Table 1 Age-adjusted baseline characteristics according to body mass index level by sex, the Hisayama Study, 1988

	Body mass index, kg m^{-2}				
	<21	*21–22.9*	*23–24.9*	*⩾25*	P *for trend*
Men					
No at risk	283	255	247	252	—
Age (years)	60.5 (0.6)	56.8 (0.6)	56.2 (0.7)	54.4 (0.6)	<0.001
SBP (mm Hg)	127.1 (1.1)	132.2 (1.2)	135.5 (1.2)	141.2 (1.2)	<0.001
DBP (mm Hg)	75.5 (0.6)	79.3 (0.7)	82.0 (0.7)	86.3 (0.7)	<0.001
Hypertension (%)	32.6	37.4	46.9	58.7	<0.001
Antihypertensive drug (%)	9.0	10.8	15.1	23.6	<0.001
ECG abnormalities (%)[a]	20.6	20.9	19.3	18.7	0.28
Diabetes (%)	10.1	16.9	13.6	20.9	0.005
Total cholesterol (mmol l^{-1})	4.95 (0.06)	5.05 (0.07)	5.13 (0.07)	5.31 (0.07)	<0.001
HDL cholesterol (mmol l^{-1})	1.37 (0.02)	1.30 (0.02)	1.22 (0.02)	1.14 (0.02)	<0.001
Triglycerides (mmol l^{-1})	1.01 (0.94–1.07)	1.28 (1.20–1.37)	1.46 (1.36–1.56)	1.77 (1.65–1.90)	<0.001
Smoking (%)	68.7	47.0	44.5	36.6	<0.001
Drinking (%)	59.7	65.9	64.7	58.6	0.63
Regular exercise (%)[b]	12.8	11.1	11.0	10.9	0.34
Women					
No at risk	380	347	318	339	
Age (years)	59.1 (0.5)	57.0 (0.6)	57.0 (0.6)	57.6 (0.6)	0.052
SBP (mm Hg)	125.2 (1.0)	130.2 (1.0)	131.1 (1.1)	136.9 (1.0)	<0.001
DBP (mm Hg)	71.8 (0.5)	74.4 (0.6)	77.0 (0.6)	80.0 (0.6)	<0.001
Hypertension (%)	24.2	30.9	34.5	50.3	<0.001
Antihypertensive drug (%)	7.5	14.1	14.2	21.5	<0.001
ECG abnormalities (%)[a]	15.2	14.3	9.4	11.6	0.03
Diabetes (%)	7.5	6.8	8.8	16.6	<0.001
Total cholesterol (mmol l^{-1})	5.31 (0.05)	5.54 (0.06)	5.74 (0.06)	5.66 (0.06)	<0.001
HDL cholesterol (mmol l^{-1})	1.44 (0.01)	1.35 (0.02)	1.30 (0.02)	1.26 (0.02)	<0.001
Triglycerides (mmol l^{-1})	0.88 (0.84–0.92)	1.04 (0.99–1.09)	1.15 (1.10–1.21)	1.24 (1.18–1.30)	<0.001
Smoking (%)	8.1	3.5	6.6	8.1	0.72
Drinking (%)	9.5	10.3	5.1	10.7	0.79
Regular exercise (%)[b]	9.4	10.5	8.9	6.3	0.11

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.
Data are shown as the means (standard error) or a percentage. Geometric mean values and 95% confidence intervals of serum triglycerides are shown attributable to the skewed distribution. Mean age was not age-adjusted.
[a]Minnesota codes: 3–1, 4–1, 2, 3 or 8–3
[b]Engaging in sports or other forms of exertion regularly ⩾three times a week during leisure time.

stroke (P=0.01), whereas the interactions between obesity and hypertension and between obesity and smoking habits were not significant.

DISCUSSION

In this prospective study of a community-dwelling Japanese population, we demonstrated that higher BMI was a significant risk factor for the development of ischemic stroke in men. This association remained unchanged even after adjustment for other risk factors. In addition, the combinations of obesity plus diabetes or obesity plus a smoking habit synergistically increased the risk of ischemic stroke. However, there was no significant association between BMI levels and the risk of hemorrhagic stroke in either sex.

Some cohort studies have shown an increased risk of total stroke or ischemic stroke with elevating BMI,[8–14] which is in accord with the findings of the risk of ischemic stroke in our male subjects. On the other hand, other studies have found no association,[15–18] an inverse or a U-shaped association.[19–22] One possible explanation for this difference in findings may be that stroke was not evaluated by its subtype in all these studies, as the effect of obesity is different among stroke subtypes. Another explanation may be that most of these studies used mortality data as an endpoint. Our previous study showed that lower BMI was a significant risk factor for death after total stroke and ischemic stroke.[26] Epidemiological studies of body weight and mortality are affected by methodological problems, such as failure to control the harmful biological effects of smoking and subclinical diseases resulting in weight loss. Thus, the association of BMI with stroke mortality should be interpreted with caution.

In the literature, the associations between BMI levels and the risk of hemorrhagic stroke have been inconsistent, with some studies showing a positive association,[8,11,14] and others showing no, a negative or a U-shaped, association.[9,12,13,16,19,21,22] In the present study, we did not find a clear association between BMI levels and hemorrhagic stroke in men or women. The lack of a clear consensus on this association may be partly due to the low number of cases of hemorrhagic stroke in most of the studies, including our present work, or differences in ethnicities, study populations or study methods. Future studies will be needed to resolve this issue.

