学研究（NILS-LSA）」は，1997年より開始された[1]．NILS-LSAは日本人の老化および老年病に関する詳細な縦断的データを収集し，日本人の老化像を明らかにするとともに，老化および老年病に関する危険因子を解明することを目的としている．対象者は長寿医療研究センター周辺の，観察開始時年齢が40歳から79歳までの地域住民であり，地方自治体（大府市および東浦町）の協力を得て，住民台帳から年齢・性別に層化した無作為抽出によって選定された．選定された者を説明会に招き，調査の目的や方法などを十分に説明し，インフォームド・コンセントを得たうえで調査は実施された．

NILS-LSAは同一人物を対象に，医学，運動生理学，身体組成，栄養学，遺伝子解析などの千項目以上に及ぶ調査を2年ごとに繰り

返し行う縦断調査であり，現在も継続して実施されている．NILS-LSAにおけるサルコペニアの評価に関連する調査としては，二重エネルギーX線吸収法（DXA）による全身の筋量測定，形態計測，筋力測定，歩行能力測定，転倒調査，ADL低下に関する調査などを実施してきた．また，日常の身体活動量調査や食事・栄養摂取量調査，さらには血液サンプルから抽出されたDNAを用いた遺伝子多型調査についても実施されている．

本稿では，NILS-LSAの第7次調査に参加した65歳以上の男性479人，女性470人を対象に，筋量，筋力，身体機能についてAsian Working Group for Sarcopenia（AWGS）の基準値を当てはめてデータ解析を行った．またAWGSのサルコペニア判定のアルゴリズムを用い，日本人高齢者におけるサルコペニアの有病率を求めるとともに，総務省統計局発表の5歳階級別人口推計（平成26年1月時点）をもとに，サルコペニアの有病者数の全国推計を行った．

## 筋量減少者の頻度

筋量はサルコペニアの古典的定義であり[2]，筋量の減少はサルコペニアの判定において重要視されている．測定には，MRIやCT，DXA，生体インピーダンス法（BIA）を用いる[3,4]．MRIやCT，DXAは機器が据え置きであることや放射線などの影響から[4]，臨床や研究場面において用いられることが多い．それに対しBIAで用いられる体組成計は，移動可能であることや測定が簡便であることなど，研究のみならず地域住民を対象とした保健指導などの場で優位性がある[4]．AWGSではDXAとBIAの基準値が示されており[4]，四肢の筋量を体重の二乗で除したskeletal muscle index（SMI，kg/m$^2$）を用いて評価する[5]．DXAの基準値は男性が7.0kg/m$^2$，女性が5.4kg/m$^2$，BIAの基準値は男性が7.0kg/m$^2$，女性が5.7kg/m$^2$とされている[4]．

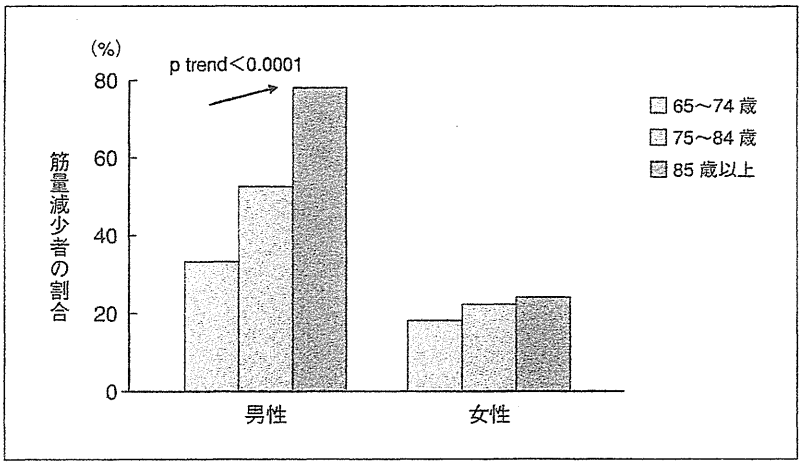
NILS-LSAのDXAによるデータを用いて筋量減少者の割合を求めたところ，65歳以上の男性全体では43.2%が，女性では20.2%が該当した．年代別に検討したところ（図1），男性では年代の上昇に伴って筋量減少者の割合は上昇したのに対し（p trend <0.0001，Cochran-Mantel-Haenszel test），女性では年代と筋量減少者の割合との間に関連は認められなかった．

筋量の測定はサルコペニアの診断において重要である反面，その測定にはDXAやBIAなど，いずれも高額な専用機器を必要とする点で制約が生じる．形態測定と簡易体力測定の結果から四肢筋量を推定する方法についても報告されているので，ここに紹介する．男性では「SMI＝0.326×BMI－0.047×腹囲（cm）－0.011×年齢＋5.135」，女性では「SMI＝0.156×BMI＋0.044×握力（kg）－0.010×腹囲（cm）＋2.747」の推定式より算出される[6]．また，40歳から89歳までを対象とした研究において，立位時の下腿最大周囲長とDXAで得られたSMIとの間に，正の相関関係があることが報告されている[7]．それによると，AWGSのDXAによるSMI基準値評価のための下腿周囲長の最適カットオフ値は，男性が34.3cm（感度89%，特異度88%），女性が32.8cm（感度78%，特異度72%）としている[7]．

## 筋力低下者の頻度

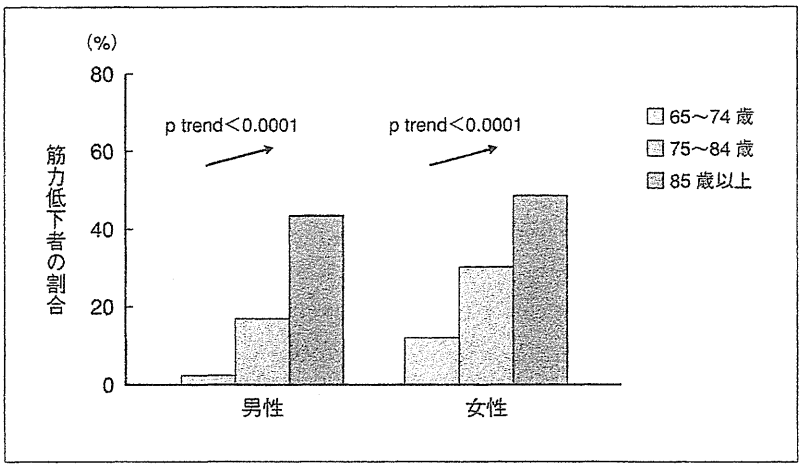
筋力の低下は実生活に直結する．とりわけ脚筋力の低下は移動の制限や転倒の原因になるなど，高齢者では特に注意が必要である．その反面，脚筋力の測定には専用の測定機器を必要とすることから，研究分野での使用が主となっている．一方，握力は脚筋力と比較して簡便に測定可能であり，我が国では新体力テストの測定項目に含まれるなど，一般に

図1 性・年代別に見た筋量減少者の割合




NILS-LSA 第7次調査に参加した65歳以上の男女949人のDXAデータを用い，AWGSにおけるSMIの基準値（男性7.0kg/m$^2$，女性5.4kg/m$^2$）に基づき，筋量減少者の割合を求めた．傾向性p値はCochran-Mantel-Haenszel testによる．

図2 性・年代別に見た筋力低下者の割合

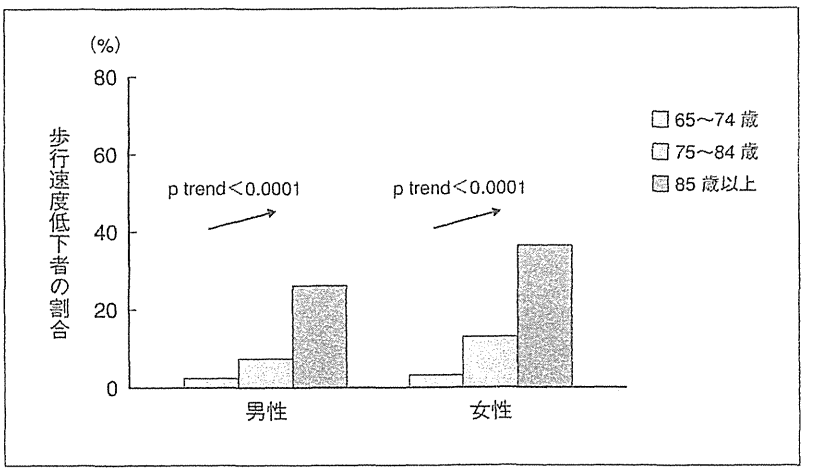



NILS-LSA 第7次調査に参加した65歳以上の男女949人の握力データを用い，AWGSにおける基準値（男性 26kg，女性 18kg）に基づき，筋力低下者の割合を求めた．傾向性p値はCochran-Mantel-Haenszel testによる．

