Table 2
うつを従属変数とする年齢・性別の重回帰分析結果[a)]

	中年期		老年期	
	男性 (n=564)	女性 (n=552)	男性 (n=551)	女性 (n=544)
基本属性要因				
配偶者	.100**	.081*	.152***	.064
身体的要因				
主観的健康感	.222***	.207***	.263***	.231***
活動能力	−.075		−.134***	−.109**
心理社会的要因				
老性自覚		.083*	.056	.078*
ローカス・オブ・コントロール	−.284***	−.203***	−.195***	−.188***
家族外サポート	−.063	−.144***	−.182***	−.104*
R^2	.211	.149	.276	.184
自由度調整済 R^2	.204	.141	.269	.174
F 値	29.81***	19.11***	34.64***	20.12***

[a)] 数値は標準偏回帰係数を示す.
*** p<.001, ** p<.01, * p<.05.

有意な効果がみられなかった．家族以外の人からのソーシャルサポートについては，中年期女性群，老年期群でCES-D得点に影響し（中年期女性群：β=−.144, p<.001，老年期男性群：β=−.182, p<.001，老年期女性群：β=−.104, p<.05），家族以外の周囲の人々からソーシャルサポートを受けている者ほど，抑うつが低いという関係がみられた．しかし，中年期男性群では有意な関連がみられなかった．

考　察

本研究では，40歳から79歳の地域住民に対し，中年期群，老年期群の年齢コホート2群，及び性別群の合計4群について，各群における抑うつに影響する要因の違いを明らかにし，その上で老年期の特徴を検討した．各群において，それぞれ特徴的な抑うつとの関係が示された．

まず，基本的な属性である配偶者の有無については，川本他（1999）やZung et al.（1993）は，配偶者を持たない人の抑うつ得点が高いことを指摘している．今回の結果では，配偶者の有無について，老年期女性群のみ抑うつとの有意な関係が認められなかった．老年期男性は，配偶者との死別や離婚が，心理的喪失体験となり，抑うつを伴うという報告があるが（Pahkala, 1990），老年期では配偶者に対する心理的依存度が，男女間で異なるのかもしれない．また，今回の結果からは，死別と未婚や離婚，別居の違いまでは分からないが，“配偶者なし”の内容が年齢や性別で異なる可能性がある．例えば，中年期には未婚・離婚の割合が高いが，老年期は死別の割合が高くなるであろう．そのため，今後は，それらの違いを含めた検討が必要である．

身体的側面と抑うつとの関連については，すべての年齢群において，主観的健康感と抑うつとの関連が強かった．つまり年齢や性にかかわらず，身体的に健康であるか否かが抑うつ状態に強く関与することが確認され，これまでの研究結果とも一致した．しかし，今回は，身体的な健康状態を測定する一つの指標として主観的健康感を変数として投入したものの，主観的健康感は，実際の健康さより，むしろ自己の健康面をどのようにとらえるかといった主観的なものである．また，CES-Dには身体的症状に関する項目がいくつか含まれている．そのため，主観的健康感と抑うつとの関連がみられたとも考えられる．従って，主観的健康感は，ある程度客観的な健康状態を反映し，その状態を把握するための一つの簡便な方法であるとする報告は多くあるが（芳賀・上野・永井・須山・安村・柴田・松崎・古谷野，1988; McGee, Liao, Cao, & Cooper, 1999），抑うつとの関連を検討するには，客観的な身体変数を用いるべきであったかもしれない．身体疾患と抑うつのかかわりを指摘した報告は多いため（Barusch et al., 1999; Black, Markides, & Miller, 1998; Meeks, Murrell, & Mehl, 2000），今後は，現病歴や慢性疾患の有無といったより客観的な変数を含め，抑うつとの関連を検討する必要がある．

次に，高齢者の場合，身体機能の低い者に抑うつ症状が生じやすいことが，多くの先行研究で報告されて

いる（Barusch et al., 1999；井原，1993；村岡他，1996）．井原（1993），村岡他（1996）は，高齢期における抑うつ状態と日常生活動作能力（Activities of Daily Living：以下ADL），またはIADLの関連について指摘しているが，今回も同様に老年期群で抑うつ状態との強い関連が認められた．今回は，食事・排泄などの基本的なADLではなく，社会生活や日常生活上で自立した生活を行う場合に必要な活動能力を測定したが，この能力に日常的な制限がある場合，うつ症状を多く訴える傾向が示された．このことから，高齢者にとって基本的な生活能力だけでなく，地域での独立した社会的な活動性が，心理的な健康に強く関連することが明らかとなった．身体的自立の低下はもちろんのこと，日常的な社会生活を送る上で支障となるような障害についても，高齢者の場合は特に配慮する必要があるだろう．

心理社会的変数のうち，まず，老性自覚と抑うつとの関連については，今回の結果では，女性群のみで，抑うつへの有意な効果を示した．女性の方が男性よりも老いに対して否定的な態度を抱きやすいという（Linn & Hunter, 1979）．これは，女性としての価値を若々しさに求めがちな社会的風潮が影響していると考えられる．今回の結果からは，Baum & Boxley（1983）が指摘するように，高齢者ほど老性自覚と抑うつとの関連が強いという点までは説明できなかった．中年期も老年期も，老いの自覚を機に，自分の人生に残された時間がどれだけあるかについて考え始め，様々な自己の変化を認識し，自己限界に気づきながらも，一方でそれを認めたくないという自己内の葛藤が起こりやすく，抑うつ状態になりやすいと考えられるが，その体験内容と抑うつとの関係は，中年期と，老年期では異なる可能性がある．例えば，中年期の女性は，閉経を初め，顕著な内分泌系・生理的な加齢現象が起こり，身体的・生理的な喪失を体験しやすく，それに伴い抑うつ状態が生じる場合が観察される．一方，老年期では，家族や友人の死亡，退職などの社会的な面で様々な喪失を体験する機会がより多くなるであろう．従って今後の詳細な検討が課題として残された．

次に，個人的な帰属スタイルの一つであるローカス・オブ・コントロールは，いずれの年齢群においても抑うつと強く関連した．老年期になると，内的統制力の低下により，抑うつ症状が強まるという説もあるが（Linn & Hunter, 1979），今回の結果からは抑うつとの関係に年齢及び性差は見出されなかった．このことから，老年期に限らず，外的統制であることは，抑うつに関連することが示唆された．内的統制の人は人生上の出来事はすべて自分の采配によると信じており，運命や偶然によって決められると信じている人よりも，ストレスに効果的に対処することができるため（Krause, 1987），抑うつ状態にもなりにくいのかもしれない．また逆に，Hoffart & Torgersen（1991）がうつ病の患者は悪い出来事の原因を外在化する傾向があることを報告しているように，抑うつ状態が外的統制に影響する場合も考えられる．

更に，ソーシャルサポートと抑うつとの関連は，これまで多くの研究により報告されている（Antonucci, Fuhrer, & Dartigues, 1997；川本他，1999; Oxman & Hull, 1997）．今回の結果においても，ソーシャルサポートを受けていることと抑うつ状態が低いことは関連することが明らかとなり，これまでの結果と一致した．従来，わが国の高齢者のソーシャルサポート及びサポートネットワークは，他の世代と同様に，夫婦・親子関係を軸として考えられてきた．しかし，中年後期から老年期において，死別や別居などにより家族形態が縮小するため，加齢と共に自分を支援してくれる家族数は自ずと小さくなる（Antonucci & Akiyama, 1987）．ネットワーク構成が変化する中で，高齢者が精神的健康を維持していくためには，家族以外の人々からの社会的支援の必要性が大きくなり，それに伴い家族以外の人々からのサポートが個人の心理面に与える影響度も大きくなるのではないだろうか．従って，今回の研究では，ソーシャルサポート尺度として，家族以外の周囲の人々から受けたサポートの程度を尋ねる尺度を用いた．その結果，老年期群において，ソーシャルサポートと抑うつの間に有意な関係が示された．家族などから支援を得ることが難しい高齢者の場合は，医師や保健婦，ヘルパーなどによるフォーマルなサポート体制を整備充実させていくことが，高齢者自身の精神的健康の維持にもつながるといえよう．一方，中年期男性群で，今回抑うつとの関連がみられなかったのは，この時期の男性の場合，親密な人間関係はやはり夫婦や家族を中心としたものであるため，今回の家族以外からのサポートには反映されなかったと考えられる．このように，サポートを提供するネットワークの構造と機能は，年齢や性別によって異なり，抑うつとサポートとの関係を検討する際には，これらの側面を考慮する必要がある．