A number of studies have reported that the association between BMI and total or ischemic stroke was attenuated or eliminated after adjustment for potential mediators, such as hypertension, diabetes

and dyslipidemia.[9,10,12–14,19,22] In our study, however, the association between BMI and ischemic stroke was not attenuated even after adjusting for these risk factors. This finding indicates an independent effect of overweight and obesity on the development of ischemic stroke. A similar independent association has been observed in other studies of stroke.[10,12,14] These findings, together with our present results, suggest a link between overweight/obesity and ischemic stroke independent of established risk factors. Some investigators have proposed that the increase in prothrombotic factors[27–29] and inflammatory markers,[30–33] and the enhancement of insulin resistance and metabolic syndrome[34] observed among overweight and obese individuals may have a role in their increased risk of ischemic stroke.

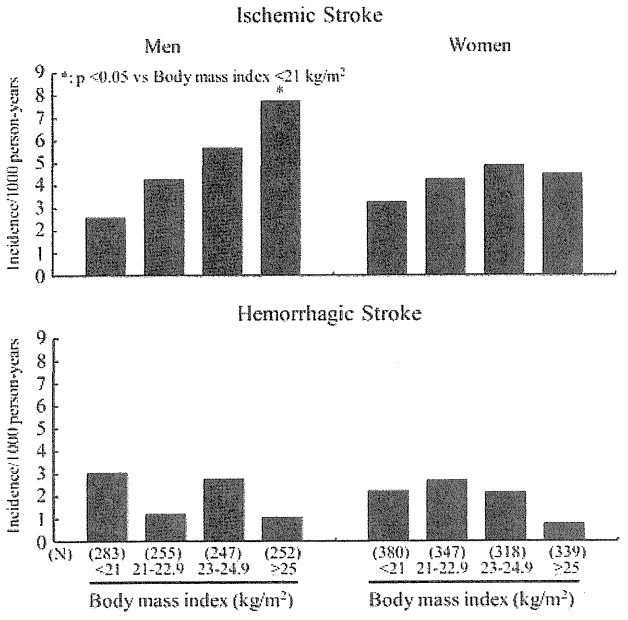

Figure 1 Age-adjusted incidence of stroke by body mass index levels during 12-year follow-up, the Hisayama Study, 1988–2000.

Our stratified analysis showed an extremely increased risk of ischemic stroke in men who have both obesity and diabetes or smoking habits. Although the mechanisms underlying this phenomenon are not clearly understood, a possible explanation can be proposed. Because diabetes and smoking are strong risk factors for the progression of systemic arteriosclerosis, it is reasonable to consider that subjects with these risk factors already have vascular injuries to some extent. Obesity-related disorders, such as inflammation, insulin resistance and metabolic syndrome, may accelerate the progression of preexisting vascular injuries, resulting in an increased risk of ischemic stroke. However, in the present study we did not find that obesity enhanced the effect of hypertension on stroke risk. Although the precise reason for this is not known, the popularization of antihypertensive treatment in our study population might have weakened the synergistic effects of these factors.

In our female subjects, we did not observe a significant association between BMI and the risk of ischemic stroke. Several cohort studies have also examined the effects of BMI on the risk of ischemic stroke in women,[9,13–15,21,22] but the findings were inconsistent, with some studies showing a positive association,[9,13,14] and others showing no association[15,21] like our study. Further studies will be needed to clarify the true association between BMI and stroke in women.

Table 2 Adjusted hazard ratio for stroke incidence according to body mass index level by sex, the Hisayama Study, 1988–2000

Body mass index, kg m^{-2}	*Person year*	*No. of events*	*Age-adjusted HR*	*95% CI*	*Multivariate-adjusted HR*[a]	*95% CI*
Men						
Ischemic stroke						
<21.0	2907	9	1.00	Referent	1.00	Referent
21.0–22.9	2736	10	1.70	0.69–4.20	2.34	0.91–6.00
23.0–24.9	2692	12	2.09	0.88–5.00	3.12	1.24–7.87
25.0⩾	2790	16	3.32	1.43–7.73	5.59	2.09–14.91
P for trend			0.005		<0.001	
Hemorrhagic stroke						
<21.0	2907	9	1.00	Referent	1.00	Referent
21.0–22.9	2736	3	0.44	0.12–1.63	0.38	0.10–1.50
23.0–24.9	2692	6	0.89	0.31–2.55	0.90	0.28–2.87
25.0⩾	2790	3	0.47	0.12–1.80	0.36	0.08–1.57
P for trend			0.41		0.31	
Women						
Ischemic stroke						
<21.0	4214	15	1.00	Referent	1.00	Referent
21.0–22.9	3935	15	1.41	0.69–2.90	1.37	0.65–2.88
23.0–24.9	3652	15	1.51	0.73–3.10	1.56	0.71–3.43
25.0⩾	3794	15	1.41	0.69–2.91	1.27	0.58–2.80
P for trend			0.32		0.55	
Hemorrhagic stroke						
<21.0	4214	10	1.00	Referent	1.00	Referent
21.0–22.9	3935	10	1.26	0.52–3.04	1.32	0.52–3.35
23.0–24.9	3652	7	0.94	0.36–2.49	1.13	0.39–3.25
25.0⩾	3794	3	0.38	0.10–1.39	0.35	0.09–1.35
P for trend			0.16		0.16	

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total and high-density lipoprotein-cholesterols, triglycerides, smoking, drinking and regular exercise.