広く知られた測定方法となっている．握力はADL低下との関連が報告されるなど，有害転帰の予測指標となることが示唆されており[3]，脚筋力とも関連することから，サルコペニアの判定においても握力が指標として採用されている[3,4]．AWGSによる握力の基準値は男性26kg，女性18kgとされている[4]．

NILS-LSAのデータを用いて筋力低下者の割合を求めたところ，65歳以上の男性全体では10.0%が，女性では21.5%が該当した．年代別に検討したところ（図2），男女ともに年代の上昇に伴って筋力低下者の割合は上昇した（p trend<0.0001；Cochran-Mantel-Haenszel test）．

図3 性・年代別に見た身体機能低下者の割合




NILS-LSA 第7次調査に参加した65歳以上の男女949人の普通歩行速度データを用い，AWGSにおける基準値（男女ともに0.8m/秒）に基づき，身体機能低下者の割合を求めた．傾向性p値はCochran-Mantel-Haenszel testによる．

### 身体機能低下者の頻度

歩行速度は筋力低下の影響を強く受け，加齢に伴い低下する．また，歩行速度の低下は転倒の発生と関連するなど，歩行速度の測定はサルコペニアの評価において重要である．歩行速度は，床面が水平であれば病棟の廊下などでも測定可能であり，簡便に実施できる．AWGSによる歩行速度の基準値は男女ともに0.8m/秒とされている[9]．

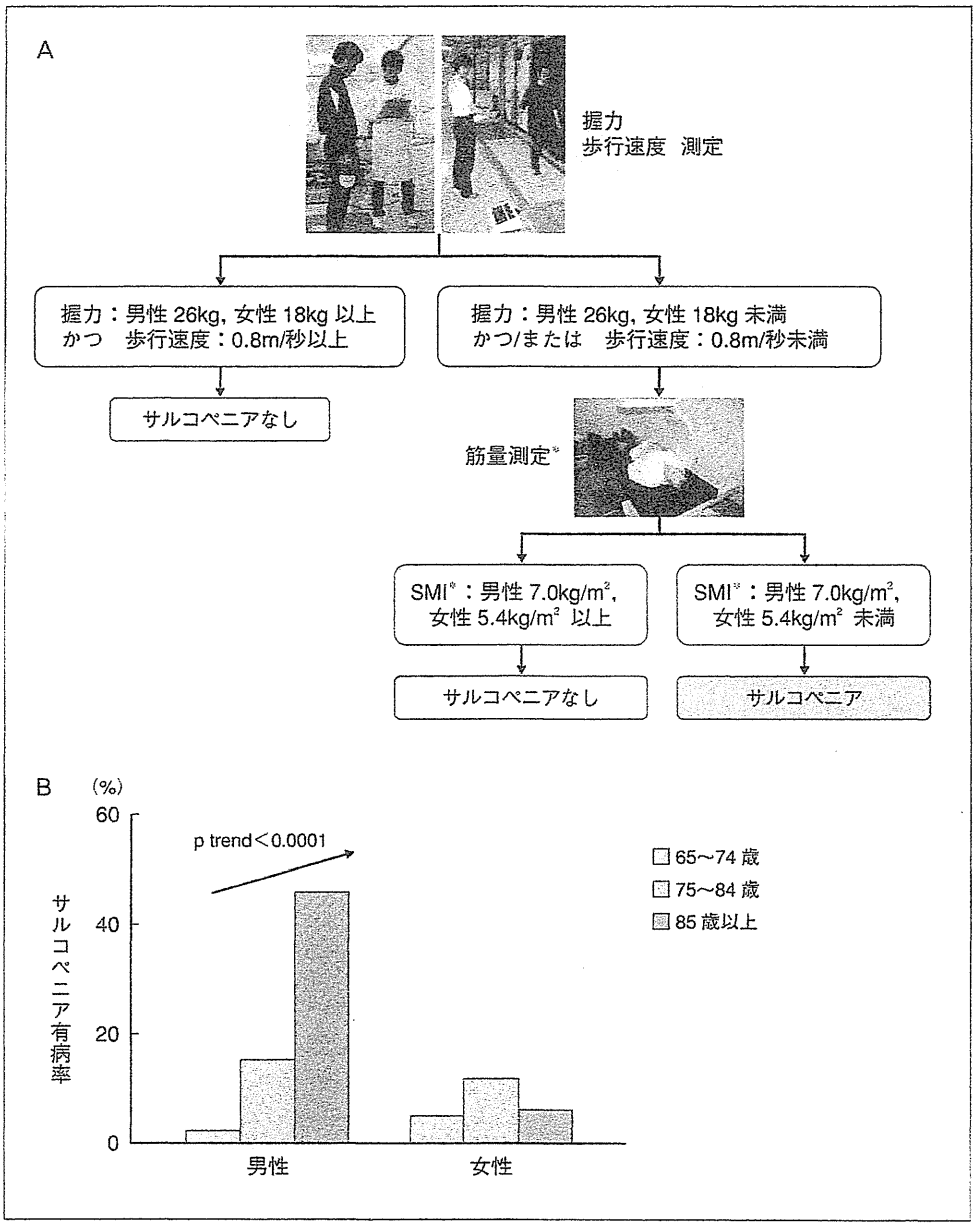
普通歩行速度0.8m/秒未満，または自立歩行困難を身体機能低下者と見なした際のNILS-LSAにおける身体機能低下者の割合は，65歳以上の男性では5.4%，女性では9.2%であった．年代別に検討したところ（図3），筋力低下者と同様に，男女ともに年代の上昇に伴って身体機能低下者の割合は上昇を示した（p trend＜0.0001，Cochran-Mantel-Haenszel test）．

### サルコペニアの判定と有病率

図4にAWGSの提示するサルコペニア判定のアルゴリズムを示す[9]．それによると，高齢者を対象として握力および歩行速度の測定を行う．続いて，握力または歩行速度のどちらか，あるいは両方の測定結果が基準値に満たない者について筋量の測定を行い，筋量が基準値以上であれば「サルコペニアなし」，基準値未満であれば「サルコペニア」として判定することとなっている．

AWGSによる診断アルゴリズムに基づき，NILS-LSAのデータを用いてサルコペニアの判定を行った．その結果，男性が46人（9.6%），女性が36人（7.7%）となった．10歳ごとの年齢階級別の比較では（図4），男性において年代の上昇とサルコペニアの有病率に有意な関連を認めた（p trend＜0.0001，Cochran-Mantel-Haenszel test）．対照的に，女性では年代とサルコペニアの有病率との間に有意な関連を認めなかった．サルコペニアの判定において筋力や身体機能がどれほど低下していたとしても，筋量が基準値を満たしている場合にはサルコペニアとは判定されない．筋量の減少について，女性は男性ほど加齢の影響を受けないとされており[9]，このことが女性において年代とサルコペニアの有病率との