以上，地域在住の中年期から老年期の男女の抑うつに関連する要因について検討したところ，主観的健康感の低さ，ローカス・オブ・コントロール（外的統制）がいずれの群でも抑うつと強く関連した．一方，各群で独自の抑うつに影響する要因が示され，老年期の抑うつの背景要因として，活動能力や家族以外からのソーシャルサポート，女性では中年期老年期共に，老性自覚が重要であることが示された．地域住民の生活の質（Quality of Life: QOL）を維持向上させていくためには，これらの背景因子の改善を含めた抑うつ予防の方策を，年齢や性の違いを考慮した上で検討していく必要がある．ただし，本研究は横断研究である

ため，今回の結果からは，抑うつと関連がみられた変数との間の因果関係までは不明である．そのため，今後縦断研究の結果の分析に期待される．

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The relationship between intraocular pressure and refractive error adjusting for age and central corneal thickness

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Abstract

Purpose: To investigate the relationship between intraocular pressure (IOP) and refractive errors after adjusting for age, central corneal thickness (CCT), and other related factors.

Methods: IOP, CCT and refractive errors were measured in the right eyes of 1855 subjects, aged 40–82 years, in a cross-sectional study design. Subjects were divided into groups by refractive status: hyperopia, emmetropia, mild myopia, moderate myopia, or high myopia. With adjustments for age, CCT, blood pressure, obesity, education, hypertension, diabetes, and smoking status, IOP was estimated for each refractive status using a general linear model.

Results: IOP increased with advancing degrees of myopia, even after adjustment for age, CCT, and other related factors ($p = 0.011$). Estimated IOP of moderate myopia was significantly higher than that of emmetropia ($p = 0.022$).

Conclusions: Our results confirm the positive association between IOP and increasing degrees of myopia. This finding would support the hypothesis that the relationship between glaucoma and myopia might be pressure mediated.

Keywords: central corneal thickness, epidemiological study, intraocular pressure, refractive error

Introduction

It is generally accepted that there is an increased prevalence of glaucoma among myopic eyes (Perkins and Phelps, 1982). In fact, two recent population-based studies demonstrated that myopic eyes had a 1.6 to 3.3 times increased risk of glaucoma (Mitchell *et al.*, 1999; Wong *et al.*, 2003). One of the reasons as to why glaucoma should be more frequent in myopic eyes seems to be higher intraocular pressure (IOP) in myopic eyes compared with non-myopic eyes (David *et al.*, 1985; Klein *et al.*, 1992; Mitchell *et al.*, 1999; Wong *et al.*, 2003). This causal relationship can be rationalised by the knowledge that IOP is still considered an important risk factor for the development of glaucoma (Racette *et al.*, 2003). The Visual Impairment Project in Australia showed that the mean IOP among patients with newly developed glaucoma over a 5-year period was significantly higher than that among the non-incident cases (Mukesh *et al.*, 2002). Furthermore, it has been suggested that myopic eyes are more susceptible to the effects of elevated IOP (Perkins and Phelps, 1982). It has been also proposed that myopic eyes have abnormal connective tissue that could predispose to glaucoma (Fong *et al.*, 1990).

There is evidence from the literature that a correlation exists between refractive status and IOP (David *et al.*, 1985; Klein *et al.*, 1992; Mitchell *et al.*, 1999; Wong *et al.*, 2003). Even after adjusting for age, sex, diabetes and blood pressure, mean IOP was approximately 0.5 mmHg higher in myopic eyes compared with non-myopic eyes in the Blue Mountains Eye Study (Mitchell

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et al., 1999). However, little is known about the true relationship between refractive status and IOP taking into account the central corneal thickness (CCT), as the CCT has a significant influence on IOP measurement. It has been reported that thinner corneas result in artificially lower IOP readings and that thicker corneas cause artificially high IOP readings (Ehlers *et al.*, 1975; Whitacre and Stein, 1993; Herndon *et al.*, 1997; Doughty *et al.*, 2002). Furthermore, our previous report showed that the influence of CCT on IOP measurement was greater than those of age, blood pressure, or obesity (Nomura *et al.*, 2002). Therefore, investigation of the relationship between refractive status and IOP after adjusting for CCT would be required. In the present study, we aimed to clarify the true relationship in a community-dwelling Japanese population.

Materials and methods

Data for the present study came from the National Institute for Longevity Sciences – the Longitudinal Study of Aging programme (NILS-LSA), a population-based survey of ageing conducted in Obu-shi and Higashiura-cho, Aichi prefecture, Japan, from April 2000 to May 2002. The subjects were randomly selected from a community-dwelling population stratified by age and gender. Their ages ranged from 40 to 82 years. A detailed description of the sampling scheme has been reported elsewhere (Shimokata *et al.*, 2000). The eye examinations were performed by two trained medical practitioners, subjected to periodical quality control, using the same instruments throughout the examination period. The Ethical Committee of the Chubu National Hospital reviewed all procedures for the study, and written informed consent was obtained from all subjects.

In the period, 2259 individuals participated in the NILS-LSA. Of these, those with a history of eye surgery (104 persons), current users of contact lenses (83 persons), or current users of ophthalmic therapy for glaucoma (100 persons) were excluded from the present study. In the present study, we assessed the right eyes of 1855 subjects (996 men and 859 women), because the data of IOP (five persons), refractive errors (37 persons), or CCT (95 persons) was missing.

IOP was measured three times with a non-contact tonometer (NT-3000; Nidek, Gamagori, Japan) between 09.00 and 12.00 hours, and the mean value of the three measurements was used for analysis. CCT was measured with a Topcon specular microscope (SP-2000P; Topcon, Tokyo, Japan). Refractive error data were obtained using an automatic refractor, ARK700A (Nidek), with subjective refinements for each participant. The spherical equivalent (sphere + 1/2 cylinder) was used to calculate the refractive error. Participants were divided into five groups according to refractive status: hyperopia, emmetropia, mild myopia, moderate myopia and high myopia.

Height and weight were measured according to a standardised protocol, and body mass index was calculated by dividing weight (in kilograms) by height squared (in metres). Systolic and diastolic blood pressures were measured with a standard mercury sphygmomanometer on the right arm between 09.00 and 12.00 hours. Information on the smoking status, years of education, and history of hypertension and diabetes was also recorded using a self-administered questionnaire.

All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC, USA) release 6.12. In each refractive group, mean values of age, CCT, and IOP were calculated. As only seven people were classified with high myopia, no further analysis was performed on this group. First, in univariate manner, the relationships between IOP and the related factors were assessed using correlation analyses or Student's *t*-tests. Subsequently, using a general linear model (PROC GLM), the least square mean values for IOP in each refractive group were determined (LSMEANS statement) after adjusting for age, CCT, systolic blood pressure, body mass index, years of education, history of hypertension and diabetes, and smoking status (as these factors seem to be related to IOP value or refractive error). Differences in the estimated IOP with the refractive status were tested using the Tukey multiple comparison method (ADJUST option) and the trend in refractive status difference was also tested using the CONTRAST option of the PROC GLM. In the present analyses, age, CCT, IOP, blood pressure, body mass index and years of education were entered as continuous variables.