Table 3 Multivariate-adjusted[a] hazard ratios for the development of ischemic stroke according to the presence or absence of obesity and each established risk factor in men, the Hisayama Study, 1988–2000

		Population at risk	*No. of events*	*HR*	*95% CI*	*P value*
Obesity[b]	*Hypertension*					
No	No	477	14	1.00	Referent	
No	Yes	308	17	1.59	0.76–3.34	0.22
Yes	No	111	7	3.79	1.44–10.00	0.007
Yes	Yes	141	9	2.95	1.19–7.30	0.02
Obesity[b]	*Diabetes*					
No	No	678	25	1.00	Referent	
No	Yes	107	6	1.60	0.65–3.97	0.31
Yes	No	200	8	1.83	0.77–4.38	0.17
Yes	Yes	52	8	7.91	3.08–20.28	<0.001
Obesity[b]	*Smoking*					
No	No	369	17	1.00	Referent	
No	Yes	416	14	1.18	0.56–2.48	0.67
Yes	No	148	8	2.13	0.83–5.46	0.11
Yes	Yes	104	8	3.62	1.39–9.43	0.008

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total and high-density lipoprotein-cholesterols, triglycerides, smoking, drinking and regular exercise, but the factor which was used for each grouping was excluded from the confounding factors.
[b]Obesity is defined as a body mass index $\geqslant 25\,kg\,m^{-2}$.

The strengths of our study include its longitudinal population-based design, the direct collection of height, weight and biological markers from all participants, long duration of follow-up, perfect follow-up of subjects and accuracy of diagnosis of stroke. One limitation of our study is that our findings are based on a one-time measurement of BMI, as was the case in most other epidemiological studies. During the follow-up, BMI and other risk factor levels were changed due to modifications in lifestyle or medication, and misclassification of BMI categories was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown here.

In conclusion, our data suggest that overweight and obesity are significant risk factors for the development of ischemic stroke in contemporary Japanese men. In Japan, BMI levels have increased steadily over the last several decades. For prevention of stroke, it is important to correct obesity while controlling other risk factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare of Japan. *Vital Statistics of Japan 2001*, Vol. 3. Health and Welfare Statistics Association: Tokyo, Japan, 2003.
2 Ueda K, Fujii I, Kawano H, Hasuo Y, Yanai T, Kiyohara Y, Wada J, Kato I, Omae T, Fujishima M. Severe disability related to cerebral stroke: incidence and risk factors observed in a Japanese community, Hisayama. *J Am Geriatr Soc* 1987; **35**: 616–622.
3 Kiyohara Y, Yoshitake T, Kato I, Ohmura T, Kawano H, Ueda K, Fujishima M. Changing patterns in the prevalence of dementia in a Japanese community: the Hisayama Study. *Gerontology* 1994; **40**(suppl 2): 29–35.
4 Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueishi K, Tsuneyoshi M, Fujishima M. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology* 1995; **45**: 1161–1168.
5 Sudlow CLM, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. *Stroke* 1997; **28**: 491–499.
6 The Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66**: 987–992.
7 Yoshiike N, Matsumura Y, Zaman MM, Yamaguchi M. Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990–1994. *Int J Obes* 1998; **22**: 684–687.
8 Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol* 2004; **33**: 751–758.
9 Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE. Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation* 2005; **111**: 1992–1998.
10 Wilson PWF, Bozeman SR, Burton TM, Hoaglin DC, Ben-Joseph R, Pashos CL. Prediction of first events of coronary heart disease and stroke with consideration of adiposity. *Circulation* 2008; **118**: 124–130.
11 Zhou M, Offer A, Yang G, Smith M, Hui G, Whitlock G, Collins R, Huang Z, Peto R, Chen Z. Body mass index, blood pressure, and mortality from stroke: a nationally representative prospective study of 212 000 Chinese men. *Stroke* 2008; **39**: 753–759.
12 Song YM, Sung J, Smith GD, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. *Stroke* 2004; **35**: 831–836.
13 Rexrode KM, Hennekens CH, Wellett WC, Colditz GA, Stampfer MJ, Rich-Edwards JW, Speizer FE, Manson JE. A prospective study of body mass index, weight change, and risk of stroke in women. *JAMA* 1997; **277**: 1539–1545.
14 Bazzano LA, Gu D, Whelton MR, Wu X, Chen CS, Duan X, Chen J, Chen J, He J. Body mass index and risk of stroke among Chinese men and women. *Ann Neurol* 2010; **67**: 11–20.
15 Hart CL, Hole DJ, Smith GD. Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley Study in Scotland. *Stroke* 1999; **30**: 1999–2007.
16 Harmsen P, Rosengren A, Tsipogianni A, Wihelmsen L. Risk factors for stroke in middle-aged men in Göthborg, Sweden. *Stroke* 1990; **21**: 223–229.
17 Shaper AG, Wannamethee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *BMJ* 1997; **314**: 1311–1317.
18 Håheim LL, Holme I, Hjermann I, Leren P. Risk factors of stroke incidence and mortality: a 12-year follow-up of the Oslo study. *Stroke* 1993; **24**: 1484–1489.
19 Jood K, Jern C, Wilhelmsen L, Rosengren A. Body mass index in mid-life is associated with a first stroke in men: a prospective study over 28 years. *Stroke* 2004; **35**: 2764–2769.
20 Selmer R, Tverdal A. Body mass index and cardiovascular mortality at different levels of blood pressure: a prospective study of Norwegian men and women. *J Epidemiol Commun H* 1995; **49**: 265–270.
21 Oki I, Nakamura Y, Okamura T, Okayama A, Hayakawa T, Kita Y, Ueshima H, NIPPON DATA 80 Research Group. Body mass index and risk of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA 80. *Cerebrovasc Dis* 2006; **22**: 409–415.
22 Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Wada Y, Inaba Y, Tamakoshi A, JACC Study Group. Body mass index and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Stroke* 2005; **36**: 1377–1382.
23 Sacco RL, Benjamini EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. Risk factors. *Stroke* 1997; **28**: 1507–1517.
24 Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama Study. *Stroke* 2000; **31**: 2616–2622.
25 World Health Organization. Cerebrovascular diseases: Prevention, Treatment, and Rehabilitation. *Technical Report Series*. World Health Organization: Geneva, Switzerland, 1971, No. 469.
26 Kiyohara Y, Kubo M, Kato I, Tanizaki Y, Tanaka K, Okubo K, Nakamura H, Iida M. Ten-year prognosis of stroke and risk factors for death in a Japanese Community: the Hisayama Study. *Stroke* 2003; **34**: 2343–2348.
27 De Pergola G, De Mitrio V, Giorgino F, Sciaraffia M, Minenna A, Di Bari L, Pannacciulli N, Giorgino R. Increase in both pro-thrombotic and anti-thrombotic factors in obese premenopausal women: relationship with body fat distribution. *Int J Obes* 1997; **21**: 527–535.