図4 AWGSにおけるサルコペニア判定のアルゴリズムとサルコペニア有病率

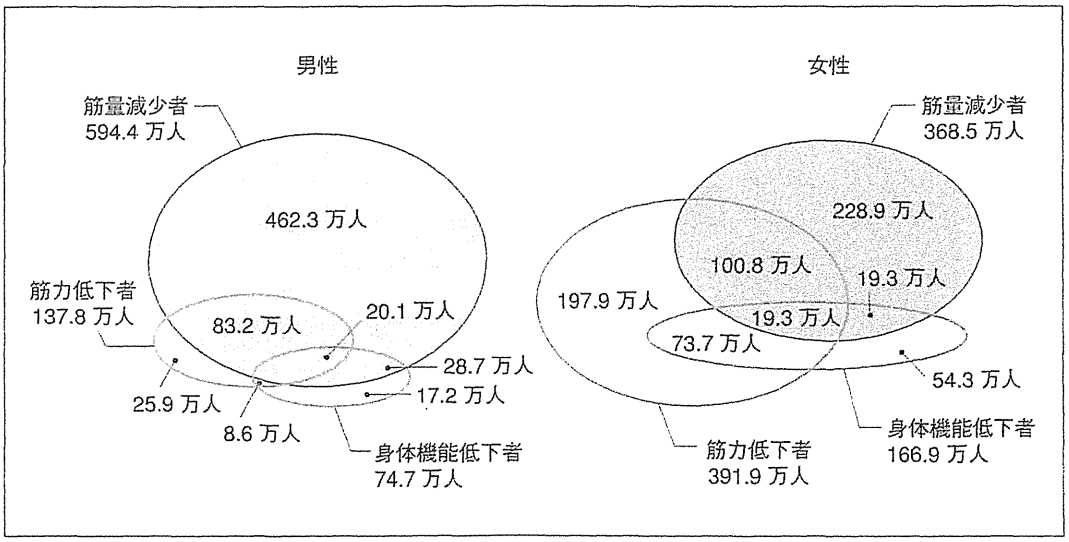



A：対象は高齢者であり，握力ならびに歩行速度の測定にてスクリーニングを行い，筋量の測定で確定診断となる（文献[4]より改変引用）．

*筋量の測定はDXAまたはBIAにより行う．図中の値はDXAの基準値を示す．BIAの場合は男性 7.0 kg/m², 女性 5.7 kg/m² を用いる．

B：男性で年代上昇とサルコペニア有病率との間に関連を認めた．傾向性p値は Cochran–Mantel–Haenszel test による．

図5　サルコペニアの有病者数




有病者数は，NILS-LSA 第7次調査における筋量，握力，普通歩行速度の測定結果と，総務省統計局発表の5歳階級別人口推計（平成26年1月時点）に基づき推計した．

関連を弱めたと思われる．

## サルコペニアの有病者数推計

図5に筋量減少者，筋力低下者，身体機能低下者を，またそれぞれの重複状況を有病者数により示した．日本人高齢者におけるサルコペニアの有病者数は男性が約132万人，女性が約139万人となった．また重複状況では，筋量減少と筋力低下の重複が男女ともに最多で，サルコペニアの原因の6割以上を占めた．

女性では，男性と比較して筋量減少に非依存的な筋力または身体機能の低下者が相当数存在していた．これは骨格筋の脂肪変性や運動神経の退廃，速筋線維の萎縮など，筋の質的問題に起因するものと考えられており，特に女性でその影響は大きいためと推察される．女性高齢者では，サルコペニアの有無にかかわらずADLの低下などに注意を払う必要がある．

## おわりに

サルコペニアに関する一般の認知度は必ずしも高いとは言えない．その理由の1つとして，骨格筋の減少や筋力の低下が単なる老化現象として理解されていることが挙げられる．しかしながら，サルコペニアはフレイル（虚弱）の中核的病態であり[10][11]，自立を著しく阻害するなど，高齢になるほどその影響は大きい．

日本人を対象としたサルコペニア研究において，筋量減少に関する知見は蓄積されつつあるが，筋力低下や身体機能低下についての報告は少ない．また，サルコペニアと有害転帰との関連性の検討を進める必要がある[9]．今後のサルコペニアの予防や治療介入を実現するうえで，遺伝子や運動および身体活動，栄養などの背景因子を含めた学際的な研究の一層の進展が望まれる．

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## Epidemiology of Sarcopenia among the Elderly in the NILS-LSA

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

# Importance of high-density lipoprotein cholesterol levels in elderly diabetic individuals with type IIb dyslipidemia: A 2-year survey of cardiovascular events

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**Aim:** The risk factors for ischemic heart disease (IHD) or cerebrovascular accident (CVA) in elderly diabetic individuals with type IIb dyslipidemia are not fully known. Therefore, we investigated the relationship between lipid levels and IHD and CVA in diabetic individuals with type IIb dyslipidemia.

**Method:** The Japan Cholesterol and Diabetes Mellitus Study is a prospective cohort study of 4014 type 2 diabetic patients (1936 women; age 67.4 ± 9.5 years). The primary end-points were the onset of IHD or CVA. Lipid and glucose levels, and other factors were investigated in relation to the occurrence of IHD or CVA. A total of 462 participants were included in the group of patients with type IIb dyslipidemia.

**Results:** The 462 diabetic participants with type IIb dyslipidemia were divided into those who were aged <65 years, 65–74 years and >75 years ($n$ = 168, 190 and 104, respectively). High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol/HDL-C were significantly associated with the risk of cardiovascular events in diabetic individuals with type IIb dyslipidemia who were aged <65 years, and HDL-C and diastolic blood pressure was significantly associated with cardiovascular events in patients aged 65–74 years. Non-HDL-C was not significantly associated with the risk of cardiovascular events. Multiple regression analysis showed that lower HDL-C was significantly associated with the risk of cardiovascular events in diabetic individuals with type IIb dyslipidemia who were aged <65 years and 65–74 years.

**Conclusions:** Lower HDL-C was an important risk factor for cardiovascular events in diabetic individuals with type IIb dyslipidemia who were aged <75 years. **Geriatr Gerontol Int 2014; 14: 806–810.**

**Keywords:** cerebrovascular accident, elderly type 2 diabetes, high-density lipoprotein cholesterol, ischemic heart disease, type IIb dyslipidemia.

## Introduction

Investigators in Western countries have reported that patients with both hypercholesterolemia and type 2 diabetes have a higher risk of coronary events than patients with hypercholesterolemia alone.[1] The incidence of ischemic heart diseases (IHD) and cerebrovascular

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accident (CVA) in patients with type 2 diabetes is reported to be high in Japan.[2] However, risk factors for IHD or CVA in elderly diabetic individuals with hypercholesterolemia are not fully known.

Many lines of evidence show that low-density lipoprotein cholesterol (LDL-C) is an important risk factor for cardiovascular disease (CVD; CVD = IHD + CVA),[3,4] but it is still debatable whether plasma triglyceride (TG) levels are associated with the occurrence of CVD. However, recent reports have shown that plasma TG levels are an independent risk factor for coronary artery disease (CAD).[3,5–8] In addition, non-fasting TG levels have been shown to be associated with CAD and stroke.[3,9,10] Despite the accumulating evidence against LDL-C and TG, few reports have addressed the effect of type IIb dyslipidemia on cardiovascular disease. We considered the fact that elevated LDL-C and TG along with an increase in atherogenic lipoproteins, such as small and dense LDL, are found in type IIb dyslipidemia, and that this type of dyslipidemia is often associated with type 2 diabetes. It is important to note that when investigating diabetic individuals with type IIb dyslipidemia, there is a synergistic effect of type 2 diabetes and dyslipidemia. This effect might pose a larger risk factor for CVD, but few reports have addressed this association.

Few data were available for the elderly diabetic individuals with type IIb dyslipidemia.[3] Therefore, it is worthwhile to analyze the data from the Japan Cholesterol and Diabetes Mellitus investigation (Japan-CDM), which is a nationwide observational cohort study of a large number of diabetic individuals who were treated in clinical practice. It was designed to assess the relationship between lipid levels and the incidence of CVD in Japanese diabetic individuals.[11,12] We investigated the relationship between lipid levels, IHD and CVA in diabetic individuals with type IIb dyslipidemia in the present study.

