Prevalence and Risk Factors for Age-Related Macular Degeneration in an Adult Japanese Population

The Funagata Study

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Objective: To describe the prevalence and risk factors for age-related macular degeneration (AMD) in a Japanese population and to compare these with data from a white population.

Design: Population-based cross-sectional epidemiologic study.

Participants: A population-based sample of Japanese persons 35 years or older from Funagata, Japan.

Methods: The Funagata study is a population-based study of 1758 (43% of eligible) Japanese persons 35 years or older from Funagata, Japan. In 2000 to 2002, 1625 (92.4%) participants had a nonmydriatic fundus photograph of one eye with sufficient quality for grading of AMD lesions, using the Wisconsin protocol. Age-standardized prevalence rates compared with the Blue Mountains Eye Study (BMES) population, odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. Risk factors were assessed by logistic regression.

Main Outcome Measures: Early and late AMD.

Results: Of 1625 participants, early AMD and late AMD were present in 3.5% and 0.5%, respectively. Age-standardized early AMD prevalence in right eyes was 4.1%, similar to the corresponding prevalence of 4.4% in the BMES. For men, age-standardized prevalences of late AMD in right eyes were 1.1% and 1.2% in the BMES; for women, the corresponding prevalences were 0.3% and 2.1%, respectively. Increasing age (per 10 years; gender-adjusted OR, 2.27; 95% CI, 1.10–4.67) and current cigarette smoking (age- and gender-adjusted OR, 5.03; 95% CI, 1.00–25.47) were associated with late AMD.

Conclusions: In this Japanese population, prevalence of early AMD was similar to that for whites in the BMES. Although the late AMD prevalence was lower in Japanese women, in Japanese men it was similar to that in whites. This could have resulted from the substantially high proportion of Japanese men who are smokers. Cigarette smoking and increasing age were the 2 principal factors found associated with late AMD. *Ophthalmology 2008;115:1376–1381*

In the last 2 decades, several population-based studies have reported on the prevalence of age-related macular degeneration (AMD) in different racial/ethnic groups.[1–6] These studies suggest that AMD is more common in whites and less common in blacks.[7–9]

It has long been hypothesized that Asians in general and Japanese people in particular may have lower rates of AMD.[10] However, there are few data in Japanese popula-

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tions to support this concept. In the Hisayama Study, a relatively low prevalence of late AMD (0.87%) was reported in a population-based sample of Japanese ≥50-year-olds[7] as compared with other studies of white populations, such as the Blue Mountains Eye Study (BMES). The prevalence of early AMD in the Hisayama Study (12.7%), however, was reportedly higher than that in the BMES (7.2%).[2] Different definitions of early AMD were used in the Hisayama Study[7] and BMES[2]; that comparison is limited, as different definitions of early AMD have been shown to result in varied prevalence within the same population.[6]

Cigarette smoking is a major risk factor for AMD in white populations.[11] However, this association has not been consistently demonstrated in either Chinese[12] or Japanese[7,13] populations. Given the high prevalence of smoking in Asia and in Japan,[14,15] further studies evaluating the relationship of cigarette smoking and AMD in Japan are clearly needed.

We had 2 purposes for conducting this study. First, we aimed to describe the prevalence of AMD in a Japanese population (the Funagata Study), in which the assessment of AMD was performed at the image-reading center of the Centre for Vision Research, University of Sydney, using definitions identical to those used in the BMES. We sought to compare the prevalence of early and late AMD between Japanese and the white BMES population after age standardization. Second, we aimed to examine risk factors associated with early or late AMD in Japanese adults.

Materials and Methods

Study Population

The Funagata Study is a population-based study among adult Japanese.[16–18] The study population and methods are described in detail elsewhere.[16] In brief, between June 2000 and June 2002, 4160 residents of Funagata, Japan 35 years or older were identified. After excluding 484 with severe disabilities such as hemiparesis after stroke, severe mental diseases, or dementia and individuals receiving treatment for diabetes, 3676 were identified as eligible subjects. Of those, 1961 (53.3% of eligible) were examined; more eligible women participated in this study than eligible men (57.6% vs. 51.5%, $P = 0.002$). The age-specific participation rate was lowest (24%) in the 35- to 40-year age group, increased to 63% in the 65 to 70 and 70 to 75 age groups, and then decreased to 50% in the ≥80 age group. Of the 3676 eligible persons, 1758 (47.8%) had a detailed ophthalmic examination and were included. The study was conducted according to the recommendations of the Declaration of Helsinki and was approved by institutional review boards at Yamagata University Faculty of Medicine.