28 Morange PE, Alessi MC, Verdier M, Casanova D, Magalon G, Juhan-Vague I. PAI-1 produced *ex vivo* by human adipose tissue is relevant to PAI-1 blood level. *Arterioscl Throm Vas Biol* 1999; **19**: 1361–1365.
29 Juhan-Vague I, Alessi MC, Morange PE. Hypofibrinolysis and increased PAI-1 are linked to atherothrombosis via insulin resistance and obesity. *Ann Med* 2000; **32** (Suppl 1): 78–84.
30 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999; **282**: 2131–2135.
31 Maseri A. Inflammation, atherosclerosis, and ischemic events: exploring the hidden side of the moon. *N Engl J Med* 1997; **336**: 1014–1016.
32 Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke* 2001; **32**: 917–924.
33 Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massero JM, D'Agostino RB, Franzblau C, Wilson PWF. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham Study. *Stroke* 2001; **32**: 2575–2579.
34 Juhan-Vague I, Morange PE, Alessi MC. The insulin resistance syndrome: implication for thrombosis and cardiovascular disease. *Pathophysiol Haemost Thromb* 2002; **32**: 269–273.

High Serum Bilirubin Levels and Diabetic Retinopathy

The Hisayama Study

Miho Yasuda, MD, PhD,[1] Yutaka Kiyohara, MD, PhD,[2] Jie Jin Wang, PhD,[3,4] Satoshi Arakawa, MD,[1] Koji Yonemoto, PhD,[2] Yasufumi Doi, MD, PhD,[5] Toshiharu Ninomiya, MD, PhD,[5] Tatsuro Ishibashi, MD, PhD[1]

Purpose: To assess the association between serum total bilirubin levels and diabetic retinopathy prevalence in participants of the Hisayama Study who had diabetes and impaired glucose metabolism.

Design: Population-based, cross-sectional study.

Participants: Of 3119 participants of the Hisayama Study Eye Examinations in 2007, Japan, 1672 aged ≥40 years with either diabetes or impaired glucose metabolism (defined by a 75-g oral glucose tolerance test) were enrolled in the present study.

Methods: Diabetic retinopathy was assessed via ophthalmic examination after pupil dilatation. The presence and the severity of diabetic retinopathy were determined by grading of color fundus photographs using the modified Airlie House classification system. Association of diabetic retinopathy with serum bilirubin quartiles was assessed using logistic regression model adjusting for age and known risk factors for diabetic retinopathy.

Main Outcome Measures: Prevalent diabetic retinopathy.

Results: Diabetic retinopathy was present in 70 of 1672 (4.2%) participants. The prevalence of diabetic retinopathy in persons with the highest bilirubin quartile (≥0.9 mg/dL) was 2.7%, compared with the prevalence of 3.4%, 5.1%, and 5.1% in those with the first (<0.6 mg/dL), second (0.6–0.69 mg/dL), and third quartiles (0.7–0.89 mg/dL). After adjusting for factors known to be associated with diabetic retinopathy, the prevalence was significantly lower among persons with the highest bilirubin quartile compared with those with the lowest quartile (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.09–0.72) or compared with those in the 3 lower quartiles (OR, 0.25; 95% CI, 0.11–0.58).

Conclusions: Elevated serum bilirubin levels may be protective against diabetic retinopathy among persons with either diabetes or impaired glucose metabolism, independent of known risk factors for diabetic retinopathy.

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Diabetic retinopathy (DR) is a common complication of diabetes and is among the leading causes of blindness and visual impairment among working age persons in developed countries.[1] A number of population-based studies have reported retinopathy lesions not only present in persons with diabetes but also in persons with impaired glucose tolerance or impaired fasting glucose.[2]

Bilirubin has been recognized as an important endogenous antioxidant.[3] In several prospective studies, an inverse relationship has been reported between high bilirubin levels and cardiovascular disease[4] as well as coronary heart disease.[5–7] Cross-sectional studies reported similar protective associations of bilirubin levels with coronary artery disease,[8] peripheral vascular disease,[9] carotid intimal medial thickness,[10] and stroke.[11] This inverse relationship of bilirubin levels to cardiovascular disease was confirmed by a meta-analysis,[12] and bilirubin has now been discussed as a therapeutic target for cardiovascular disease.[13] However, several clinical studies have examined the associations between serum bilirubin levels and retinopathy of prematurity and concluded that there is no protective effect of bilirubin on the development of this retinopathy.[14,15]

Although bilirubin has been recognized as an endogenous inhibitor of cardiovascular disease,[4–12] the relationship between bilirubin and diabetic vascular complications has not been fully understood, with limited relevant reports available.[16–18] There has been no population-based study about the association between serum bilirubin levels and DR. We therefore aimed to examine the association between serum bilirubin levels and DR in patients with diabetes and impaired glucose metabolism in a general Japanese population.