## Methods

### *Data source*

The Japan Cholesterol and Diabetes Mellitus Study is a single-center prospective cohort study comprising 4014 Japanese diabetic individuals on a consecutive outpatient basis who were recruited between September 2004 and March 2005 (1936 women; age 67.4 ± 9.5 years [range 35–83 years]) from 40 Japanese hospitals. Patients with coronary artery disease, which was defined as previous myocardial infarction, coronary intervention or confirmed angina pectoris and recent stroke, who had been admitted within the past 24 months were excluded. Follow-up information was available for 98.2% and 92.3% of patients enrolled in the first and second years, respectively. Patients were divided into those who were aged <65 years, 65–74 years and <75 years ($n$ = 1267, 1731 and 1016, respectively). The primary end-points were onset of IHD or CVA. Plasma lipid, glucose, glycated hemoglobin (National Glycohemoglobin Standardization Program) and other relevant levels were measured annually. Lipid and glucose levels, and other factors were investigated in relation to occurrence of IHD or CVA.[11,12]

From this study, we investigated patients with type IIb dyslipidemia. Patients with type IIb dyslipidemia were defined by having both TG ≥150 and LDL-C ≥120. A total of 462 participants were included in the patient group showing type IIb dyslipidemia. The study was approved by institutional review boards and by the safety monitoring board. All events were confirmed annually by the organizing committee. The guidelines of the Japan Atherosclerosis Society (2002), stating that LDL-C should be <120 mg/dL and high-density lipoprotein cholesterol (HDL-C) >40 mg/dL in diabetic individuals, and the American Diabetes Association criteria for diagnosis of type 2 diabetes were used.

### *Statistical analysis*

Results are presented as means ± SD. All statistical analyses were carried out using JMP software (SAS Institute, Cary, NC, USA). Incidences were analyzed in relation to risk factors. Univariate and multiple logistic regression analysis were used. We included both SBP and DBP in the same multivariable model, because systolic hypertension is very often observed in the elderly, and those variables did not show a strong correlation in the present study ($r$ = 0.48). Values of $P < 0.05$ were considered significant.

## Results

The characteristics of the 462 participants are shown in Table 1. The mean age was 67.4 ± 9.5 years, and 52.2% of participants used antihyperlipidemic agents. The 462 participants with type IIb dyslipidemia were divided into those who were aged <65 years, 65–74 years and <75 years ($n$ = 168, 190 and 104, respectively). IHD and CVA occurred in 1.6 and 1.4% of participants, respectively, over a 2-year study period. The occurrence of IHD and CVA in participants with type IIb dyslipidemia was 2.4 and 1.7%, respectively. Participants with type IIb dyslipidemia made up a higher proportion of occurrence of cardiovascular events (Fig. 1). The relationship between IHD or CVA and background factors, such as LDL-C levels, in each age-group was analyzed by univariate logistic regression. Lower HDL-C was significantly associated with a risk of cardiovascular events in diabetic individuals with type IIb dyslipidemia aged <65 years and 65–74 years (Fig. 2a). Higher diastolic blood

**Table 1** Clinical background of diabetic patients with type IIb dyslipidemia

| | Total | <65 years ($n$ = 168) | 65–74 years ($n$ = 190) | ≥75 years ($n$ = 104) |
|---|---|---|---|---|
| Age | 66.4 ± 10.6 | 54.8 ± 7.2 | 70.0 ± 2.77 | 78.6 ± 3.18 |
| Sex ratio (m/f) | 0.99 | 1.46 | 0.87 | 0.66 |
| SBP (mmHg) | 136.9 ± 18.3 | 133.8 ± 17.6 | 138.0 ± 18.4 | 139.9 ± 18.8 |
| DBP (mmHg) | 75.7 ± 11.3 | 78.5 ± 10.5 | 74.3 ± 11.8 | 73.5 ± 10.8 |
| LDL (mg/dl) | 145.6 ± 24.1 | 150.1 ± 26.1 | 145.1 ± 24.8 | 139.0 ± 16.7 |
| HDL (mg/dl) | 46.8 ± 11.6 | 47.6 ± 11.2 | 46.8 ± 12.8 | 45.7 ± 10.2 |
| LDL-C/HDL-C | 3.4 ± 2.4 | 3.4 ± 1.8 | 3.6 ± 3.3 | 3.2 ± 0.9 |
| Non-HDL-C (mg/dL) | 187.1 ± 29.8 | 194.0 ± 31.1 | 185.6 ± 31.6 | 178.7 ± 20.5 |
| TG (mg/dL) | 211.8 ± 65.1 | 227.5 ± 79.5 | 204.4 ± 55.1 | 199.6 ± 49.9 |
| HbA1c (%) | 7.86 ± 1.38 | 7.96 ± 1.54 | 7.74 ± 1.29 | 7.91 ± 1.25 |
| Antihyperlipidemic agents (%) | (52.2) | (60.1) | (51.6) | (40.4) |

DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

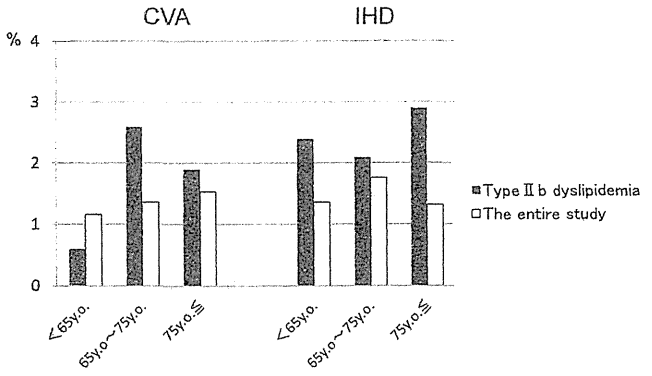


**Figure 1** A 2-year survey of cardiovascular events in each generation's type IIb dyslipidemia and of the entire study. CVA, cerebrovascular accident; IHD, ischemic heart disease.

pressure (DBP) was significantly associated with the risk of cardiovascular events in diabetic individuals with type IIb dyslipidemia who were aged 65–74 years, and LDL-C/HDL-C was significantly associated with individuals who were aged <65 years (Fig. 2a,b). Non-HDL-C was not significantly associated with the risk of cardiovascular events. We carried out multiple regression analysis. The data shown were after adjustment for age, sex, systolic blood pressure (SBP), DBP, glycated hemoglobin, plasma lipid levels and antihyperlipidemic agents. With regard to LDL-C/HDL-C, the data obtained were after adjustments for the same factors except for lipid levels. With regard to non-HDL-C, the data obtained were after adjustment for the same factors, but lipid factor is only TG. We investigated three age groups. Lower HDL-C was associated with the risk of cardiovascular events in patients who were aged <65 years and 65–74 years (Table 2).

## Discussion

Type IIb dyslipidemia is important, because it sometimes accompanies atherogenic lipid profiles, such as small dense LDL, remnant lipoprotein and low HDL cholesterolemia. It is also associated with type 2 diabetes mellitus, metabolic syndrome and chronic kidney disease (CKD), and most patients with familial combined hyperlipidemia (FCHL) show this phenotype.[3,13–16] Therefore, it is necessary to understand that patients with type IIb dyslipidemia have a high risk for CVD. The management of type IIb dyslipidemia is key to the prevention of CVD.[3] Therefore, we assessed the relationship between lipid levels and IHD, and CVA in diabetic individuals with type IIb dyslipidemia.

The present study showed that lower HDL-C was an important risk factor for cardiovascular events in diabetic individuals with type IIb dyslipidemia who were aged <75 years. Multiple regression analysis showed lower HDL-C levels were associated with the risk of cardiovascular events in patients who were aged <75 years. We could not show the significant association between HDL-C levels and each event. One of the reasons for this inability was the small number of type IIb patients, and the relatively short duration of observation for participants with type IIb dyslipidemia. We showed there was a significant association between HDL-C levels and total events (IHD + CVA). We could not show the significant association between non-HDL-C levels or LDL-C/HDL-C and each event by multiple regression analysis. We speculate that HDL-C was the most important risk factor for cardiovascular events in diabetic individuals with type IIb dyslipidemia. Other studies including Japanese patients with type 2 diabetes (mean age 58.2 years) showed serum TG levels were a leading predictor of coronary