Results

Table 1 shows the characteristics of the subjects. IOP value significantly positively correlated with the value of CCT, systolic blood pressure, diastolic blood pressure, body mass index and years of education ($p < 0.0001$). IOP had a significant inverse correlation with age and refractive error ($p < 0.0001$). The mean IOP value of those with hypertension was significantly higher than that of those without hypertension (Student's *t*-tests, $p = 0.003$), or diabetes (Student's *t*-tests, $p = 0.0002$). There was no significant difference in IOP value between current smokers and past or non-smokers. When compared with the included subjects using Student's *t*-tests, those excluded were older (mean: 63.7 years, $p < 0.0001$), and had low IOP value (mean: 12.6 mmHg, $p = 0.002$), myopic eye (mean: −1.30 dioptres, $p < 0.0001$), thinner CCT (mean: 511 μm, $p = 0.014$), higher systolic blood pressure (mean: 124.5 mmHg, $p = 0.005$), and were less educated (mean: 11.3 years, $p < 0.0001$).

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Table 1. Characteristics of subjects ($n = 1855$)

Characteristics	Mean	S.D.
Age (years)	58.9	10.9
Intraocular pressure (mmHg)	13.0	2.6
Refractive errors (dioptres)	−0.61	1.35
Central corneal thickness (μm)	516	33
Systolic blood pressure (mmHg)	121.6	18.9
Diastolic blood pressure (mmHg)	74.6	11.1
Body mass index (kg m^{-2})	23.0	3.0
Years of education (years)	11.9	2.8
	N	%
History of hypertension	472	25.4
History of diabetes	141	7.6
Smoking status		
Non-smoker	996	53.8
Past smoker	448	24.2
Current smoker	407	22.0

As shown in the *Table 2*, the mean IOP value of the moderate myopia group was significantly higher than those of the hyperopia ($p < 0.0001$), emmetropia ($p < 0.0001$), or mild myopia ($p = 0.004$) groups. The mean IOP value of the mild myopia group was also significantly higher than that of the hyperopia group ($p = 0.012$). Similarly, the CCT value of the moderate myopia group was significantly higher than the CCT value from the hyperopia ($p = 0.003$), emmetropia ($p = 0.032$), or mild myopia ($p = 0.020$) groups. Even after adjustment for the related factors (age, gender, CCT, systolic blood pressure, body mass index, years of education, history of hypertension and diabetes, and smoking status), there was a significant trend of increasing IOP with increasing degrees of myopia ($p = 0.011$). The estimated IOP value for moderate myopia was significantly higher than the emmetropia values ($p = 0.022$).

Discussion

There have been several reports of a positive correlation between IOP and increasing degrees of myopia (David *et al.*, 1985; Klein *et al.*, 1992; Mitchell *et al.*, 1999; Wong *et al.*, 2003). Nevertheless, it has also been reported that no difference in IOP was detected between the two eyes in anisometropic subjects with unilateral high myopia (Bonomi *et al.*, 1982). Therefore, the relationship between IOP and myopia has been inconclusive. However, little or no evidence considering the influence of CCT on this relationship has been reported, although the influence of CCT on IOP measurement seems critical. The data reported here show that there is a positive significant association between IOP and advancing degrees of myopia, even after adjusting for age, CCT, and other relevant factors.

It is unclear why people with myopia are found to have higher IOPs than those with hyperopia or emmetropia. David *et al.* (1985) investigated the relationships between IOP and other factors using analysis of variance and reported that mean IOP values were associated with age, refractive status, country of birth and interaction between refractive status and country of birth. They suggested that there was a complex relationship between IOP and refractive status.

It has also been reported that IOP in children, as in the adult population, may be higher in myopic than non-myopic eyes (Quinn *et al.*, 1995). It has been controversial whether high IOP could contribute to

Table 2. Comparison of age, central corneal thickness, and intraocular pressure according to refractive status

Refractive status	No. of subjects	Mean (S.E.)			Estimated IOP value (S.E.) adjusted for related factors[1]
		Age (years)	CCT (μm)	IOP (mmHg)	
Hyperopia	284	67.8 (0.6)	512.5 (1.9)	12.6 (0.2)	13.1 (0.2)
Emmetropia	764	60.2 (0.4)	516.0 (1.2)	12.9 (0.1)	13.1 (0.1)
Mild myopia	673	54.9 (0.4)	515.4 (1.3)	13.1 (0.1)	13.3 (0.1)
Moderate myopia	127	52.8 (0.9)	525.0 (2.9)	14.0 (0.2)	13.7 (0.2)
High myopia	7	58.4 (3.8)	520.6 (12.3)	13.2 (1.0)	N/A
p Value for trend[2]		<0.0001	0.0007	<0.0001	0.011

IOP, intraocular pressure; CCT, central corneal thickness; S.E., standard errors; N/A, not applicable.

[1] Related factors consist of age, CCT, systolic blood pressure, body mass index, years of education, history of hypertension and diabetes, and smoking status.

[2] p Values for trend were calculated after the exclusion of those with high myopia.

Hyperopia: spherical equivalent greater than +0.5 D.

Emmetropia: spherical equivalent ≤+0.5 D and >−0.5 D.

Mild myopia: spherical equivalent ≥−0.5 D and <−3 D.

Moderate myopia: spherical equivalent ≥−3 D and <−6.0 D.

High myopia: spherical equivalent ≥−6.0 D.

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axial elongation and myopia in children. However, a recent prospective study indicated that a high IOP follows the onset of myopia and cannot cause myopia (Edwards and Brown, 1996), which would imply that myopic eyes have a peculiar mechanism causing high IOP.

There are some limitations in the present study. A non-contact tonometer is used to measure IOP, which should give a wider variation in the IOP measurement values than the Goldmann applanation tonometer (Mackie *et al.*, 1996). However, in many studies, comparisons with Goldmann applanation indicate that the non-contact tonometer is reliable within the normal IOP range (Forbes *et al.*, 1974; Koopmans *et al.*, 1991; Cho and Lui, 1997; Katsushima *et al.*, 2002). In particular, it has been reported that the Nidek non-contact tonometer produces repeatable IOP readings and is comparable with the Goldmann applanation tonometer (Cho and Lui, 1997). We were also unable to assess the lens status. Previous population-based surveys demonstrated that nuclear sclerosis of the lens was associated with high IOP (Klein *et al.*, 1992), and that myopia was found to be greater in people with higher degrees of nuclear opacity (Wensor *et al.*, 1999), We cannot exclude the possibility that nuclear sclerosis or opacity is responsible for the relationship between IOP and myopia, although the participants of NILS-LSA should be subject to nuclear sclerosis or opacity of the lens commensurate with their age range. In addition, a number of people excluded in the present study, such as those with a history of eye surgery and current contact lens users, may influence our findings. Cataract surgery should influence the IOP value and the refractive errors of the subjects (Cekic *et al.*, 1998; Dimitrov *et al.*, 2001), and epithelial oedema caused by contact lens wearing should lead to the overestimate of corneal thickness (Whitacre and Stein, 1993). Therefore, some differences between those individuals included and excluded in the present study seems to be inevitable.

Further work including assessment of the lens will be necessary to distinguish the relationship. However, it is noteworthy that mean IOP in myopic eyes is higher compared with non-myopic eyes after adjusting for age and CCT. This finding supports the hypothesis that the relationship between glaucoma and myopia might be pressure mediated.

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CLINICAL INVESTIGATION

Visual Acuity in a Community-dwelling Japanese Population and Factors Associated with Visual Impairment

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Abstract

Purpose: The aim of this study was to describe the distribution of visual acuity and investigate the predictors of visual impairment in a Japanese population.

Methods: Best-corrected visual acuity was measured in 2263 subjects aged 40–79 years randomly selected from a local community. Relations between visual impairment and possible risk factors were investigated.

Results: Among these subjects, 41 individuals (1.8%) were identified as visually impaired (best-corrected visual acuity in the better eye <0.5). Both sexes in the older age groups had a higher frequency of visual impairment (Mantel-Haenszel chi-square test: $P < 0.001$). A multiple logistic regression indicated that an increase in age of 10 years [odds ratio (OR) 3.9; 95% confidence interval (CI) 2.3–6.7] and myopia (OR 2.9; 95%CI 1.4–6.0) were independent risk factors for visual impairment. Individuals with the highest level of education (college or higher) had a lower risk of visual impairment (OR 0.1; 95%CI 0–0.7) compared to individuals with the lowest level of education.