Fundus Photography

Nonstereoscopic fundus photographs of one eye (generally the right eye) were obtained using a 45° nonmydriatic fundus camera (either CR5-NM45 [Canon Inc., Tokyo, Japan] or TRC-NW [Topcon Inc., Tokyo, Japan]) after sitting in a darkened room for around 5 minutes without using pharmacological dilating agents; those images were recorded on 35-mm slide film. Images were centered on the optic disc and macula. If the fundus photography of the right eye was not possible because of media opacity or other reasons, photographs of the left eye were taken.

Grading of Fundus Photographs for Age-Related Macular Degeneration

One thousand six hundred twenty-five (92.4%) participants had a nonmydriatic fundus photograph of one eye with sufficient quality for grading of AMD lesions. All fundus photographs were evaluated at the Centre for Vision Research by the team that conducted the BMES (Principal Investigators: PM, JJW). Details of the AMD photograph grading followed protocols used for the BMES, as described elsewhere.[2,16] In brief, a trained grader (BT) assessed photographs for AMD signs in masked fashion, following the modified Wisconsin Age-Related Maculopathy Grading System[19] protocol used in the BMES,[2] with adjudication provided by a senior researcher (JJW) and retinal specialist (PM). We used the International Age-Related Maculopathy Epidemiological Study Group nomenclature to describe AMD lesions.[20]

Definition of Lesions in Early Age-Related Macular Degeneration

Drusen type was classified based on the size and sharpness of the edges; drusen were classified as hard or soft; soft drusen were then divided into distinct and indistinct types by the appearance of their borders.[2,20] The grading of maximal lesion size within the macula was estimated using grading circles measuring 63 μm, 125 μm, 175 μm, 250 μm, and 500 μm. Retinal pigmentary abnormalities were graded to hypopigmentation and hyperpigmentation; hypopigmentation was defined as an area of retinal pigment epithelial depigmentation without visible choroidal vessels, and hyperpigmentation as increased pigment beneath the retina associated with drusen.[2,20] Early AMD was defined using the BMES definition as either soft indistinct or reticular drusen or soft distinct drusen plus retinal pigment epithelium (RPE) abnormalities.[2]

Definition of Lesions in Late Age-Related Macular Degeneration

Neovascular AMD lesions included the presence of RPE detachment, with or without neurosensory detachment; subretinal or sub-RPE hemorrhages; or epiretinal, intraretinal, subretinal, or sub-RPE scar tissue.[2,20] Subretinal hemorrhages or hard exudates within the macular area related to the above lesions and not related to other retinal vascular disease were also included as neovascular AMD.[2,20] Geographic atrophy was defined by presence of visible choroidal vessels and a discrete border and needed to be of an area at least equal to a circle 175 μm in diameter.[2,20] Late AMD was defined as either neovascular AMD or geographic atrophy.

Assessment of Risk Factors

Details of systemic assessment are provided elsewhere.[16] In summary, blood pressure (BP) was measured after participants were seated comfortably for at least 5 minutes. A single measure of systolic and diastolic BPs was used. Hypertension was defined using the 2003 World Health Organization guidelines[21]; persons with hypertension stages I to III (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) or a previous diagnosis of hypertension were defined as having hypertension. Diabetes and glucose tolerance status were defined using the results of a 75-g oral glucose tolerance test, following World Health Organization guidelines.[22] Prediabetes was defined as either impaired glucose tolerance or impaired fasting glucose. Total cholesterol and high-density lipoprotein cholesterol were also measured. Self-reported smoking status was assessed. Body mass index was calculated as weight (kilograms) divided by the square of height (meters).

Data Analysis

Age- and gender-specific prevalences of individual AMD lesions, plus early AMD and late AMD, were assessed. Analysis of variance and analysis of covariance or the chi-square test was used to compare demographic characteristics. Direct age standardization of our study population to the BMES population was conducted to compare early and late AMD prevalences using data from right eyes for the 2 populations.[2] Logistic regression models were used to determine the odds of early or late AMD by unit change for a risk category versus a reference category. Possible risk factors included in the analyses were age, gender, systolic and diastolic BPs, hypertension (present vs. absent), body mass index, total cholesterol, high-density lipoprotein cholesterol, smoking status (current smoker vs. never or past smoker), fasting plasma glucose, 2-hour postload glucose, and diabetes status (prediabetes or diabetes vs. nondiabetes). SPSS software (version 13.0, SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

Participants with adequate photographs were significantly younger (60.2 vs. 69.4 years, $P<0.0001$) than participants with poorer photographs. There were no differences in other risk factors between those included in the analyses and those excluded from them (data not shown). The age distribution of the participants is shown in Figure 1 (available at http://aaojournal.org).