Materials and Methods

Study Population

The Hisayama Study is an ongoing, long-term, cohort study on cardiovascular disease and its risk factors in the town of Hisayama adjoining Fukuoka City, a metropolitan area in southern Ja-

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pan.[19,20] As a part of the study, an epidemiologic study of eye disease among residents of the town has been underway since 1998.[20] In 2007, of the 4298 residents aged ≥40 years, 3119 (79.8%) consented to participate and underwent an ophthalmic examination for the present study; of these, 2880 (92.3%) underwent a 75-g oral glucose tolerance test. Of the 2880 subjects examined, 1672 (58.1%; 466 with diabetes, 583 with impaired glucose tolerance, and 623 with impaired fasting glucose) were included in this study.

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Ophthalmic Examination and Definition of Diabetic Retinopathy

The methods used for the ophthalmic examination have been described in detail previously.[21] Briefly, each participant underwent comprehensive ophthalmic examination, including stereoscopic fundus examination using indirect ophthalmoscopy, and examination with a slit lamp biomicroscope with a "superfield lens" (Volk, Mentor, OH) after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken from both eyes of each participant using a Topcon digital TRC NW-6SF fundus camera (Topcon Corporation, Tokyo, Japan). The photographs were taken in 1-field per eye, centered on the macula. The presence of DR was determined based on both fundus examinations using indirect ophthalmoscopy and slit lamp, and grading of color fundus photographs. The photographs were assessed by photographic graders who were masked to clinical information, following the modified Airlie House Diabetic Retinopathy Classification System, and classified as (i) no retinopathy, (ii) mild retinopathy, (iii) moderate retinopathy, or (iv) proliferative retinopathy.[22,23] The presence of any DR was defined as the presence of mild or moderate or proliferative retinopathy in either eye.

Data Collection

Blood samples were collected from an antecubital vein after an overnight fast for the determination of the serum bilirubin, lipid, gamma-glutamyl transpeptidase, plasma glucose, and hemoglobin A_{1c} levels. After the fasting blood specimen had been taken, the 75-g oral glucose tolerance test was performed between 08.00 and 10.30 hours. At 120 minutes after ingestion of the solution, a blood sample was obtained to determine postloading plasma glucose levels. These specimens were analyzed within 24 hours. The serum bilirubin concentration was measured enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan). The normal range of serum total bilirubin levels as measured used in the study was 0.3 to 1.2 mg/dL. The plasma glucose concentration was determined using the glucose-oxidase method, and the hemoglobin A_{1c} levels were measured by the high-pressure lipid chromatographic assay. Serum total cholesterol and high-density lipoprotein cholesterol were determined enzymatically using the same autoanalyzer, and gamma-glutamyl transpeptidase was measured using Orlowsky's method.

Diabetes classification was based on plasma glucose results, using the 2003 American Diabetes Association criteria.[24] Diabetes was diagnosed on the basis of fasting plasma glucose (FPG) of ≥126 mg/dL (7.0 mmol/L), 2-hour postload plasma glucose (2-hour PG) of ≥ 200 mg/dL (11.1 mmol/L), or current treatment with insulin or oral hypoglycemic medication, impaired glucose tolerance was defined if FPG <126 mg/dL (7.0 mmol/L) and 2-hour PG ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.1 mmol/L), and impaired fasting glucose was defined if FPG ≥100 mg/dL (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L) and 2-hour PG <140 mg/dL (7.8 mmol/L). Blood pressure was measured 3 times after the subject had rested for ≥5 minutes in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Body height and weight were measured in light clothing without shoes, and the body mass index was calculated as the weight in kilograms divided by the height in meters squared. Information on smoking habits, alcohol intake, and physical activity during leisure time was obtained using a standard questionnaire, and smoking habits and alcohol intake were classified into either current habitual use or not, and those subjects who engaged in sports or other forms of exertion ≥3 times per week during their leisure time were designated the regular exercise group. The questionnaire also covered questions about histories of cardiovascular disease, including stroke and coronary heart disease.

Statistical Methods

Age-adjusted prevalence of DR was calculated via direct standardization to the whole Hisayama Study population. A linear pattern of the association was assessed initially for per unit change in bilirubin levels associated with DR prevalence. We further divided bilirubin levels into quartiles (<0.60, 0.60–0.69, 0.70–0.89, and ≥0.90 mg/dL), and considered the lowest quartile or the 3 lower quartiles as reference. Test for trend across quartiles was performed in the logistic regression model. The age- and gender-adjusted or multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In the multivariable-adjusted analysis, we included possible associated factors of either DR or serum bilirubin level that were available in our study, namely, age, gender, 2-hour PG, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase, smoking habits, alcohol intake, and history of cardiovascular disease. We also performed additional analysis restricted to subjects with diabetes. In the multivariable-adjusted analysis of this subsample, we included risk factors for DR, namely, age, gender, duration of diabetes, hemoglobin A_1c, insulin treatment, and history of cardiovascular disease. The SAS software package (SAS Inc., Cary, NC) was used to perform all statistical analyses. A 2-sided $P<0.05$ was considered significant.

Results

Of the study participants, 70 (4.2%) were found to have DR. Mild, nonproliferative retinopathy (category ii), moderate retinopathy (category iii), and proliferative retinopathy (category iv) were found in 40 (2.4%), 29 (1.7%), and 1 (0.1%) participants, respectively.

Participants with DR were more likely to be men (Table 1). The mean age and mean levels of FPG, 2-hour PG, hemoglobin A_{1c} and systolic blood pressure, the frequency of hypertension and having history of cardiovascular disease were significantly higher among subjects with DR, whereas the mean level of total cholesterol and the frequency of smoking habits were significantly lower in those with DR (Table 1). Furthermore, we compared the mean values or frequencies of risk factors between subjects having diabetes with DR and those without DR. The mean duration of diabetes and mean hemoglobin A_{1c}, and the frequency of insulin treatment and history of cardiovascular disease were significantly higher among subjects with DR (Table 1).