Conclusions: As expected, visual impairment increased with advancing age, although the prevalence of visual impairment in our population was lower than in other surveys. Racial and regional differences and differences in study design may be responsible for discrepancies between surveys. It is noteworthy that myopia was a significant risk factor for visual impairment, although the reasons for this association are uncertain and need further investigation. **Jpn J Ophthalmol** 2004;48:37–43 © Japanese Ophthalmological Society 2004

Key Words: Japanese population, population-based survey, visual acuity, visual impairment

Introduction

The populations of many countries around the world are aging, and the proportion of the elderly is increasing rapidly. This may be especially important for Japan because the average life span for the Japanese is longer than for other nationalities. It is generally accepted that vision, like other functions, declines with age,[1–15] so it is conceivable that many elderly people live with vision disabilities. Adequate vision is essential for maintaining independence in the lives of the elderly. According to a report from the Ministry of Health and Welfare in 1996, more than 300000 people in Japan had visual handicaps and 45.2% of them were 70 years of age or older.[16] This rate had increased from 41.6%

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in 1991.[17] For planning health services or for risk factor analysis, it is necessary to know the magnitude and distribution of visual impairment and blindness in a community-dwelling population. To our knowledge, however, there has been no population-based analysis of visual acuity among Japanese adults.

This is the first report on visual acuity in a community-dwelling, middle-aged to elderly population in Japan. In addition, we present the age-specific and sex-specific prevalence of visual impairment as assessed by visual acuity measurements and investigate its risk factors using data from the National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS-LSA).

Subjects and Methods

Data for this report come from the NILS-LSA, a population-based survey of aging conducted in Obu-shi and Higashiura-cho, Aichi Prefecture, Japan. Random sampling from the municipal register, which was stratified by age and sex, identified noninstitutionalized eligible subjects from the same racial and ethnic origins, aged 40–79 years. Details about the methodology used in this survey have been reported elsewhere.[18] In brief, the NILS-LSA report consists of clinical evaluations, body composition and anthropometry, physical function, nutritional analysis, and psychological tests. At the research center, participants were interviewed regarding demographic characteristics, medical and ophthalmologic history, and self-reported vision problems. The Ethics Committee of the Chubu National Hospital reviewed all procedures for the study, and written informed consent was obtained from all subjects.

This research area is geographically located at the center of Japan, and the climate is generally average for Japan. We examined how representative the area is via a national postal questionnaire sent to 3000 households from all the prefectures in Japan and found that the lifestyle in this area was the most typical of all areas in Japan. Therefore, it was thought that the results of examinations in this area would be representative of the entire population of Japan.[19]

In the present study, we analyzed the baseline data of NILS-LSA obtained from November 1997 to April 2000. A total of 7790 eligible subjects were identified during recruitment, and 3430 people responded to the request for participation. Of this group, 2267 individuals (66.1%) participated in the NILS-LSA. In the present study, only 2263 subjects (29.1% of those eligible) (1134 men, 1129 women) were evaluated (the visual acuity data were missing for four people).

As part of the standardized examination, automatic objective refraction evaluation with the ARK700A (NIDEK, Gamagori, Japan) was carried out on each participant. Visual acuity was then measured in each eye with the Landolt broken ring chart at 5 m under standard lighting conditions and assessed initially using any corrective devices the participant was currently using. If the participant was unable to read the chart at the 1.0 equivalent line in either eye, refraction was determined using the results of the objective refraction as a starting point. The best-corrected visual acuity was defined as the visual acuity after subjective refinement of refraction in the participant's better eye, and both the derived refraction data and the visual acuity were recorded. When the presenting acuity of the participant was 1.0 or better, the initial objective refraction result was recorded as the participant's refraction data. The spherical equivalent (sphere + $^1/_2$ cylinder) was used for calculations of refractive error. Myopia was defined as the spherical equivalent of −0.5 diopter (D) or less. Because of the age of our study population, no cycloplegia was used.

We used both the World Health Organization (WHO) criteria and the United States (U.S.) criteria for visual impairment in the present study. With the WHO criteria,[20] *blindness* is defined as a best-corrected visual acuity of <0.05 in the better eye and *low vision* as a best-corrected visual acuity of <0.3 but ≥0.05 in the better eye. *Visual impairment* is defined as a best-corrected visual acuity of <0.3 in the better eye. With the U.S. criteria,[3,10,13] *blindness* is defined as a best-corrected visual acuity of ≤0.1 in the better eye and *low vision* as a best-corrected visual acuity of <0.5 but >0.1 in the better eye. *Visual impairment* is defined as a best-corrected visual acuity of <0.5 in the better eye.

Information on household income, education level, and history of diabetes, hypertension, and cataract surgery was obtained from questionnaires filled out by the participants. Cataract surgery was defined as a history of cataract surgery in the participant's better eye. We grouped household income and education level into three categories each.

For analysis, the exact Mantel-Haenszel chi-square test and multiple logistic regressions were used to assess the relations between visual impairment and other potential risk factors: age, sex, household income, education level, myopia, diabetes, hypertension, history of cataract surgery. Data were analyzed using the Statistical Analysis System (SAS), release 6.12.[21]

Results

The 2263 participants in our study underwent visual acuity measurements at the NILS-LSA center. The mean age of the participants was 59.2 years. Distribution of the best-corrected visual acuity is shown in Table 1. Using the WHO criteria only 10 individuals (0.44%) were identified as being visually impaired (2 with blindness, 8 with low vision), whereas with the U.S. criteria we identified 41 individuals (1.81%) who were visually impaired (4 with blindness, 37 with low vision). If the WHO criteria had been used, the number of the participants classified as visually impaired would have been too small to analyze. We therefore used the U.S. criteria for visual impairment in the following analyses.

There were four age groups: 40–49, 50–59, 60–69, and 70–79 years. There was no significant difference between

Table 1. Percentage distribution of best-corrected visual acuity in the better eye, by age and sex

		Visual acuity						
		According to WHO criteria			According to U.S. criteria			
Age (years)	No.	<0.05	0.05 to <0.3	0.3 to <1.0	−0.1	>0.1 to <0.5	0.5 to <1.0	1.0+
Men								
40–49	289	0	0	5.54	0	0	5.54	94.46
50–59	283	0.35	0.35	10.65	0.35	0.71	10.60	88.34
60–69	287	0	0	25.09	0	0.35	24.74	74.91
70–79	275	0	1.09	42.91	0.36	4.73	38.91	56.00
Total	1134	0.09	0.35	20.90	0.18	1.41	19.75	78.66
Women								
40–49	280	0	0	3.21	0	0	3.21	96.79
50–59	284	0	0	10.90	0	0	10.92	89.08
60–69	283	0	0.35	29.33	0.35	1.77	27.56	70.32
70–79	282	0.35	1.06	52.13	0.35	5.67	47.52	46.45
Total	1129	0.09	0.35	23.91	0.18	1.86	22.32	75.64
All								
40–49	569	0	0	4.39	0	0	4.39	95.61
50–59	567	0.18	0.18	10.93	0.18	0.35	10.76	88.71
60–69	570	0	0.18	27.19	0.18	1.05	26.14	72.63
70–79	557	0.18	1.08	47.58	0.36	5.21	43.27	51.17
Total	2263	0.09	0.35	22.40	0.18	1.63	21.03	77.15

WHO, World Health Organization; U.S., United States.