The prevalence of early AMD was 3.5% among all participants 35 years and older or 4.3% among those 50 and over. Corresponding prevalences of late AMD were 0.5% and 0.6%, respectively, among participants 35 and older and 50 and older. Participant characteristics by the presence or absence of early and late AMD are shown in Table 1. Persons with early AMD were significantly older than those without early AMD. Persons with late AMD were significantly older and more likely to be current cigarette smokers than those without late AMD. There were more men with late AMD than women, but there was no statistically significant gender difference after adjusting for age.

Table 2 shows the prevalence of specific AMD lesions by age and gender. Overall prevalences of distinct drusen, indistinct drusen, and large drusen (>125 μm) were 15.1%, 1.7%, and 15.6%, respectively; there was an age-related trend ($P<0.0001$). Men were more likely to have distinct drusen and large drusen than women (Ps = 0.02 and 0.03, respectively). Prevalences of hyperpigmentation and hypopigmentation were 4.0% and 4.2%, respectively, but these lesions showed no age-related trend (Ps = 0.83 and 0.76, respectively). Pigmentary abnormalities were more frequent in men than in women; this difference was statistically significant for hypopigmentation (5.6% vs. 2.7%, $P = 0.01$) but not for hyperpigmentation (5.1% vs. 3.5%, $P = 0.16$). Although late AMD and its component lesions, neovascular AMD and geographic atrophy, were more prevalent in men (0.8%, 0.6%, and 0.4% in men, vs. 0.2%, 0.1%, and 0.1% in women), these gender differences were not statistically significant (Ps = 0.08, 0.24, and 0.45, respectively).

We compared age-standardized prevalences of early and late AMD in the right eyes of our population with the corresponding prevalences in the right eyes of BMES participants (Table 3 [available at http://aaojournal.org]). The age-standardized prevalence of early AMD in our study (4.2%) was similar to that in the BMES (4.4%). For men, the age-standardized prevalence of late AMD in right eyes (1.1%) was also similar to that in the BMES (1.2%), but the corresponding late AMD prevalence in women differed between the 2 studies (0.3% in this study and 2.1% in the BMES).

Table 4 (available at http://aaojournal.org) shows associations of risk factors with AMD. Older age was associated with increased odds of both early and late AMD after adjusting for gender (early AMD: odds ratio [OR], 1.75; 95% confidence interval [CI], 1.36–2.25) (late AMD: OR, 2.27; 95% CI, 1.10–4.67), per 10-year increase in age. Current smoking was associated with late AMD after adjusting for age and gender (OR, 5.03; 95% CI, 1.00–25.47). This association was stronger in men (OR, 6.19; 95% CI, 1.08–35.5). There was no significant association between current smoking and early AMD. Although 2-hour postload glucose was associated with early AMD, this association was reduced after adjusting for age and gender. None of the other factors assessed was found to be associated with either early or late AMD.

Discussion

In this adult Japanese population, prevalences of early and late AMD, defined from right eyes only, were 3.5% and 0.5%, respectively, among those 35 years or older. Our study sample was weighted with relatively older persons, which may have led to an overestimation of AMD prevalence. After direct age standardization of our study sample to the BMES population, the prevalence of early AMD in

Table 1. Demographic Characteristics by Presence or Absence of Early and Late Age-Related Macular Degeneration (AMD) in the Funagata Study, Japan 2000–2002

Characteristic	No AMD (n = 1559)	Early AMD (n = 58)	Late AMD (n = 8)
Age (yrs)	60.1±12.2	67.5±9.1	70.6±6.8
Female gender (%)	56.0	56.9	25.0
Systolic blood pressure (mmHg)	127.4±16.8	130.6±17.5	129.3±11.6
Diastolic blood pressure (mmHg)	75.9±10.0	77.4±10.4	79.3±10.0
Hypertension (%)	35.4	43.1	50.0
Current smoker (%)	18.0	17.2	50.0
Body mass index (kg/m^2)	23.8±3.5	23.2±3.1	22.4±2.7
Total cholesterol (mg/dl)	201.7±33.8	198.5±27.5	191.6±35.3
High-density lipoprotein cholesterol (mg/dl)	58.5±14.5	60.8±14.1	55.6±10.3
Fasting plasma glucose (mg/dl)	98.5±27.0	97.9±23.5	93.4±3.7
2-hr postload glucose (mg/dl)	122.4±46.2	135.4±67.3	132.0±31.1
Prediabetes (%)	18.9	17.2	37.5
Diabetes (%)	9.9	12.7	0.0