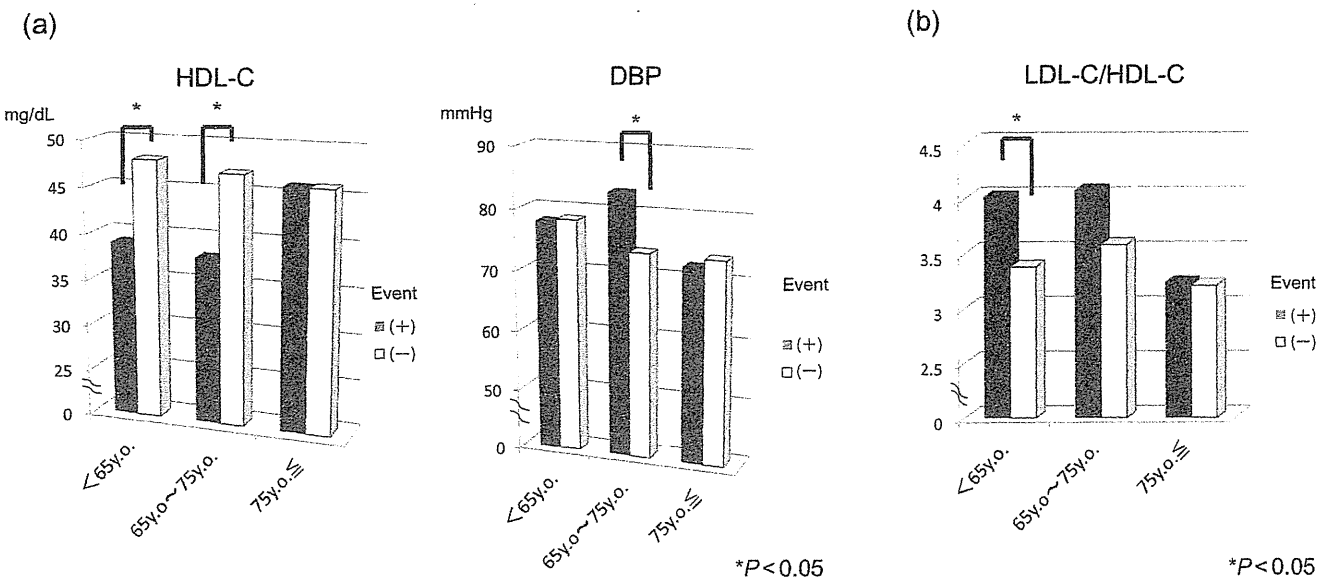


**Figure 2** (a) The relationship between high-density lipoprotein (HDL-C) and diastolic blood pressure (DBP) levels, and the occurrence of events. (b) The relationship between low-density lipoprotein cholesterol (LDL-C)/HDL-C and the occurrence of events.

**Table 2** Adjusted multiple regression analyses of factors found to be significant by univariate regression analysis for cardiovascular disease, as well as major atherogenic risk factors

| | <65 years ($n$ = 168) Adjusted OR (95%CI) | $P$ | 65–74 years ($n$ = 190) Adjusted OR (95%CI) | $P$ | ≥75 years ($n$ = 104) Adjusted OR (95%CI) | $P$ |
|---|---|---|---|---|---|---|
| Age | 1.117 (0.98–1.33) | 0.14 | 0.818 (0.57–1.13) | 0.24 | 1.068 (0.81–1.39) | 0.62 |
| LDL-C | 0.980 (0.93–1.02) | 0.38 | 1.000 (0.95–1.03) | 0.97 | 1.036 (0.98–1.09) | 0.17 |
| HDL-C | 0.910 (0.82–0.99) | 0.04* | 0.900 (0.81–0.98) | 0.03* | 1.000 (0.92–1.09) | 0.99 |
| TG | 0.996 (0.98–1.01) | 0.62 | 1.000 (0.98–1.01) | 0.94 | 0.996 (0.97–1.01) | 0.68 |
| HbA1c | 1.030 (0.56–1.80) | 0.92 | 0.921 (0.38–1.96) | 0.84 | 0.803 (0.37–1.50) | 0.52 |
| SBP | 1.027 (0.96–1.10) | 0.45 | 1.008 (0.95–1.07) | 0.77 | 0.980 (0.94–1.02) | 0.33 |
| DBP | 0.992 (0.89–1.10) | 0.87 | 1.065 (0.98–1.17) | 0.14 | 0.975 (0.90–1.06) | 0.55 |
| LDL-C/HDL-C | 1.120 (0.57–1.57) | 0.57 | 1.161 (0.85–1.39) | 0.12 | 1.173 (0.41–2.68) | 0.72 |
| Non-HDL-C | 0.988 (0.96–1.01) | 0.43 | 1.002 (0.96–1.03) | 0.89 | 1.016 (0.97–1.06) | 0.45 |

*$P$ < 0.05. DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

heart disease (CHD), comparable with LDL-C or HDL-C.[17] However, our former study including all participants showed the importance of HDL-C in CVA in elderly diabetic individuals, and in IHD in middle-aged diabetic individuals.[12] In our previous study, lower HDL-C was significantly related to CVA in participants aged ≥65 years, and especially in those aged >75 years.[12] The Prospective Study of Pravastatin in the Elderly at Risk study showed that simple LDL-C control might not prevent IHD or CVA in elderly individuals.[18] Our former study showed the importance of HDL cholesterol in CVA in elderly diabetic individuals.[12]

In addition to LDL-C, HDL-C is also a key risk factor in elderly diabetic individuals.[11,12] Because diabetic individuals with type IIb dyslipidemia have a higher risk for CVD, the importance of HDL-C might be different than that of usual diabetic individuals. Therapeutic lifestyle changes, including those to diet and exercise, constitute the cornerstone of management in patients with type IIb dyslipidemia. Restriction of dietary cholesterol (less than 300 mg/day) and saturated fat in addition to increasing dietary fiber and plant sterols can lower LDL-C, and restriction of alcohol, sugar, saturated fat and high intake of omega-3 fatty acids can reduce serum TG.[3,19] Because weight reduction can further lower LDL-C and TG, and raise HDL-C levels, maximal improvement in dyslipidemia should be attempted with lifestyle intervention before prescribing lipid-lowering medications.

Risk factors for cardiovascular events appear to change with advancing age.[12] The importance of HDL-C is different for each age-group. The present study on diabetic individuals with type IIb dyslipidemia was small in size, so a larger study will be required. However, HDL-C might help prevent cardiovascular events diabetic patients with type IIb dyslipidemia who are aged <75 years.

With regard to antihypertensive agents, approximately half of the participants used antihypertensive agents. There were no significant relationships between CVD and antihypertensive agents. Although we did not focus on antihypertensive agents in the present study, investigation of antihypertensive agents is important, and further study will be required in the future.

In conclusion, the present study showed that lower HDL-C was an important risk factor for cardiovascular events in diabetic individuals with type IIb dyslipidemia who are aged <75 years. If HDL-C is well controlled in elderly diabetic individuals who are aged <75 years with type IIb dyslipidemia, then IHD and CVA might be decreased to the levels found in diabetic patients of middle-aged cohorts.

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## Disclosure statement

All authors have no conflict of interests.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

# Relationship between small cerebral white matter lesions and cognitive function in patients with Alzheimer's disease and amnestic mild cognitive impairment

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**Aim:** The main purpose of the present study was to investigate the influence of small cerebral white matter lesions on cognitive functions, and its difference by clinical stage.

**Methods:** A total of 160 patients with Alzheimer's disease and 40 older adults with amnestic mild cognitive impairment were enrolled in the present study. The Fazekas rating scale was used for the semi-quantitative measurement of white matter lesions. Participants whose scales were more than grade 2 were excluded. Associations between the degree of small white matter lesions and cognitive functions including memory, verbal fluency, working memory, processing speed, and executive function were examined.

**Results:** We found that small white matter lesions influenced the performances of neuropsychological tests differently between Alzheimer's disease and amnestic mild cognitive impairment. Analysis of covariance showed significant effects of interaction on a test that assessed categorical verbal fluency. In the amnestic mild cognitive impairment group, small periventricular white matter hyperintensities were significantly associated with poor performances in categorical verbal fluency; whereas in the Alzheimer's disease group, such associations were not observed. Deep white matter hyperintensities did not influence any cognitive functions examined in both groups.