Table 1. Characteristics of Subjects by Status of Diabetic Retinopathy

Variable	Without Diabetic Retinopathy	With Diabetic Retinopathy
All subjects (n)	1602	70
Age (y)	64±11	68±10**
Men (%)	52.5	72.9**
Bilirubin level (mg/dL)	0.78±0.32	0.76±0.30
Fasting plasma glucose (mmol/L)	6.1±1.2	8.7±2.5**
2-hour post-load plasma glucose (mmol/L)	9.1±3.9	18.0±5.1**
Hemoglobin A_1c (%)	5.3±0.8	7.0±1.4**
Systolic blood pressure (mmHg)	135±18	142±17**
Diastolic blood pressure (mmHg)	82±10	81±11
Hypertension (%)	57.7	77.1**
Total cholesterol (mmol/L)	5.5±0.9	5.1±0.8**
High-density lipoprotein cholesterol (mmol/L)	1.7±0.4	1.7±0.4
Gamma-glutamyl transpeptidase (IU/L)	3.5±0.8	3.7±0.9
Body mass index (kg/m^2)	23.9±3.5	24.5±3.6
History of cardiovascular disease (%)	4.9	22.9**
Smoking habits (%)	21.3	11.4*
Alcohol intake (%)	51.9	51.4
Regular exercise (%)	12.7	10.0
Subjects with diabetes (n)	398	68
Duration of diabetes (year)	5.7±4.9	16.2±8.8**
Hemoglobin A_1c (%)	6.1±1.1	7.0±1.4**
Insulin treatment (%)	1.3	17.7**
History of cardiovascular disease (%)	9.5	23.5**
Duration of diabetes (y)	5.7±4.9	16.2±8.8**

Values are expressed as means ± standard deviation or percentages. Serum gamma-glutamyl transpeptidase was transformed to logarithm.
*P<0.05, **P<0.01 versus without diabetic retinopathy.

Table 2 compares the mean values or frequencies of potential factors associated with DR by bilirubin quartiles. Subjects with higher bilirubin levels were more likely to be men. Among subjects with the highest quartile of bilirubin levels, the mean values of 2-hour PG and high-density lipoprotein cholesterol were significantly higher, although the mean values of total cholesterol, the frequencies of history of cardiovascular disease or smoking were significantly lower, compared with subjects in other 3 lower quartiles. The prevalence of DR in persons with the highest bilirubin quartile (≥0.9 mg/dL) was 2.7%, compared with the prevalence of 3.4%, 5.1% and 5.1%, respectively, in those within the first (<0.6 mg/dL), second (0.6–0.69 mg/dL), and third (0.7–0.89 mg/dL) quartiles (Table 2).

When bilirubin levels were assessed continuously, we found that each 0.1 mg/dL increase in bilirubin levels was associated with a 16% reduction of the likelihood of having DR (OR, 0.84; 95% CI, 0.76–0.93), after multivariable adjustment. Compared with persons in the lowest quartile of bilirubin levels, those with the highest quartile had a significantly lower odds of having DR, after adjustment for age, gender, 2-hour PG, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase, history of cardiovascular disease, smoking habits, and alcohol intake (OR, 0.25; 95% CI, 0.09–0.72; Table 3). When the lower 3 quartiles were combined to form a reference group, persons in the highest quartile also had reduced prevalence of DR (OR, 0.25; 95% CI, 0.11–0.56). We also examined the age- and gender-adjusted OR of having DR by quartiles of serum total bilirubin levels among subjects with diabetes. The OR of DR decreased as quartiles of bilirubin levels increased, but the trend did not reach significance (P = .07), probably because of the small number of subjects. This association did not change even after adjustment for age, gender, duration of diabetes, hemoglobin A_1c level, insulin treatment, and history of cardiovascular disease (Table 3).

Discussion

We investigated the association of serum bilirubin levels with DR among participants of Hisayama Study who had either diabetes or impaired glucose metabolism. After adjusting for age, gender, and known risk factors for DR, serum bilirubin level was found to be independently and inversely associated with the prevalence of DR. Persons with diabetes or impaired glucose metabolism who were also in the highest quartile of bilirubin levels were 75% less likely to have DR, compared with those in the lowest quartile. Although this observed protective association of bilirubin with DR is in keeping with the documented protective associations of bilirubin with cardiovascular disease and the antioxidant property of bilirubin,[4–12] our findings need to be confirmed in future studies.

Several clinical studies have examined the association between serum bilirubin and diabetic vascular complications.[16–18] Among these, 2 case-control studies reported the association between serum bilirubin level and DR, and the findings were inconsistent.[16,17] One study showed that although serum bilirubin concentrations were significantly higher among normal subjects compared with patients with diabetes, there was no significant difference in mean serum bilirubin levels between patients having diabetes with DR and those without DR.[16] The other study reported a lower prevalence of diabetic vascular complications (retinopathy, macroalbuminuria, coronary artery disease, and cerebrovascular disease) in patients with both diabetes and Gilbert's syndrome, a congenital hyperbilirubinemia defined as serum bilirubin level >1.2 mg/dL.[17] Our findings are consistent with those of the latter report.