Table 2. Prevalence of Age-Related Macular Degeneration (AMD) Lesions (Right Eye) in the Funagata Study, Japan 2000–2002

	Age Groups (yrs)	No. at Risk	Drusen (%)		Pigmentary Abnormality (%)		Early AMD (%)	Late AMD (%)
			Soft Distinct Drusen	*Soft Indistinct Drusen*	*Hyperpigmentation*	*Hypopigmentation*		
Men	35–54	259	5.0	0.4	4.6	5.8	0.0	0.0
	55–64	143	17.5	1.4	4.2	5.6	0.0	0.0
	65–74	211	24.6	2.8	6.6	6.6	1.4	1.4
	≥75	99	35.4	2.0	4.0	3.0	3.0	3.0
	Total	712	17.6	1.5	5.1	5.6	0.8	0.8
P value for age trend			<0.001	0.10	0.75	0.53	0.04	0.03
Women	35–54	329	4.0	0.3	3.0	2.1	0.0	0.0
	55–64	205	10.2	1.0	3.4	2.4	0.5	0.5
	65–74	278	22.3	3.2	4.3	2.9	0.4	0.4
	≥75	101	24.8	5.0	3.0	5.0	0.0	0.0
	Total	913	13.3	1.9	3.5	2.7	0.2	0.2
P value for age trend			<0.001	<0.001	0.89	0.29	<0.001	0.57
P values between genders			0.02	0.77	0.16	0.01	0.89	0.08
Total	35–54	588	4.4	0.3	3.7	3.7	0.0	0.0
	55–64	348	13.2	1.2	3.7	3.7	0.3	0.3
	65–74	489	23.3	3.1	5.3	4.5	0.8	0.8
	≥75	200	30.0	3.5	3.5	4.0	1.5	1.5
	Total	1625	15.1	1.7	4.2	4.0	0.5	0.5
P value for age trend			<0.001	<0.001	0.83	0.76	<0.001	0.02

our Japanese participants (4.1%) was quite similar to that in the right eyes of BMES participants (4.4%). For men, the age-standardized prevalence of late AMD in our sample (1.1%) was also comparable to that in the BMES (1.2%), but for women, it was lower than in the BMES (0.3% and 2.1%, respectively). The overall late AMD prevalence of 0.7% in this Japanese sample is lower than that in the BMES (1.8%). We also documented 2 consistent AMD risk factors (increasing age and current smoking) in our Japanese population, consistent with findings from studies elsewhere in whites.

There has long been a belief that AMD is less common in Asians than in whites.[7] Our study in Japanese people, after age standardization and direct comparability of results with the BMES, does not support this concept, at least for early AMD. As we had a small number of late AMD cases, comparative estimates of late AMD prevalence between Japanese and whites will need confirmation in larger future studies. Our data suggest that among Japanese men, late AMD appears to be just as frequent as in all whites.

Cigarette smoking has consistently been identified as a risk factor for AMD in whites,[11] but this association has not previously been reported in a Japanese population-based sample.[7,13] Although cigarette smoking has been shown to be a risk factor of AMD in a case–control study,[23] our report is the first to confirm a link between current smoking and AMD in a Japanese population–based sample.[7,13] Current smoking remains highly prevalent among Japanese men (36.8% of participants in this study), which translates to a 66% population-attributable risk for late AMD cases in Japanese men that are attributable to their smoking behavior. As smoking is a well-recognized, modifiable AMD risk factor, smoking cessation is an important public health measure to reduce the burden of AMD, particularly among Japanese men.