Table 2. General and clinical characteristics of subjects with visual impairment

Characteristic	Blindness (n = 4)	Low vision (n = 37)	Visual acuity ≥0.5 (n = 2222)
Age (years)			
Mean	66.5	71.6	59.0
SD	10.7	7.0	10.9
Women (%)	50.0	56.8	49.8
Myopia (%)[a]	50.0	41.2	37.1
History of diabetes (%)[b]	0	16.2	7.1
History of hypertension (%)[c]	25.0	51.4	25.2
History of cataract surgery (%)	50.0	8.1	3.4
Education level (%)[d]			
1	75.0	56.8	32.5
2	25.0	40.5	40.2
3	0	2.7	27.2
Household income (%)[e]			
1	66.7	76.5	41.6
2	33.3	14.7	31.5
3	0	8.8	26.9

[a–e]The data for [a]17 people, [b]11 people, [c]7 people, [d]8 people, and [e]84 people were missing.

Definitions: blindness, best-corrected visual acuity of ≤0.1 in the better eye; low vision, best-corrected visual acuity of <0.5 but >0.1 in the better eye; myopia, spherical equivalent of −0.5 diopter or less.

Education level: 1, elementary school or junior high school; 2, high school; 3, college or university or higher.

Household income: 1, less than 6.5 million yen; 2, 6.5 million to 10.0 million yen; 3, more than 10.0 million yen.

sexes within any age group in terms of the distribution of best-corrected visual acuity. Both sexes in the older age groups had higher frequencies of visual impairment (exact Mantel-Haenszel chi-square test, $P < 0.001$). Among those 40–49 years of age, none of the participants had visual impairment. In contrast, 5.57% of those 70–79 years old were classified as visually impaired. In our total population 77% had good visual acuity (≥1.0), and even at 70–79 years of age about 50% of the subjects had a best-corrected visual acuity of ≥1.0.

Table 2 shows the general and clinical characteristics of visually impaired subjects compared to those with no visual impairment. Visually impaired participants were of a significantly higher mean age (71.1 years) than those with no

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Table 3. Results of multiple logistic regression for risk of visual impairment (n = 2159)

Variable	OR	95%CI
Age (10 years)	3.91	2.28–6.70
Sex (female = 1)	1.14	0.58–2.27
Myopia	2.92	1.42–5.99
Education level		
1	1.00	
2	0.98	0.48–1.98
3	0.10	0.01–0.74
Household income		
1	1.00	
2	0.73	0.29–1.87
3	0.44	0.13–1.53
History of diabetes	1.24	0.48–3.20
History of hypertension	1.34	0.68–2.68
History of cataract surgery	0.99	0.33–2.97

OR, odds ratio; CI, confidence interval.

visual impairment (59.0 years) (Student's t-test, $P < 0.001$). There was a significantly higher frequency of visual impairment when there was a history of hypertension or cataract surgery (chi-square test, $P < 0.001$ and $P = 0.003$, respectively). There was a significantly higher frequency of visual impairment when participants had either a lower education level or a lower household income (Cochran-Mantel- Haenszel test, $P < 0.001$). No significant association was found between the frequency of visual impairment and sex, myopia, or history of diabetes.

Table 3 summarizes the results of a multiple logistic regression analysis for risk of visual impairment in the NILS-LSA population. A 10-year increase in age was associated with a 3.91 (95% CI 2.28–6.70) higher probability of having visual impairment. The presence of myopia was associated with a higher prevalence of visual impairment (OR 2.92; 95%CI 1.42–5.99). Those who completed college or more were at lower risk for visual impairment (OR 0.10; 95%CI 0.01–0.74) compared with the least educated group. Sex, household income, diabetes, hypertension, and cataract surgery did not have a significant influence on the risk of visual impairment.

Discussion

This is the first survey to report the prevalence of visual impairment and its risk factors among community-dwelling Japanese adults. According to the U.S. criteria, of the 2263 participants in this study aged 40–79 years only 4 people (0.18%) were classified as being blind and 37 (1.63%) were classified as having low vision. Many of those with visual impairment (75.6%) were in the oldest age group. Using the multiple logistic regression analysis, we also demonstrated that increasing age and the presence of myopia were independent risk factors for visual impairment. In contrast, being highly educated had an independent inverse association with visual impairment. Remarkably, 77.2% of the NILS-LSA participants had good visual acuity (≥1.0). Even in the 70- to 79-year old group, 51.2% of the participants had good acuity.

Table 4 summarizes the visual impairment rates from previous studies. Based on the WHO criteria, all studies have reported that the rates of blindness are less than 1%, except in Barbados black and mixed populations. The rates of low vision are 3% or less, except in Barbados black and Salisbury black populations. The Barbados study,[6] however, adopted the pinhole correction method instead of subjective refraction, which would overestimate the visual impairment rates. Among Asian countries, the Andhra Pradesh Eye Disease Study[14] described the best-corrected visual acuity in an Indian population and showed that 3.9% of those 60–69 years old and 6.2% of those over age 70 had visual impairment. Michon et al. reported that 0.5% of the elderly population (≥60 years old) were blind in Hong Kong.[12] The Malaysian National Eye Survey[11] showed that 2.7% of the whole population (0–96 years old) had visual impairment. As for the elderly population, the rates of blindness and low vision were 0.7% and 4.8%, respectively, among those 60–69 years old and 12.3% and 30.6%, respectively, for those 70 years or older. However, these two surveys also adopted the pinhole correction method instead of using subjective refraction. In Japan, there has been no previous study for visual impairment among community-dwelling, elderly populations. In the institutionalized, elderly population, it has been reported that blindness (visual acuity <0.1) is apparent in 3.4% of those 65–69 years old, 7.4% of those 70–74 years old, 9.7% of those 75–79 years old, and 10.8% of those 80–84 years old.[22] Ichikawa measured visual acuity of outpatients at his hospital, and reported that, on average, it showed a linear decrease with advancing age starting at 45 years of age.[23]

Compared with the above population-based study, the NILS-LSA population, as well as the populations studied in the Visual Impairment Project[9] and the Proyecto Vision Evaluation and Research Project, had low visual impairment rates.[13] One of the likely reasons is racial differences. It is known that visual impairment occurs more frequently in black populations than in white populations, as shown in Table 4. Comparisons between Asian and other populations have not been reported previously. Regional differences can also account for different frequencies of visual impairment, as sunlight exposure is a risk factor in the development of cataracts.[24]

Another reason for the low visual impairment rate in our results could be the age range of our population. Many studies[3–15] have indicated that visual impairment was more frequent in the elderly, especially those over 75 years of age, as the prevalence of age-related eye disorders, such as age-related macular degeneration, cataract, and glaucoma increases with advancing age. Our results showed that the prevalence of visual impairment was strikingly higher in the 70- to 79-year-old group than in the other age groups. The NILS-LSA evaluates the participants longitudinally; therefore, we invited participants under 80 years old to participate in the baseline examination of the NILS-LSA. However, the lower visual impairment rate of our study

Table 4. Comparison of NILS-LSA and other population-based studies on visual impairment

Study name	Study year	Country	Age (years)	Sample size	Race	WHO criteria		US criteria		Sex difference
						Low vision (%)	Blindness (%)	Low vision (%)	Blindness (%)	
NILS-LSA	1997–2000	Japan	40–79	2263	Asian	0.4	0.1	1.6	0.2	No
Baltimore Eye Survey[3,a]	1985–1988	U.S.	40+	2911	White	1.3	0.5	2.7	0.9	No
				2389	Black	1.9	0.9	3.3	1.6	
Beaver Dam Eye Study[5,b]	1988–1990	U.S.	43–86	4926	White	N/A	N/A	4.7	0.5	Yes
Barbados Eye Study[4,a]	1988–1992	Barbados	40–84	4314	Black	5.9	1.7	8.9	3.0	No
				184	Mixed	2.7	1.6	5.4	2.2	
				133	White	3.0	0.0	6.0	0.8	
Rotterdam Study[7,b]	1990–1993	The Netherlands	55–106	6775	White	1.4	0.5	3.8	0.8	No
Blue Mountains Eye Study[8]	1992–1993	Australia	49–97	3647	White	N/A	N/A	4.0	0.7	Yes
Visual Impairment Project[9,b]	1992–1996	Australia	40–98	3268	White	0.6	0.1	1.0	0.3	Yes
Salisbury Eye Evaluation Study[10]	1993–1995	U.S.	65–84	1853	White	1.6	0.2	3.0	0.5	Yes
				666	Black	3.3	0.8	5.6	1.7	
National Eye Survey[11,a]	1996–1997	Malaysia	0–96	18027	Asian	2.4	0.3	N/A	N/A	Yes
Not defined[12,a]	1998	Hong Kong	60+	3434	Asian	N/A	0.5	N/A	N/A	Yes
Proyecto Vision Evaluation and Research[13]	1997–	U.S.	40+	4774	Hispanic	N/A	N/A	1.9	0.3	No
Andhra Pradesh Eye Disease Study[14]	1996–2000	India	whole	10293	Asian	1.05	N/A	N/A	0.4	No