**Conclusions:** The results suggested the involvement of periventricular small white matter lesions on impairment in verbal fluency, and such influence might be different depending on an individual's clinical stage. **Geriatr Gerontol Int 2014; 14: 819–826.**

**Keywords:** Alzheimer's disease, cognitive function, mild cognitive impairment, verbal fluency, white matter lesions.

## Introduction

Cerebral white matter lesions (WML) are identified as white matter hyperintensities, areas with high signal intensities on T2-weighed magnetic resonance imaging (MRI). The pathogenesis of WML has not been fully clarified, and the clinical relevance of WML also remains ambiguous. Several histopathological correlates have been reported: enlarged WML including myelin pallor, tissue rarefaction associated with loss of myelin and axons, and mild gliosis.[1,2] The occurrence of WML has been shown to increase with advancing age,[3,4] and the progression of WML has been associated with vascular risk factors.[5] In a meta-analysis, WML predicted an increased risk of stroke, dementia and death.[6]

In some non-demented population-based studies, WML predicted a higher rate of cognitive decline,[4,7–10] especially when located in the periventricular regions.[11–14] In some studies of Alzheimer's disease (AD) patients, it has been suggested that AD patients with WML had worse cognitive performances than those without WML,[15–17] whereas other studies did not find any association between WML and cognitive decline in AD patients.[18,19] Diversities in study samples with varying clinical stages or different methods for the assessment of WML might explain the inconsistent results in those studies. Several studies have suggested that WML could influence cognitive performance in the

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early stages of AD, but not in the late stages.[18,20] If this is true, WML might have greater influence on cognitive profiles in amnestic mild cognitive impairment (aMCI) patients than AD patients, because aMCI has been considered a preclinical and prodromal stage of AD. In some studies of MCI patients, WML were associated with cognitive decline,[21] and predicted a higher rate of conversion to dementia.[22,23] Studies investigating the influence of WML on cognitive function both in AD and aMCI patients have been sparse to date.

In view of investigating the influence of small WML on cognitive profiles of AD pathology, one has to preclude with caution a possible contamination of mixed pathology, such as vascular dementia or vascular mild cognitive impairment, from analysis. Therefore, in the present study, we focused on investigating neuropsychological traits in patients with AD or aMCI, and examined their associations with the degree of small WML, assessed by a semi-quantitative method based on MRI findings after carefully excluding patients with diffuse or extensive WML. If any difference was observed between the groups, the finding might suggest temporal profiles regarding the influence of small WML on cognitive performances during the progression of this neurocognitive disorder.

## Methods

### *Participants*

The present study was carried out among outpatients attending the Nagoya University Hospital department of geriatrics in Nagoya, Japan, between January 2010 and March 2012. Among 641 consecutive patients aged 60 years or older, 268 patients who were diagnosed with neither AD nor aMCI, and 109 patients who could not complete the relevant cognitive tasks were excluded. Regarding methods for objectively assessing the degree of WML, the Fazekas rating scale[24] was used in the present study. It is a visual semi-quantitative rating scale of WML volume, and this scale is one of the most widely-used and well-validated. This scoring system is a four-point scale, rated on a 0- to 3-point scale of increasing severity. As explained in the Introduction, in order to eliminate a possible contamination of mixed pathology, those who were graded more than 2 on the Fazekas rating scale (64 patients) were not included in the study, and only those who were graded either 0 or 1 on the scale were included, eventually leaving 200 patients subjected for analyses.

Of the participants, 160 patients were diagnosed as probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[25] and 40 cases were diagnosed as aMCI according to the Mayo Clinic Criteria.[26] The patients with aMCI all met the criteria for single-domain amnestic MCI or multiple-domain amnestic MCI proposed by Petersen.[27] All of them had the complaint of memory impairment. Patients with single-domain amnestic MCI had impaired performance (more than 1.5 SD below controls) on one or more of the memory tests used in the neuropsychological battery, but not on the other tests. Patients with multiple-domain amnestic MCI had impaired performance on one or more of the memory tests, and impaired performance on one or more of the other tests. None of them had dementia according to the clinical assessment. Hereafter, aMCI includes both the single- and multiple-domain subtypes.

The evaluation procedure consisted of a detailed medical history, cognitive assessment, laboratory tests and cerebral MRI. The patients also underwent a clinical examination to exclude other etiologies. Patients who had a history of cerebrovascular disorders or the presence of significant vascular risk factors were excluded, as well as patients who had previously received an actual diagnosis of major depression.[28] Japanese was the primary language for all participants.

### *Cognitive assessment*

All participants underwent a battery of neuropsychological tests. The battery of neuropsychological tests included the following tests: the Mini-Mental State Examination (MMSE)[29] for general cognitive function; the Logical Memory I and II subtests of the Wechsler Memory Scale-revised (WMS-R)[30] for memory; the category fluency test (participants were required to generate as many animal names as possible within 1 min) and the letter fluency test (participants were required to generate as many words beginning with the syllable "ka" (the Japanese version of the phonemic fluency task) as possible within 1 min for verbal fluency; the Digit Span Forward and Backward subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R)[31] for working memory; the Digit Symbol subtests of WAIS-R[31] for processing speed; and the Stroop colored word test for executive functions (controlled inhibition). All patients were also assessed for depressive mood using the Geriatric Depression Scale-15 (GDS-15).[32]

Testing and scoring of the neuropsychological tests were carried out by a trained clinical psychologist with a Master's degree in clinical psychology. Participants were tested individually in a single session. Written informed consent was obtained at the start of the evaluation from all participants or their closest relative.

### *White matter assessment*

The MRI scans were carried out on a 1.5T machine. Ratings of WML on MRI images were carried out on a

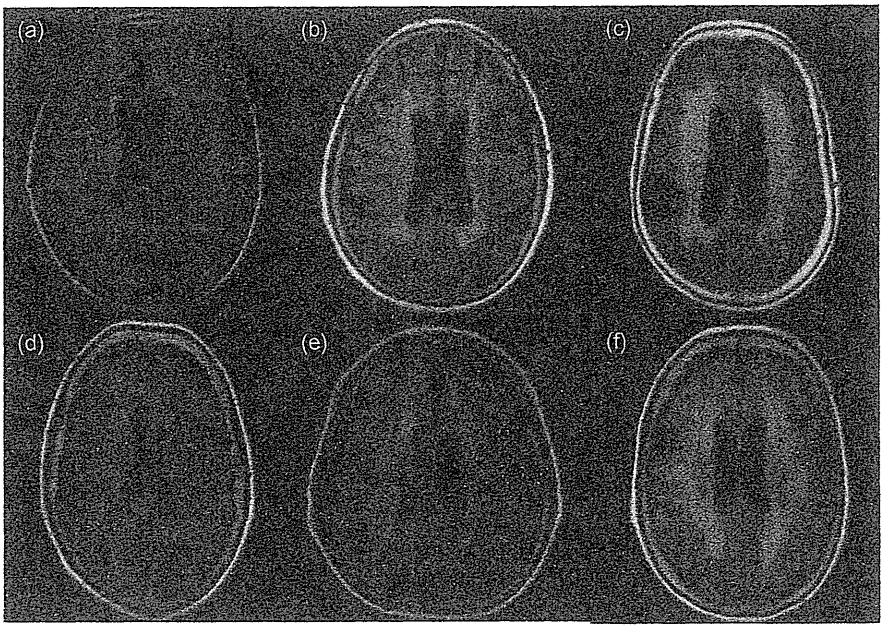


**Figure 1** Examples of Fazekas scale ratings. (a) Periventricular hyperintensities (PVH) score = 1. (b) PVH score = 2. (c) PVH score = 3. (d) Deep white matter hyperintensities (DWMH) score = 1. (e) DWMH score = 2. (f) DWMH score = 3.

**Table 1** Numbers of patients for Fazekas scale ratings

| | | AD ($n$ = 160) DWMH | | | | aMCI ($n$ = 40) DWMH | |
|---|---|---|---|---|---|---|---|
| | | Grade 0 | Grade 1 | | | Grade 0 | Grade 1 |
| PVH | Grade 0 | 30 | 14 | PVH | Grade 0 | 5 | 4 |
| | Grade 1 | 21 | 95 | | Grade 1 | 7 | 24 |

Definitions of rating scores of periventricular white matter hyperintensity (PVH): grade 0, absence; grade 1, caps or pencil-thin lining. Definitions of rating scores of deep subcortical white matter hyperintensity (DWMH): grade 0, absence; grade 1, punctate.
AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment.

computer screen with axial fluid-attenuated inversion recovery (FLAIR) images. The visual semi-quantitative rating scale of WML volume described by Fazekas *et al.*[24] was used. This scoring system is a four-point scale for separately assessing the increasing severity of periventricular white matter hyperintensity (PVH) and deep subcortical white matter hyperintensity (DWMH). PVH severity was scored according to the following categories: absence (grade 0); caps or pencil-thin lining (grade 1); smooth halo (grade 2) and irregular PVH extending into the deep white matter (grade 3). DWMH severity was scored according to the following categories: absence (grade 0); punctate (grade 1); beginning confluence (grade 2) and large confluence (grade 3). Examples of PVH and DWMH severities are shown in Figure 1. Participants who were graded more than grade 2 of PVH or DWMH were excluded from the present study. Table 1 shows the numbers of patients for the Fazekas rating scale included in this study. All ratings were carried out by two raters (the second and third authors). Each rater rated each case individually and then consulted with each other to reach a consensus.