Mechanisms underlying the protective association of bilirubin with DR are not yet fully understood, and possible explanations have been proposed. Bilirubin has been recognized as an endogenous antioxidant[1] and suppresses inflammation in the vasculature.[5] The microvasculature of the retina responds to hyperglycemic milieu through a number of biochemical changes, including increased oxidative stress, polyol pathway, protein kinase C activation, and advanced glycation end product formation.[25] Oxidative stress and inflammation are considered crucial contributors in the pathogenesis of DR.[25,26] Oxidative stress-induced biochemical changes contribute to both functional and structural changes in the retina microvasculature, including basement membrane thickening, microvascular cell loss, capillary closure, and acellular capillary formation.[27] Structural changes may contribute to, and also result from, functional changes such as altered blood flow, loss of intercellular junctions, and increased vessel permeability. Animal models of DR have shown beneficial effects of antioxidants on the development of retinopathy in diabetic rats.[25] An-

Table 2. Mean Values or Frequencies of Relevant Factors by Quartiles of Serum Total Bilirubin Levels

Variable	Quartile of Serum Total Bilirubin Level (mg/dL)				P-Value for Trend
	<0.6	0.6–0.69	0.7–0.89	≥0.9	
n	358	548	396	370	
Age (y)	63±11	64±11	64±10	64±11	0.22
Men (%)	54.2	47.8	51.5	62.7	<0.001
Diabetic retinopathy (%)	3.4	5.1	5.1	2.7	0.65
Fasting plasma glucose (mmol/L)	6.2±1.4	6.2±1.3	6.3±1.5	6.2±1.3	0.45
2-hour post-load plasma glucose (mmol/L)	8.6±3.8	9.6±4.4	9.8±4.7	9.9±4.4	<0.001
Hemoglobin A_1c (%)	5.4±0.8	5.4±0.8	5.5±1.0	5.3±0.9	0.09
Systolic blood pressure (mmHg)	135±17	135±18	136±19	137±18	0.34
Diastolic blood pressure (mmHg)	81±10	81±10	82±10	83±10	0.06
Hypertension (%)	55.6	57.1	61.9	59.7	0.29
Total cholesterol (mmol/L)	5.4±0.9	5.5±0.9	5.5±0.9	5.3±0.9	0.005
High-density lipoprotein cholesterol (mmol/L)	1.5±0.4	1.7±0.4	1.7±0.4	1.7±0.5	<0.001
Gamma-glutamyl transpeptidase (IU/L)	3.5±0.8	3.5±0.7	3.5±0.8	3.6±0.8	0.51
Body mass index (kg/m^2)	24.1±3.4	23.9±3.2	24.1±3.8	23.7±3.5	0.43
History of cardiovascular disease (%)	9.2	5.1	4.5	4.5	0.002
Smoking habits (%)	33.5	20.6	17.7	12.4	<0.001
Alcohol intake (%)	51.7	49.3	50.0	58.1	0.05
Regular exercise (%)	12.3	12.1	10.7	15.7	0.19

Values are expressed as the means ± standard deviation or percentages. Serum gamma-glutamyl transpeptidase was transformed to logarithm.

other experimental study of animals has shown that inhibition of the inflammatory cascade at any stage of disease course could inhibit the progression of early stage DR.[25] Therefore, it is possible that an increase in serum bilirubin level inhibits oxidative stress and inflammation processes and thus slows or interrupts the pathways to the development of DR.

Before adjustment for other known DR risk factors, subjects with the highest quartile of bilirubin levels had a significantly higher mean value of 2-hour PG levels than subjects in other quartiles. The findings were carefully rendered to ensure that there was no mistake in the findings presented in this report. Our data seem to indicate a countereffect of elevated bilirubin levels against the effect of elevated 2-hour PG levels on DR prevalence. We also documented that the protective effect of elevated bilirubin level on DR prevalence was independent of other DR risk factors, suggesting that the underlying mechanisms for the

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Diabetic Retinopathy by Quartiles of Serum Total Bilirubin Levels*

	Quartile of Serum Total Bilirubin Level (mg/dL)				P Value for Trend
	<0.6	0.6–0.69	0.7–0.89	≥0.9	
All subjects					
Population at risk (n)	358	548	396	370	0.35
Case of diabetic retinopathy (n)	12	28	20	10	
Age- and gender-adjusted OR (95% CI)	1.0	1.59 (0.79–3.18)	1.55 (0.74–3.23)	0.70 (0.30–1.66)	
Multivariable-adjusted OR (95% CI)	1.0	1.11 (0.48–2.57)	0.86 (0.35–2.11)	0.25 (0.09–0.72)*	0.004
Subjects with diabetes					
Population at risk (n)	83	151	116	116	0.09
Case of diabetic retinopathy (n)	11	28	19	10	
Age- and gender-adjusted OR (95% CI)	1.0	1.41 (0.65–3.03)	1.27 (0.56–2.87)	0.52 (0.21–1.31)	
Multivariable-adjusted OR (95% CI)	1.0	1.41 (0.56–3.54)	1.12 (0.41–3.01)	0.39 (0.12–1.30)	0.07

Multivariable adjustment was made for age, gender, 2-hour post-load plasma glucose, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase, history of cardiovascular disease, smoking habits, and alcohol intake.
*P<0.01versus first quartile.

association with bilirubin levels are likely different from the common pathway via elevated serum blood glucose levels. If confirmed, this may provide a new therapeutic approach to complement current available therapies for patients with diabetes (e.g., lowering serum glucose, lipid levels, and blood pressure levels).

In our data, there also seemed to be a threshold of bilirubin levels at the highest quartile (≥0.9 mg/dL) for the significant protective effect on DR (Table 2). However, because of the relatively small numbers of DR cases in this group, caution should be taken and confirmation of our findings in studies with large sample size is necessary.

Several limitations of our study should be discussed. Our findings were based on a single serum bilirubin level measurement, which might not capture various ranges of bilirubin levels over times in particular participants. However, if such a variation is random and nondifferentiated between cases and controls, it would only dilute the association and bias the results toward the null. A cross-sectional association has no implication of causal relationship. Because the numbers of DR cases were relatively small in our sample, particularly in the highest quartile of bilirubin group, we cannot exclude the possibility of a chance finding.