NILS-LSA, National Institute for Longevity Sciences–Longitudinal Study of Aging; N/A: not applicable.
[a]Only pinhole correction, not using refraction.
[b]Institutionalized people were included.

compared to that of other studies is likely due to our subjects all being under the age of 80. It is also possible that the exclusion of institutionalized individuals caused underestimation of the visual impairment rate in our results, as this portion of the population tends to have visual impairment more frequently than the community-dwelling population.[5,7]

In addition to age, the risk factor for visual impairment that remained in the multivariate logistic regression model was the presence of myopia. One of the reasons for the association between myopia and visual impairment seems to be the frequent occurrence of cataract in myopic eyes. Several epidemiological surveys[25–27] have shown that myopia is an independent risk factor for cataract. Another explanation may be myopic macular degeneration. The Rotterdam Study reported that myopic macular degeneration was the predominant cause of visual impairment in subjects younger than 75 years of age.[7] In fact, our previous study demonstrated that the frequency of high myopia subjects, who are prone to myopic macular degeneration, is 0.5% in the NILS-LSA population.[28]

The inverse association between education level and household income with visual impairment is consistent with a study in an Appalachian community[4] and the Beaver Dam Eye Study.[29] Remarkably, the strong association between education level and visual impairment persisted even after being adjusted for age and myopia in the multiple logistic analysis. One would expect, them, that those with less education or a lower household income would have less knowledge of appropriate eye care. In fact, some previous studies[24,29,30] indicated that the risk of cataract decreased with higher education. We could not estimate the degree of cataract in the present study, but a similar association between education level and cataracts may be responsible for our results. Although our study showed an inverse relation between income level and visual acuity, no association was found between visual acuity and socioeconomic status in the Blue Mountains Eye Study.[8] Therefore, the association between visual impairment and socioeconomic status needs further investigation.

Contrary to our expectation, there was no significant association between a history of diabetes and visual impairment, even though diabetic retinopathy is the leading cause of blindness in the Japanese.[31] A probable reason is that, although diabetes is a relatively frequent disorder, active proliferative retinopathy (which causes visual impairment) seems to be rare in community-dwelling populations. The lack of association between visual impairment and cataract surgery in the multiple logistic analysis also seems to be due to the small number of our subjects having a history of cataract surgery.

In the present study, we did not use the Japanese criteria for the visually handicapped to compare our data with the data of other countries. It is advisable to identify visual impairment by assessing both visual acuity and visual field testing, as is done in the Japanese classification. In epidemiological surveys for community-dwelling populations, however, it is difficult to assess the visual field in detail with

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Goldmann perimetry, as stipulated in the Japanese criteria. Visual impairment is assessed by summing the visual acuities in both eyes in Japan, which is different from the criteria of WHO and other countries. In the WHO classification, visual impairment is also assessed by both visual acuity and visual field testing, and visual field loss is based on the results of a Bjerrum screen, a simple apparatus for standardized perimetry.[20] The low vision criteria (<0.3 in the better eye) in the WHO classification based on visual acuity seems convenient for assessing visual impairment worldwide, including developing countries. However, it seems reasonable that stricter criteria for visual impairment should be adopted, in addition to the WHO criteria, to investigate the risk factors for visual impairment in developed countries.

Two relative limitations of the present study are noted. First, the cause of visual impairment was not investigated. Previous surveys[7,8,10,32,33] have shown that the leading cause of visual impairment in white populations was age-related macular degeneration, and in black populations it was cataract. In Japan, it was reported that the main causes of blindness were diabetic retinopathy, cataract, and glaucoma.[31] As mentioned above, we considered cataract a main factor accounting for the association between visual impairment and the independent predictors (older age, myopia, low education). However, the true cause of visual impairment in our population has not been identified. Second, it seems likely that there is a selection bias in our population. Because the examinations of the NILS-LSA are performed at the research center, those with low physical abilities (including blindness) or those living in an institution are unlikely to participate in our survey, which may influence our findings. However, it is reasonable to conclude that our findings accurately represent the range of visual acuity among the community-dwelling middle-aged, and elderly, as most of them are self-supporting.

Despite the acknowledged limitations of our approach, we conclude that the visual impairment rate in our population is considerably lower than the rates for populations in other surveys. In addition to racial differences, a difference in lifestyle and environment, such as food intake or exposure to sunlight, may be responsible for the different visual impairment rates. The medical insurance system in Japan may also allow those with a lower socioeconomic status to avail themselves of appropriate eye care, which may decrease the prevalence of visual impairment in the Japanese compared to that for other nationalities.

We also reported previously on the higher prevalence of myopia in the younger population[28] and emphasize here that the presence of myopia is a significant risk factor for visual impairment. Further study of this relation may help prevent future visual impairment for those who have myopia at a young age.

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Cognitive function in Japanese elderly with type 2 diabetes mellitus

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Abstract

The current study was conducted to investigate the cognitive function in Japanese elderly with type 2 diabetes mellitus (DM). Participants included 69 diabetic and 27 nondiabetic subjects (60 to 85 years old). The cognitive functional tests conducted were the Mini-Mental State Examination (MMSE), Word Lists Recall (immediate, delayed), Digit Symbol Test (Wechsler Adult Intelligence Scale—Revised [WAIS-R]), and the Stroop Color Word Test. Hemoglobin A1c (HbA1c) was measured as the index of glycemic control, and information about recent hypoglycemic episodes was gathered by using questionnaires. Student's *t* test showed that DM subjects had significantly lower scores in the MMSE ($P<.01$) and Digit Symbol Test ($P<.05$) than non-DM subjects. The scores of the Digit Symbol Test in diabetes subjects had a significant negative relationship with HbA1c ($r=-.433$; $P<.001$), and insulin-use had a significant relationship with the scores of the MMSE and Digit Symbol Test. Subjects in the DM group were further divided by insulin use. Comparison of insulin-treated DM subjects, non-insulin-treated DM subjects, and nondiabetic subjects by analysis of variance followed by Bonferroni's post hoc test showed that insulin-treated DM subjects had significantly lower scores in the MMSE and Digit Symbol Tests than both non-insulin-treated DM subjects ($P<.05$) and nondiabetic subjects ($P<.01$). Our study suggests that Japanese elderly DM subjects, especially those with insulin treatment, have poor cognitive function.
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Keywords: Digit Symbol Test; MMSE; HbA1c; Insulin; Hypoglycemia

1. Introduction

Cognitive function in elderly diabetes mellitus (DM) subjects has been of interest for more than 80 years and has been explored in several studies; however, the outcomes of these studies have not been entirely conclusive (Strachan, Deary, Ewing, & Frier, 1997). Although most studies have concluded that cognitive performance is worse in elderly DM subjects (Gradman, Laws, Thompson, & Reaven, 1993; Miles & Root, 1922; Perlmuter et al., 1984; Reaven, Thompson, Nahum, & Haskins, 1990), some studies have reported that cognitive function in type 2 DM subjects is comparable to that in non-DM subjects (Atiea, Moses, & Sinclair, 1995; Mattlar, Falck, Ronnemaa, & Hyyppa, 1985). These studies have been performed mainly in Western countries. Because cognitive functional tests are based on language communication, studies should be performed using subjects with different genetic and cultural backgrounds in different languages.