### *Statistical analysis*

The statistical analyses were carried out using IBM SPSS Statistics version 19 for Windows (SPSS Japan, Tokyo, Japan). A value of $P < 0.05$ was used in all analyses to show statistical significance.

First, we carried out descriptive analyses of sociodemographic and clinical characteristics. Table 2 shows the mean and standard deviations, and the frequency and percentage. We used the $\chi^2$-test for the comparison of categorical data, and we applied Student's $t$-test for continuous data.

Analysis of covariance (ANCOVA) was used to determine the correlation of WML and cognitive data between AD and aMCI. It is well known that age and

**Table 2** Clinical characteristics and cognitive performance of Alzheimer's disease and amnestic mild cognitive impairment patients

| | AD ($n$ = 160) | | | | aMCI ($n$ = 40) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sex (male/female) | 66/94 | | | | 15/25 | | | | |
| Diabetes mellitus (%) | 29 (18.13%) | | | | 7 (17.50%) | | | | |
| Hypertension (%) | 70 (43.75%) | | | | 20 (50.00%) | | | | |
| Hyperlipidemia (%) | 70 (43.75%) | | | | 20 (50.00%) | | | | |
| aMCI subtype (single domain/multiple domain) | | | | | 19/21 | | | | |
| | MEAN | SD | MIN | MAX | MEAN | SD | MIN | MAX | $P$-value |
| Age (years) | 77.01 | 6.87 | 61 | 92 | 76.08 | 6.56 | 60 | 90 | 0.440 |
| Education (years) | 11.40 | 2.78 | 6 | 20 | 12.26 | 2.95 | 8 | 18 | 0.084 |
| GDS15 | 4.33 | 3.37 | 0 | 14 | 3.83 | 2.94 | 0 | 13 | 0.390 |
| MMSE | 21.94 | 3.69 | 11 | 29 | 27.13 | 1.49 | 24 | 30 | <0.001 |
| WMS-R Logical Memory I | 6.26 | 4.30 | 0 | 22 | 10.05 | 4.65 | 1 | 22 | <0.001 |
| WMS-R Logical Memory I | 1.16 | 2.40 | 0 | 12 | 3.20 | 2.83 | 0 | 9 | <0.001 |
| Category Fluency Test | 11.67 | 3.72 | 2 | 23 | 14.90 | 4.02 | 6 | 24 | <0.001 |
| Letter Fluency Test | 7.76 | 3.15 | 2 | 20 | 9.18 | 3.40 | 0 | 15 | 0.013 |
| WAIS-R Digit-Span Forward | 5.63 | 1.89 | 2 | 10 | 6.20 | 1.68 | 3 | 9 | 0.084 |
| WAIS-R Digit-Span Backward | 4.34 | 1.45 | 1 | 8 | 5.05 | 1.38 | 2 | 8 | 0.006 |
| WAIS-R Digit-Symbol | 33.22 | 11.73 | 3 | 77 | 38.38 | 12.01 | 9 | 68 | 0.014 |
| Stroop Test Color | 21.86 | 10.03 | 9.56 | 78.09 | 17.67 | 3.94 | 8.85 | 30.79 | <0.001 |
| Stroop Test Colored Word | 46.75 | 20.04 | 15.40 | 134.19 | 40.08 | 18.03 | 20.32 | 113.21 | 0.056 |

$P$-values were calculated by Student's $t$-tests. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; Education, total number of years of schooling; GDS15, 15-item version of the Geriatric Depression Scale; MAX, maximum score; MIN, minimum score; MMSE, Mini-Mental State Examination; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

education level influence cognitive function, so these two variables were considered to be covariables in the analysis carried out later. As a post-hoc analysis, pairwise multiple comparisons of the cognitive data were tested with Bonferroni test after ANCOVA.

## Results

Table 2 presents the sociodemographic and clinical characteristics of the participants, and the raw neuropsychological test results for both AD and aMCI. The means and standard deviations, and maximal and minimal values are shown.

The groups with different diagnoses were not statistically different in terms of the following variables: distribution of sex, clinical comorbidity (diabetes mellitus, hypertension, hyperlipidemia), age, years of education and depressive mood (GDS-15). Likewise, the MCI subtypes were similar in their distributions of the variables. Regarding the comparison of cognitive performances between the two groups, AD group performed significantly worse than did the aMCI group in tests as follows: MMSE ($t$ [158.87] = 13.84, $P < 0.001$), logical memory I ($t$ [198] = 4.91, $P < 0.001$), logical memory II ($t$ [198] = 4.63, $P < 0.001$), category fluency ($t$ [198] = 4.83, $P < 0.001$), letter fluency ($t$ [198] = 2.51, $P < 0.05$), digit span backward ($t$ [198] = 2.80, $P < 0.01$), digit symbol ($t$ [198] = 2.47, $P < 0.05$) and Stroop color test ($t$ [162.81] = 2.59, $P < 0.001$).

Table 3 shows the influence diagnosis and PVH had on participants' performances in the neuropsychological tests, as well as the interaction between the two factors. We found that diagnosis significantly influenced the results of the following tests: MMSE ($F$ [1,194] = 49.43, $P < 0.001$), logical memory I ($F$ [1,194] = 16.81, $P < 0.001$), logical memory II ($F$ [1,194] = 14.68, $P < 0.001$), category fluency ($F$ [1,194] = 29.43, $P < 0.001$), letter fluency ($F$ [1,194] = 8.02, $P < 0.01$), digit symbol ($F$ [1,194] = 4.86, $P < 0.05$) and Stroop colored word test ($F$ [1,194] = 4.06, $P < 0.05$). PVH had a significant influence on the results of the tests that assess the following variables: category fluency ($F$ [1,194] = 8.11, $P < 0.01$) and letter fluency ($F$ [1,194] = 5.47, $P < 0.05$). Individuals having small PVH, independent of their diagnosis, performed worse than those having no PVH in terms of verbal fluency. We found significant effects of interaction on the results of the category fluency test ($F$ [1,194] = 7.01, $P < 0.01$). The

**Table 3** Cognitive performance according to periventricular hyperintensities

| | AD | | | | aMCI | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PVH grade0 ($n$ = 44) | | PVH grade1 ($n$ = 116) | | PVH grade0 ($n$ = 9) | | PVH grade1 ($n$ = 31) | | $P$ Diagnosis | $P$ PVH | $P$ Diagnosis × PVH |
| | MEAN | SD | MEAN | SD | MEAN | SD | MEAN | SD | | | |
| MMSE | 22.82 | 3.04 | 21.60 | 3.86 | 27.67 | 1.22 | 26.97 | 1.54 | <0.001 | 0.294 | 0.678 |
| WMS-R Logical Memory-I | 6.77 | 4.19 | 6.06 | 4.35 | 11.22 | 5.45 | 9.71 | 4.43 | <0.001 | 0.500 | 0.651 |
| WMS-R Logical Memory-II | 1.09 | 2.61 | 1.19 | 2.32 | 3.44 | 3.32 | 3.13 | 2.73 | <0.001 | 0.819 | 0.676 |
| Category Fluency Test | 12.25 | 3.11 | 11.45 | 3.92 | 18.44 | 3.68 | 13.87 | 3.55 | <0.001 | 0.005 | 0.009 |
| Letter Fluency Test | 8.34 | 2.96 | 7.53 | 3.20 | 11.44 | 1.33 | 8.52 | 3.54 | 0.005 | 0.020 | 0.094 |
| WAIS-R Digit-Span Forward | 6.11 | 1.98 | 5.45 | 1.83 | 6.22 | 1.79 | 6.19 | 1.68 | 0.473 | 0.723 | 0.402 |
| WAIS-R Digit-Span Backward | 4.86 | 1.29 | 4.14 | 1.47 | 5.33 | 1.80 | 4.97 | 1.25 | 0.074 | 0.165 | 0.503 |
| WAIS-R Digit-Symbol | 36.11 | 12.24 | 32.12 | 11.40 | 44.78 | 11.97 | 36.52 | 11.55 | 0.029 | 0.105 | 0.304 |
| Stroop Test Color | 20.54 | 8.28 | 22.36 | 10.61 | 16.46 | 3.13 | 18.01 | 4.13 | 0.051 | 0.701 | 0.991 |
| Stroop Test Colored Word | 44.37 | 16.03 | 47.66 | 21.36 | 30.75 | 7.09 | 42.78 | 19.38 | 0.045 | 0.163 | 0.259 |