In conclusion, we demonstrated that elevated serum bilirubin levels were significantly associated with low prevalence of DR in persons with diabetes or impaired glucose metabolism, independent of known DR risk factors. Further studies with a larger sample size, either cross-sectional or prospective, are needed to confirm these findings. If confirmed, our finding may have important implications to clinical management of diabetes and to the prevention of diabetic complications.

References

1. Klaver CC, Wolfs RC, Vingerling JR, et al. Age-specific prevalence and cause of blindness and visual impairment in an older population: the Rotterdam Study. Arch Ophthalmol 1998;116:653–8.
2. Wong TY, Barr EL, Tapp RJ, et al. Retinopathy in persons with impaired glucose metabolism: the Australian Diabetes Obesity and Lifestyle (AusDiab) Study. Am J Ophthalmol 2005;140:1157–9.
3. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. Science 1987;235:1043–6.
4. Djoussé L, Levy D, Cupples LA, et al. Total serum bilirubin and risk of cardiovascular disease in the Framingham Offspring Study. Am J Cardiol 2001;87:1196–200;A4, 7.
5. Troughton JA, Woodside JV, Young IS, et al, PRIME Study Group. Bilirubin and coronary heart disease risk in the Prospective Epidemiological study of Myocardial Infarction (PRIME). Eur J Cardiovasc Prev Rehabil 2007;14:79–84.
6. Djoussé L, Rothman KJ, Cupples LA, et al. Effect of serum albumin and bilirubin on the risk of myocardial infarction (the Framinghan Offspring Study). Am J Cardiol 2003;91:485–8.
7. Breimer LH, Wannamethee G, Ebrahim S, Shaper AG. Serum bilirubin and risk of ischemic heart disease in middle-aged British men. Clin Chem 1995;41:1504–8.
8. Schwertner HA, Jackson WC, Tolan G. Association of low serum concentration of bilirubin with increased risk of coronary artery disease. Clin Chem 1994;40:18–23.
9. Perlstein TS, Pande RL, Beckmen JA, Creager MA. Serum total bilirubin level and prevalent lower-extremity peripheral arterial disease: National Health and Nutrition Examination Survey (NHANES) 1994 to 2004. Arterioscler Thromb Vasc Biol 2008;28:166–72.
10. Erdogan D, Gullu H, Yildirim E, et al. Low serum bilirubin levels are independently and inversely related to impaired flow-mediated vasodilation and increased carotid intima-media thickness in both men and women. Atherosclerosis 2006;184:431–7.
11. Perlstein TS, Pande RL, Creager MA, et al. Serum total bilirubin level, prevalent stroke, and stroke outcomes: NHANES 1999–2004. Am J Med 2008;121:781–8.
12. Novotný L, Vítek L. Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. Exp Biol Med (Maywood) 2003;228:568–71.
13. Schwertner HA, Vítek L. Gilbert syndrome, UGT1A1*28 allele, and cardiovascular disease risk: possible protective effects and therapeutic applications of bilirubin. Atherosclerosis 2008;198:1–11.
14. Hosono S, Ohno T, Kimoto H, et al. No clinical correlation between bilirubin levels and severity of retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 2002;39:151–6.
15. DeJonge MH, Khuntia A, Maisels MJ, Bandagi A. Bilirubin levels and severe retinopathy of prematurity in infants with estimated gestational ages of 23 to 26 weeks. J Pediatr 1999; 135:102–4.
16. Huang EJ, Kuo WW, Chen YJ, et al. Homocysteine and other biochemical parameters in type 2 diabetes mellitus with different diabetic duration or diabetic retinopathy. Clin Chim Acta 2006;366:293–8.
17. Inoguchi T, Sasaki S, Kobayashi K, et al. Relationship between Gilbert syndrome and prevalence of vascular complications in patients with diabetes [letter]. JAMA 2007;298: 1398–400.
18. Fukui M, Tanaka M, Shiraishi E, et al. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. Kidney Int 2008;74:1197–201.
19. Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. Prog Brain Res 1966;21: 64–89.
20. Ohmura T, Ueda K, Kiyohara Y, et al. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. Diabetologia 1993;36:1198–203.
21. Oshima Y, Ishibashi T, Murata T, et al. Prevalence of age related maculopathy in a representative Japanese population: the Hisayama study. Br J Ophthalmol 2001;85:1153–7.
22. Diabetic Retinopathy Study Research Group. A modification of the Airlie House classification of diabetic retinopathy: Diabetic Retinopathy Study (DRS) report number 7. Invest Ophthalmol Vis Sci 1981;21:210–26.
23. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification: ETDRS report number 10. Ophthalmology 1991;98(suppl):786–806.
24. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–7.

25. Madsen-Bouterse SA, Kowluru RA. Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. Rev Endocr Metab Disord 2008;9:315–27.
26. Kern TS. Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy. Exp Diabetes Res 2007;2007:95103. Available at: http://www.hindawi.com/journals/edr/2007/095103.abs.html. Accessed November 28, 2010.
27. Frank RN. Diabetic retinopathy. N Engl J Med 2004;350:48–58.

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[1] Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[2] Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[3] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Australia.

[4] Centre for Vision Research, Westmead Millennium Institute, University of Sydney, Australia.

[5] Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

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Correspondence:
Miho Yasuda, MD, PhD, The Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: miho-m@med.kyushu-u.ac.jp.

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班　長　　熊谷　秋三
〒816－8580　春日市春日公園6-1
九州大学健康科学センター
TEL: 092-583-7853　　FAX: 092-583-7853

印　刷　　大和印刷　有限会社
〒812－0044　福岡市博多区千代2-4-31
TEL: 092-621-0550　FAX: 092-621-0555