Among the factors involved in the mechanism of cognitive impairment in DM subjects, glycemic control may be one of the most important (Gradman et al., 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993). Few studies have investigated the relationship between glycemic control and cognitive function in DM patients. However, one study reported that glycemic control, as measured by hemoglobin A1c (HbA1c) levels, showed a significant negative correlation with cognitive function in DM patients (Reaven et al., 1990). Another reported that oral hypoglycemic medication improved some domains of cognitive ability (attention/concentration, new learning, and problem solving) (Gradman

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et al., 1993). To maintain glycemic control, a combination of several kinds of treatments—including diet regulation, oral medication, and/or insulin treatment—is needed for DM patients. Large prospective studies have shown that persons with DM are at an increased risk of developing dementia, including Alzheimer's disease, particularly when treated with insulin (Ott et al., 1996, 1999). However, the effects of various treatments on cognitive function in DM patients have not been well investigated. For example, there has been only one study—that of Jagusch, Cramon, Renner, & Hepp, 1992—on the effect of treatment in nondemented DM patients; the results showed that insulin-treated subjects had slower simple reaction times. Recently we investigated the effect of treatment on the brain atrophy in elderly DM subjects, and found that the insulin-treated group had the most severe atrophy (Ushida et al., 2001).

Given this situation, the present study was initiated with the following three goals. First, we compared the domains of cognitive functional tests in elderly Japanese subjects (age >60 years) with type 2 DM with a group of elderly non-DM subjects (age >60 years). Second, we wanted to determine whether there was any correlation between the measures of cognitive function and the degree of glycemic control in patients with type 2 DM. Third, we investigated the effect of DM treatment on the performance of cognitive function tests.

2. Subjects and methods

2.1. Subjects

There were 69 subjects with type 2 DM and 27 non-DM subjects. All subjects were outpatients at Nagoya University Hospital in Aichi, Japan, at Gifu Prefectural Tajimi Hospital in Gifu, Japan, at Chiaki Hospital in Aichi, Japan, or at Aoki Kinen Hospital in Mie, Japan. They ranged in age from 60 to 85 years old. All subjects with diagnosis of dementia, depressive disorders by the clinical criteria defined by DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994), respectively, or any other diseases known to affect cognitive function, or subjects who had cerebral infarctions of more than 1 cm in diameter as visualized by brain CT or MRI, and/or had neurological sings or symptoms, and/or clinical histories of stroke including transient ischemic attacks were excluded. No subjects had audio–visual deficiencies sufficient to impair their performance in the cognitive functional assessments. All participants were independent in terms of performing their daily activities.

An ethical committee approved the study protocol and all patients gave their written informed consent prior to the investigation. After the provision of informed consent, the cognitive functional tests were administered individually to each subject. HbA1c was measured as a marker of glycemic control. DM patients were asked if they had had any hypoglycemic episodes during the recent month over the last month by questionnaire. At the day of the assessment subjects had breakfast as usual and the assessment was performed before noon. The doctors checked the physical conditions of the subjects before the assessment and confirmed that they were not hypoglycemic. Hypertension was diagnosed as follows: prescription of antihypertensive medicine, systolic blood pressure (SBP) of 160 mm Hg or higher, and/or diastolic blood pressure (DBP) of 95 mm Hg or higher. The diagnosis of hyperlipidemia was based on the *Japan atherosclerosis society guidelines for diagnosis and treatment of atherosclerotic cardiovascular disease* (Japan Atherosclerosis Society, 2002). Regarding complications of

Table 1
Characteristics of participants by diabetes status

Variable	DM subjects	Non-DM subjects	*P* value
N	69	27	–
Age	71.6 ± 5.6	73.4 ± 6.6	0.164
Gender (% female)	70.4	52.2	0.107
Education (years)	10.4 ± 2.7	11.4 ± 3.0	0.167
Hypertension (%)	52.5	50.0	0.845
Hyperlipidemia (%)	36.5	60.0	0.074
HbA1c (%)	8.0 ± 1.0	5.7 ± 0.4	*P*<.01

Data are the mean ± S.D. unless otherwise indicated.
Student's unpaired *t*–test (age, education, HbA1c) and Kruskal–Wallis analysis (other variables).

Table 2
Performance on measures of cognitive function by diabetes status

Measure	DM subjects	Non-DM subjects	*P* value
MMSE	27.1 ± 2.2	28.3 ± 1.7	*P*<.05
Word List (immediate)	5.7 ± 1.7	6.2 ± 1.7	0.254
(delayed)	7.1 ± 2.2	6.7 ± 2.0	0.364
WAIS-R Digit Symbol	36.3 ± 10.9	43.0 ± 12.1	*P*<.05
Stroop Color Word Test	19.2 ± 12.8	15.0 ± 6.7	0.113

Data are the means ± S.D., unless otherwise indicated.
A higher score indicates better performance, except in the case of the Stroop Color Word Test.
Student's unpaired *t*–test.
WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 3
Correlation coefficients between scores of cognitive tests and diabetic characteristics

Variables	MMSE	WAIS-R
WAIS-R Digit Symbol	0.456**	–
Diabetes duration	0.078	−0.155
HbA1c	−0.205	−0.433**
Neuropathy	−0.075	0.005
Nephropathy	−0.008	−0.021
Retinopathy	−0.095	0.015
Hypoglycemia	−0.265	−0.229
Insulin-treatment	−0.379**	−0.304*

Pearson's correlation coefficients analysis (MMSE, WAIS-R digit symbol, Diabetes duration HbA1c) and Spearman's correlation coefficients analysis (other variables).
* *P*<.05.
** *P*<.01.

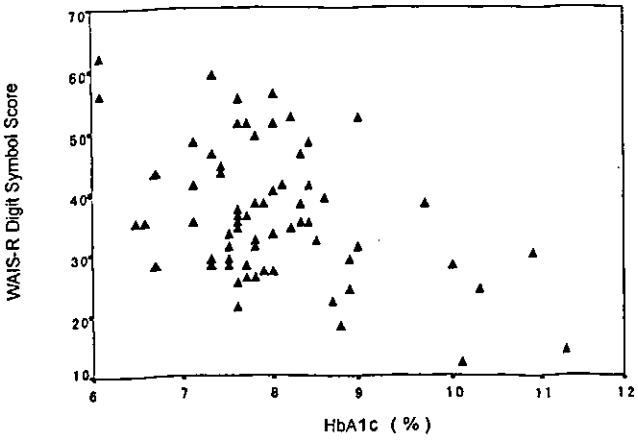

Fig. 1. Relationship between glycosylated hemoglobin (HbA1c) concentration and score of WAIS-R Digit Symbol on DM subjects (N = 69 r = −0.433, $P<0.001$).

DM, neuropathy was diagnosed as elevated vibratory perception thresholds or symptomatic neuropathy including parethesia; retinopathy was diagnosed as simple retinopathy and more advanced; and nephropathy was diagnosed as microalbuminuria (30 mg/g ≦ albumin-to-creatine ratio < 200 mg/g) and more advanced.

2.2. Assessment of cognitive function

Cognitive function was assessed by structured performance tests that were selected to represent a broad range of cognitive domains, including those measured in previous studies in type 2 DM. Strachan et al. (1997) summarized psychological tests used among the previous studies into six broad categories. In considering total administration time and elderly subjects' burden to complete the test battery, we decided to investigate four of these categories, and selected the following standardized psychological tests for measurement of each. (1) Mental Status: the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHigh, 1978) was used to evaluate this category. The MMSE assesses orientation, registration, attention, calculation, language, and recall with a score range from 0 to 30. (2) Verbal Memory: the Word List (a subtest of the Alzheimer's Disease Assessment Scale [ADAS] (Mohs, Rosen, & Davis, 1983)) was used. This test asks subjects to read aloud and remember 10 concrete words printed on individual cards. The subjects' immediate recall is evaluated directly after reading the words, and the delayed recall is assessed at 30 min after reading the words. The score range is 0–10. (3) Complex Psychomotor Skill: the Digit Symbol Test (a subtest of the Wechsler Adult Intelligence Scale—Revised [WAIS-R]; Shinagawa, Kobayashi, Fujita, & Maekawa, 1990) was used. This test consists of a sample line with nine pairs of numbers and meaningless symbols. Subjects are asked to fill in the blanks with the correctly paired symbols in 90 s. The score range is 0–93. (4) Attention: the Stroop Color Word Test (Stroop, 1935; Japanese version) employs a card with 24 colored dots and a card with 24 names of colors printed in different colored ink, e.g., the word "yellow" printed in blue ink. Subjects are asked to name the color of the dots as quickly as possible, and then to name the color of the ink that a color word was printed in as quickly as possible. Seconds to completion are recorded and the difference between the time required to read the word card and that required to read the dots card is calculated. Well-trained psychological testers administered all four tests in the same order for all subjects.