The Hisayama study showed that hypertension and male gender were associated with AMD,[13] but we could not definitively confirm these associations. Although not statistically significant, there was a suggestion of higher late AMD prevalence in men than in women. Gender differences in AMD prevalence have been inconsistently reported,[24] with a higher prevalence of late AMD in men reported in 2 Asian populations (the Hisayama Study[13] and a United States Chinese population[9]). In contrast, most studies conducted in Western white populations have shown a higher prevalence of AMD in women.[24,25] There might be several reasons for a higher prevalence of late AMD in Japanese men relative to women. First, the proportion of current smokers is much higher in Japanese men (36.8% vs. 2.8%), so this seems likely to be the main reason for the gender difference in late AMD prevalence. Because the proportion of current smoking among women was 14.4% in the BMES,[26] compared with only 2.8% among women of our sample, this could explain the lower prevalence of late AMD in Japanese women compared with the corresponding BMES rates. Second, it has been hypothesized that polypoidal choroidal vasculopathy (PCV), a possible variant of neovascular AMD, is relatively prevalent among Japanese, particularly men.[27] Maruko et al,[28] in a Japanese case series, reported that 54.7% of the clinical neovascular AMD cases had PCV, with over 70% of these PCV cases occurring in men. It is possible that the higher prevalence of neovascular AMD in men in our study is related to the higher frequency of PCV in Japanese men. Unfortunately, we are unable to verify this using appropriate tests (e.g., indocyanine green angiography) in our epidemiological study. Finally, differences in the genetic composition of late AMD, such as the complement factor H gene, between different racial/ethnic groups may relate to this observation.[29,30]

Limitations and potential biases of this study should be noted. First, the overall response rate was only 53%. Of those with fundus photographs, 7.6% had insufficient quality for AMD lesion grading, mainly due to media opacity (cornea or lens) among older participants. These limitations could have introduced selection bias, resulting in either underestimation or overestimation of AMD prevalence. Second, only one nonmydriatic fundus photograph was taken from a single eye of each participant examined in the study. This is likely to have underestimated AMD prevalence by 21.5% to 45%.[6,7,31] Nevertheless, we were able to compare the prevalence of early and late AMD in right eyes with corresponding prevalence in the BMES population, after age standardization. Third, comparisons between studies are limited because of differences in the fundus cameras used. The nonmydriatic fundus photography used in our study could have underestimated the prevalence of AMD lesions.[32]

In conclusion, our Funagata study indicates an early AMD prevalence in adult Japanese similar to that of the Australian white population, after age standardization to enhance comparability. The overall prevalence of late AMD was lower but could have reflected the relatively small number of Japanese in this study over 80 years. We confirm older age and cigarette smoking as major risk factors for AMD in Japanese people. Thus, our study does not support the concept that AMD is uncommon in Japan or is unrelated to cigarette smoking.

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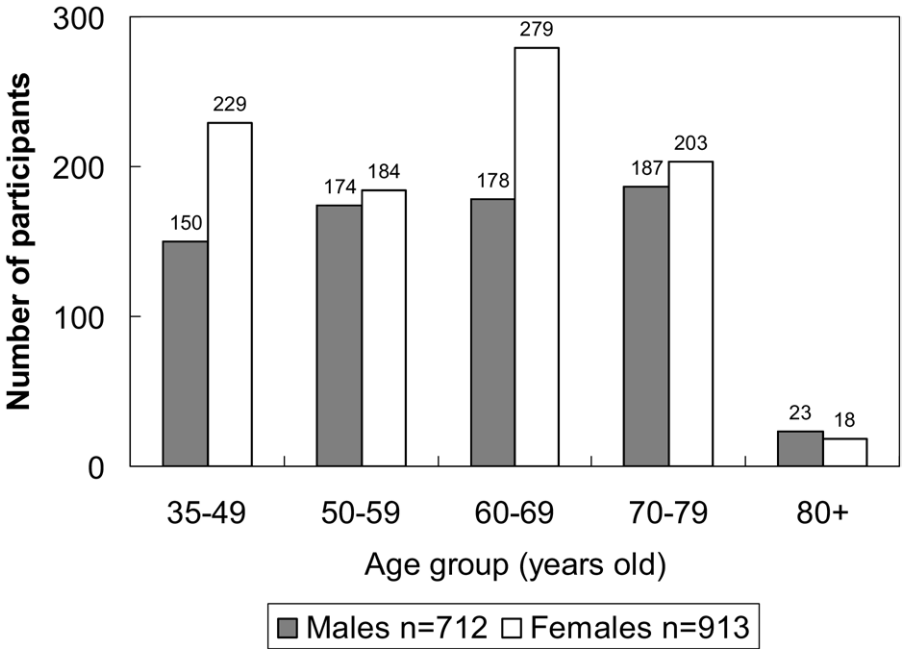

Figure 1. Number of participants by age group in the Funagata study.