$P$-values were calculated by analysis of covariance and adjusted for age and education. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; PVH, periventricular white matter hyperintensity; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

combination of aMCI and category fluency showed a significant negative influence ($F$ [1,194] = 9.28, $P < 0.01$); whereas in the AD group, such an association was not observed.

Table 4 shows the influence that diagnosis and DWMH had on participants' performances on neuropsychological tests, as well as the interaction between the two factors. We found that diagnosis significantly influenced the results of the following tests: MMSE ($F$ [1,194] = 56.00, $P < 0.001$), logical memory I ($F$ [1,194] = 22.54, $P < 0.001$), logical memory II ($F$ [1,194]= 21.09, $P < 0.001$), category fluency ($F$ [1,194] = 16.06, $P < 0.001$), letter fluency ($F$ [1,194] = 4.34, $P < 0.05$), digit span backward ($F$ [1,194] = 4.02, $P < 0.05$). DWMH did not significantly influence any other neuropsychological tests. We did not find any other significant effects of the interaction between diagnosis and DWMH.

## Discussion

The primary objective of the present study was to examine the association between small WML and cognitive function in older patients with AD or aMCI. To this end, two subgroups of patients with AD or aMCI differed regarding the influence of small WML on cognitive function.

Among aMCI participants, those without PVH had higher scores than those with PVH on the category fluency test. In contrast, the existence of small PVH did not significantly affect the score on the same test in AD patients. These findings might support a notion suggesting that WML could influence cognitive performance in the early stage of cognitive impairment, but not in the later stage of degenerative dementia.[18,20] Changes of relative involvement of WML on cognition by disease progression could explain the results obtained. It is well known that as AD pathology advances, cortical atrophy extends. Therefore, one could speculate that the relative influence of cortical atrophy on cognition compared with that of WML becomes increased in the later stage of AD. Further investigations focusing on patients with earlier stages of AD whose extent of cortical atrophy are considered minimal could address this speculation.

We found significant effects of interaction between diagnosis and PVH on the results of the category fluency test, whereas on the results of the letter fluency such interaction was not found. The category fluency task is associated with the ability to access semantic knowledge, whereas letter fluency is considered an index of frontal control function.[33] In a meta-analysis of verbal fluency in AD, it was suggested that impairment in category fluency rather than letter fluency might be among the early changes associated with AD.[34] A previous study has shown that the aMCI groups have

**Table 4** Cognitive performance according to deep subcortical white matter hyperintensity

| | AD | | | | aMCI | | | | *P* | *P* | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | DWMH grade 0 ($n$ = 51) | | DWMH grade 1 ($n$ = 109) | | DWMH grade 0 ($n$ = 12) | | DWMH grade 1 ($n$ = 28) | | Diagnosis | DWMH | Diagnosis × DWMH |
| | MEAN | SD | MEAN | SD | MEAN | SD | MEAN | SD | | | |
| MMSE | 22.53 | 3.48 | 21.66 | 3.76 | 27.00 | 1.48 | 27.18 | 1.52 | <0.001 | 0.756 | 0.444 |
| WMS-R Logical Memory-I | 6.45 | 3.98 | 6.17 | 4.46 | 11.75 | 4.58 | 9.32 | 4.56 | <0.001 | 0.213 | 0.161 |
| WMS-R Logical Memory-II | 1.16 | 2.41 | 1.17 | 2.40 | 4.17 | 2.98 | 2.79 | 2.71 | <0.001 | 0.254 | 0.126 |
| Category Fluency Test | 11.96 | 3.65 | 11.53 | 3.76 | 14.67 | 4.96 | 15.00 | 3.65 | <0.001 | 0.590 | 0.670 |
| Letter Fluency Test | 8.24 | 3.62 | 7.53 | 2.89 | 9.75 | 3.14 | 8.93 | 3.53 | 0.038 | 0.394 | 0.856 |
| WAIS-R Digit-Span Forward | 5.94 | 2.01 | 5.49 | 1.82 | 6.75 | 1.42 | 5.96 | 1.75 | 0.147 | 0.170 | 0.569 |
| WAIS-R Digit-Span Backward | 4.39 | 1.36 | 4.31 | 1.50 | 5.08 | 1.51 | 5.04 | 1.35 | 0.032 | 0.874 | 0.975 |
| WAIS-R Digit-Symbol | 36.96 | 12.60 | 31.47 | 10.93 | 40.33 | 12.22 | 37.54 | 12.04 | 0.112 | 0.221 | 0.621 |
| Stroop Test Color | 20.13 | 6.60 | 22.67 | 11.22 | 17.43 | 3.74 | 17.77 | 4.09 | 0.056 | 0.656 | 0.574 |
| Stroop Test Colored Word | 46.58 | 16.92 | 46.84 | 21.42 | 40.89 | 26.01 | 39.73 | 13.92 | 0.158 | 0.606 | 0.913 |

*P*-values were calculated by analysis of covariance and adjusted for age and education. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; DWMH, deep subcortical white matter hyperintensity; MMSE, Mini-Mental State Examination; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

greater impairment in category fluency performance than in letter fluency performance relative to healthy controls.[35] Neuroanatomically, category fluency relies on the medial temporal lobe regions, whereas letter fluency has been found to correlate with prefrontal lobe functioning.[36] Differences in the anatomical substrates for each verbal fluency task might explain the present results. Because of advanced medial temporal lobe atrophy, WML might not influence category fluency in the later stage of AD.

When diagnosis was not added, associations between the small PVH and low verbal fluency performance were shown in the present study. Several studies found that WML was particularly associated with a decline in mental processing speed, executive functions, but not with a decline in memory functions,[10,37-39] which could suggest that WML have an influence on frontal lobe functions. Memory decline is particularly related to medial temporal lobe atrophy, and might be less affected by WML.[17,40] The disruption of long associating fibers by PVH might be particularly deleterious for frontal lobe domain functions.[21] In the present results, small PVH contributed to cognitive decline in verbal fluency, but not in any other domains of cognitive function. It remains unclear why small PVH was correlated only with verbal fluency.

Our results are in line with several population-based studies[11-14] in which PVH and not are associated with different clinical conditions. It is also suggested that the pathology presenting PVH might impair cognitive functioning more easily than that affecting the subcortical area. Anatomically, the periventricular regions have a high density of long associating fibers, which connect the cortex with the subcortical nuclei and other distant brain territories, whereas the subcortical area has a high density of short-looped U fibers connecting adjacent gyri.[11] The mechanism underlying the present results requires further substantiation.

The main limitation of the present study was the rating system of WML. Regarding the semi-quantitative rating of white matter lesions used in our study, it could be argued that it is not sufficiently accurate, but this rating system has been shown to correlate well with quantitative volumetric measurements.[41] The present study showed that small amounts of WML were correlated with cognitive impairment. We assumed that greater degrees of WML correspond to different patterns of cognitive decline. WML could trigger or enhance neurodegenerative processes when the lesion load reaches a certain threshold.[19]

Because of the smaller sample size of aMCI patients, the statistical power of the study might have been insufficient to detect an association between cognitive deficit and small WML. Our sample size was also inadequate to examine the association of cognitive decline with the different locations of DWMH, which might have some