Table 4
Characteristics and performance on measures of cognitive function by diabetes subgroup

Variable	Insulin-treated diabetes	Noninsulin diabetes	Nondiabetic subjects	P value
N	13	56	27	
Age	72.8 ± 6.3	71.3 ± 5.4	73.4 ± 6.6	0.261
Education (year)	10.5 ± 2.6	10.4 ± 2.7	11.4 ± 3.0	0.386
MMSE	25.4 ± 2.0††	27.5 ± 2.0¶	28.3 ± 1.7§	$P<.01$
Word List (immediate)	5.2 ± 1.5	5.9 ± 1.7	6.2 ± 1.7	0.205
(delayed)	6.8 ± 1.3	7.2 ± 2.3	6.7 ± 2.0	0.567
WAIS-R Digit Symbol	29.2 ± 8.1††	37.9 ± 10.8¶	43.0 ± 12.1§	$P<.01$
Stroop Color Word Test	17.8 ± 7.6	19.5 ± 13.8	15.0 ± 6.7	0.252
HbA1c (%)	8.7 ± 1.5†	7.9 ± 0.8¶¶	5.7 ± 0.4§§	$P<.01$
Hypertension (%)	53.2	50.0	50.0	0.845
Hyperlipidemia (%)	36.4	36.6	60.0	0.074

Data are the mean ± S.D., unless otherwise indicated.
A higher score indicates better performance, except in the case of the Stroop Color Word Test.
ANOVA. Bonferroni's post-hoc test showed following;
† Significant difference with noninsulin diabetes ($P<.05$) and nondiabetic subjects ($P<.01$).
†† Significant difference with noninsulin diabetes ($P<.05$) and nondiabetic subjects ($P<.05$).
¶ Significant difference with insulin-treated diabetes ($P<.05$).
¶¶ Significant difference with insulin-treated diabetes ($P<.05$) and nondiabetic subjects ($P<.05$).
§ Significant difference with insulin-treated diabetes ($P<.01$).
§§ Significant difference with insulin-treated diabetes ($P<.05$) and noninsulin subjects ($P<.05$).

2.3. Statistical analysis

All data are presented as the means ± S.D. Comparisons between two groups were made by using Student's t–test or the Kruskal–Wallis analysis. Pearson's correlation coefficients and Spearman's correlation coefficients were calculated for parametric and nonparametric variables, respectively. For the Spearman's correlation coefficients, nonparametric variables were coded as follows. The existence of DM complication or hypoglycemic episode was scored as 1, and the absence of these parameters was scored as 0. The use of insulin was scored as 1, and the nonuse as 0. Comparisons among three groups were made by using analysis of variance (ANOVA) followed by Bonferroni's post hoc test. In all analyses, values of $P<.05$ were considered to indicate statistical significance. All analysiswas performed with SPSS software for Windows (SPSS Inc., 2001).

3. Results

The characteristics of the subjects included in the current study are shown in Table 1. There were no significant differences between DM patients and non-DM subjects in any area except HbA1c ($P<.01$). Table 2 shows the means and S.D. for four measures of cognitive function in DM and control subjects. The DM group performed significantly worse in the MMSE ($P<.05$) and Digit Symbol Test ($P<.05$), and tended to perform more poorly in other tests, although these differences were not significant. The results of the correlation analysis between cognitive tests scores and diabetic characteristics are shown in Table 3. The scores of the Digit Symbol Test in DM subjects had a significant negative correlation with HbA1c ($r=-.433$, $P<.001$, Fig. 1). The insulin-use for DM treatment was also significantly correlated to the Digit Symbol Test ($r=-.304$, $P<.05$). Further, we divided the DM group into two subgroups: an insulin-treated and a non-insulin-treated group. The history of insulin treatment ranged from 1 to 30 years (mean = 10.85; S.D. = 11.10). The frequencies of daily insulin injection were scored as follows: once = 3, twice = 6, three times = 3, four times = 1. ANOVA showed that both the MMSE and Digit Symbol Test scores were significantly different among the three groups ($P<.01$, $P<.01$, respectively, Table 4). Bonferroni's post hoc test showed that the scores of the MMSE and Digit Symbol Test in the insulin-treated DM group was significantly lower than those in the non-insulin-treated DM ($P<.05$), and non-DM ($P<.01$) subjects. Insulin-treated DM subjects had significantly higher HbA1c. The prevalence of DM complications and hypoglycemic episodes by DM treatment were compared and are shown in Table 5. The frequency of hypoglycemic episodes was from three times a year to once a month. No subjects experienced hypoglycemic coma or hospitalization from hypoglycemia-related events. Only prevalence of retinopathy was significantly different between insulin-treated and non-insulin-treated DM subjects.

Table 5
The characteristics and presence of diabetic complication and hypoglycemia by diabetic treatment groups

Variable	Insulin-treated DM	Noninsulin DM	P value
Diabetes Duration (year)	19.2 ± 12.6	13.7 ± 11.2	.164
Neuropathy (%)	66.7	59.2	.637
Retinopathy (%)	63.6	31.2	$P<.05$
Nephropathy (%)	58.3	31.2	.084
Hypoglycemia (%)	36.4	11.4	.060

Data are [the] mean ± S.D., unless otherwise indicated.
Student's t–test. (diabetes history), Kruskal–Wallis analysis (other variables).

4. Discussion

In the current study we investigated cognitive function in the Japanese elderly with type 2 DM. Recently many studies—primarily from Western countries—have reported cognitive functional deficits in elderly DM subjects, and the term "diabetic encephalopathy" is seeing increasing use (Biessels, der Heide, Kamal, Bleys, & Gispen, 2002). Nonetheless, there have been few reports showing cognitive deficits in Japanese subjects with DM. Our results suggest that DM-related cognitive impairment does exist in Japanese subjects, and that such impairment is not dependent on cultural or genetic background.

In the present study the insulin-treated subjects had the worst cognitive function. Three possible mechanisms could be hypothesized for the poor cognitive function in insulin-treated subjects. In the present study, subjects receiving insulin-treatment had significantly higher HbA1c, and the scores of the Digit Symbol test were negatively correlated with HbA1c; therefore, the effects of hyperglycemia should be given primary consideration. Secondly, hypoglycemia-related neuronal damage may have been involved, since insulin-treated elderly DM subjects reportedly have more risks for hypoglycemia (Schorr, Ray, Daugherty, & Griffin, 1997). However, several studies have shown that subjects with impaired glucose tolerance who receive no drug treatment and are at minimum risk for hypoglycemia also sometimes show cognitive impairment (Convit, Wolf, Tarshish, & de Leon, 2003; Vanhanen et al., 1988). This suggests that hypoglycemia may not be a major factor for cognitive functional deficits. Our study failed to show a significant correlation between hypoglycemia and the scores of cognitive functional tests. Thirdly, direct effects of insulin on the neuronal system may have played a role in the poor cognitive function of insulin-treated subjects. Recently, insulin and its receptor have been shown to be present in the brain and appear to play a modulatory role in synaptic transmission (Schwartz, Figlewicz, Baskin, Woods, & Porte, 1992). Ott et al. (1996, 1999) reported that insulin-treated subjects are at greater risk for dementia. In the present study,