Table 3. Prevalence of Early and Late Age-Related Macular Degeneration (AMD) in the Funagata Study, Japan 2000–2002, Age Standardized to the Blue Mountains Eye Study, Australia 1992–1993

		Early AMD			Late AMD		
		Funagata Study	*Blue Mountains Eye Study*		*Funagata Study*	*Blue Mountains Eye Study*	
	Age Group (yrs)	*Right Eye*	*Right Eye*	*Either Eye*	*Right Eye*	*Right Eye*	*Either Eye*
Men	≤54	1.2%	0.5%	2.4%	0.0%	0.0%	0.0%
	55–64	3.5%	0.8%	3.2%	0.0%	0.0%	0.0%
	65–74	6.6%	4.9%	7.5%	1.4%	0.6%	0.6%
	≥75	3.0%	11.6%	15.9%	3.0%	4.8%	5.5%
	Total	4.1%	4.2%	6.9%	1.1%	1.2%	1.3%
Women	≤54	1.2%	0.0%	0.4%	0.0%	0.0%	0.0%
	55–64	2.0%	0.8%	2.2%	0.5%	0.2%	0.3%
	65–74	5.4%	5.7%	9.3%	0.4%	0.7%	0.9%
	≥75	8.9%	11.9%	17.8%	0.0%	8.3%	9.1%
	Total	4.2%	4.6%	7.4%	0.3%	2.1%	2.4%
Total	≤54	1.2%	0.2%	1.3%	0.0%	0.0%	0.0%
	55–64	2.6%	0.8%	2.6%	0.3%	0.1%	0.2%
	65–74	5.9%	5.4%	8.5%	0.8%	0.7%	0.7%
	≥75	6.0%	11.8%	17.1%	1.5%	6.9%	7.6%
	Total	4.1%	4.4%	7.2%	0.7%	1.7%	1.9%

Table 4. Associations with Early and Late Age-Related Macular Degeneration (AMD): The Funagata Study, 2000–2002

	Early AMD				Late AMD			
	Crude		*Age and Gender Adjusted*		*Crude*		*Age and Gender Adjusted*	
Risk Factors	*OR*	*CI*	*OR*	*CI*	*OR*	*CI*	*OR*	*CI*
Age (10 yrs)	1.75	1.36–2.25*	1.75	1.36–2.25†‡	2.36	1.12–4.98*	2.27	1.10–4.67*‡
Gender (female/male)	1.04	0.61–1.76	1.09	0.64–1.85§	0.26	0.05–1.29	0.28	0.06–1.40§
Systolic blood pressure (10 mmHg)	1.11	0.96–1.29	1.00	0.85–1.18	1.06	0.71–1.58	0.90	0.58–1.38
Diastolic blood pressure (10 mmHg)	1.16	0.89–1.50	1.10	0.84–1.44	1.38	0.71–2.69	1.27	0.62–2.61
Hypertension (present vs. absent)	1.38	0.81–2.34	0.90	0.52–1.57	1.80	0.45–7.24	1.06	0.25–4.40
Smoking (current vs. other)	0.94	0.47–1.87	1.37	0.62–3.02	4.55	1.13–18.30*	5.03	1.00–25.47*
Body mass index (kg/m^2)	0.94	0.87–1.02	0.95	0.88–1.03	0.87	0.70–1.10	0.91	0.72–1.13
Total cholesterol (10 mg/dl)	0.97	0.90–1.05	0.95	0.88–1.04	0.91	0.73–1.13	0.93	0.74–1.17
HDL cholesterol (10 mg/dl)	1.11	0.94–1.32	1.11	0.93–1.32	0.86	0.52–1.44	0.91	0.55–1.51
Fasting plasma glucose (10 mg/dl)	0.99	0.89–1.10	0.96	0.85–1.08	0.87	0.52–1.44	0.76	0.43–1.35
2-hr postload glucose (10 mg/dl)	1.04	1.00–1.09*	1.03	0.98–1.08	1.03	0.92–1.16	0.99	0.87–1.14
Prediabetes (vs.nondiabetes)	0.89	0.44–1.78	0.71	0.35–1.43	2.58	0.61–10.86	1.80	0.42–7.67
Diabetes (vs. nondiabetes)	1.25	0.56–2.81	0.93	0.41–2.11		N/A		N/A

CI = 95% confidence interval; HDL = high-density lipoprotein; NA = not available because no cases had diabetes; OR = odds ratio.
*Significant at $P<0.05$.
†Significant at $P<0.001$.
‡Gender-adjusted OR.
§Age-adjusted OR.