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PURPOSE. To investigate the prevalence and risk factors of age-related macular degeneration (AMD) in the general Korean adult population.

METHODS. The study involved a nationally representative Korean population from the 2010 to 2011 Korea National Health and Nutrition Examination Survey. A total of 7899 subjects ≥40 years old participated in health interviews, physical examinations, and ophthalmologic assessment including fundus photography.

RESULTS. The overall prevalence of early AMD was estimated at 6.7% (95% confidence interval [CI], 6.1–7.4), and that of late AMD was estimated at 0.7% (95% CI, 0.5–0.9), which included 0.5% prevalence of neovascular AMD and 0.2% prevalence of geographic atrophy. The prevalence rates of early and late AMD among participants aged ≥65 years were 16.9% and 1.8%, respectively. Hyperopia was positively associated with the presence of any AMD type (odds ratio [OR], 1.08 for every 1 diopter increase). In multivariate analyses, significant risk factors for the presence of any AMD type were age, serum high-density lipoprotein (HDL) level, serum gamma-glutamyl transferase (GGT) level, and hepatitis B surface antigen (HBsAg) serum positivity (OR, 2.26). The risk factors for late AMD included age, ever-smoking history (OR, 2.18), serum GGT level, and systolic blood pressure.

CONCLUSIONS. The prevalence of AMD in Korea was similar to the prevalence of pooled Asian and Western populations. Age and serum GGT level were strongly associated with both the presence of any AMD and late AMD. Additionally, serum HDL level, HBsAg serum positivity, ever-smoking history, and systolic blood pressure were identified as risk factors for AMD.

Keywords: age-related macular degeneration, prevalence, risk factor

Age-related macular degeneration (AMD) is the leading cause of visual impairment among the elderly in industrialized countries.1 The prevalence of AMD has been estimated at 3.5% to 13.2% for early AMD and 0.3% to 1.9% for late AMD.2–6 Several risk factors have been associated with AMD, including age, smoking, and hyperopia.7–9 However, studies involving many other risk factors have yielded controversial results among different ethnic groups.7,10–12

South Korea is an Asian country with approximately 50 million people and is almost entirely composed of a single ethnic group.13 This ethnic homogeneity might help to reveal the risk factors of a disease, but there have been insufficient data for the prevalence and risk factors of AMD in the Korean population. One study reporting the prevalence of major eye diseases estimated the prevalence of early and late AMD at 5.1% and 0.5%, respectively.14 Nevertheless, there is as yet no population-based data for the risk factors of AMD in the general Korean population.

The primary aim of the present study was to investigate the age-specific and sex-specific prevalence of several AMD types in the general Korean adult population, aged ≥40 years; our secondary aims included identifying the risk and protective factors for AMD. In order to achieve these objectives, we used data acquired from the Korea National Health and Nutrition Examination Survey (KNHANES), which is a nationally representative investigation conducted by the Korea Center for Disease Control and Prevention (KCDC).14 To the best of our knowledge, this is the first study that reports the risk factors of AMD in the general Korean population.

METHODS

Study Population

The KNHANES is a nationwide population-based cross-sectional survey involving a representative civilian noninstitutionalized South Korean population, which was initiated in 1998 and has been conducted annually since 2007.14 There were some modifications to the measurement of items in 2009 and 2010 compared to those of previous years, such as the involvement of low-density lipoprotein and gamma-glutamyl transferase (GGT). Ophthalmologic examinations were included in the survey from the latter half of 2008. To keep the measurement of items homogeneous across the dataset and to assess the recent prevalence rate of AMD, the data analyzed in this study were...
Prevalence and Risk Factors of AMD in Korea

The Health Interview Survey included standardized questionnaires on demographic variables, as well as current and past medical conditions. Health-influencing behaviors such as smoking, drinking, and exercise, as well as socioeconomic status were also investigated. In the Health Examination Survey, body height and weight, waist circumference, and average blood pressure in a sitting position corrected by arm length were measured. Blood tests, routine urinalysis, and pulmonary function tests were also performed. Blood tests assessed differential cell counts and hemoglobin, glucose, and serum lipid profile, as well as kidney function, liver enzyme, and GGT levels. As data of high-density lipoprotein (HDL) level were not open for year 2011, only 2010 data were used in analyses involving HDL. Serum concentrations of lead and cadmium were measured by atomic absorption spectroscopy and that of mercury was measured by the gold amalgamation method.

A comprehensive ophthalmologic examination was conducted after the interview, and physical examinations in a vehicle equipped with ophthalmic devices were performed by ophthalmologists dispatched by the Korean Ophthalmological Society (KOS), who were periodically trained by the KOS National Epidemiologic Survey Committee. The examination involved visual acuity testing using the Snellen chart, Goldmann applanation tonometry, automatic refractometry (KR-8800; Topcon, Tokyo, Japan), slit-lamp biomicroscopy, and automated visual field testing (Humphrey Matrix frequency-doubling perimeter; Carl Zeiss Meditec, Inc., Dublin, CA). Retinal examinations were performed by obtaining a 45° field angle nonmydriatic fundus photograph of each eye from all participants aged ≥19 years. The photographs were taken with a digital fundus camera (TRC-NW6S; Topcon) using preinstalled software (IMAGEnet; Topcon) in a dark room to allow for physiological dilation of pupils. In cases where the nonmydriatic photograph was of insufficient quality for grading due to media opacity or a small pupil, a mydriatic fundus photograph was taken after achieving maximal pupillary dilation, using 1.0% tropicamide and 10% phenylephrine.

AMD Grading Using Fundus Photographs

All fundus photographs were graded twice. Preliminary grading was done at the scene of photography by trained ophthalmologists using the International Age-related Maculopathy Epidemiological Study Group grading system. Detailed grading was done later by 9 retina specialists experienced in grading early and late AMD, who were masked to the patients’ characteristics and were entrusted by the KOS. Final grading was based on the detailed grading, and any discrepancy between preliminary grading and detailed grading was resolved by 1 reading specialist. Patients were diagnosed with early AMD if they met one of the following criteria: (1) the presence of soft, indistinct drusen or reticular drusen; (2) the presence of hard or soft distinct drusen with pigmentary abnormalities in the absence of signs of late AMD. Retinal pigmentary abnormalities were graded as depigmentation or hyperpigmentation. Late AMD was defined as either neovascular AMD or geographic atrophy. Neovascular AMD was identified by the detachment of the retinal pigment epithelium (RPE), serous detachment of the neurosensory retina, subretinal or sub-RPE hemorrhages, or subretinal fibrous scars. Geographic atrophy was identified by the presence of a round sharply-edged area of RPE hypopigmentation measuring ≥175 μm in diameter, with visible choroidal blood vessels, in the absence of neovascular AMD. When the severity of AMD varied between both a participant’s eyes, the subject was assigned the more advanced grade. When 1 eye could not be definitively assessed, the subject was categorized according to the AMD grade assigned to the other eye.

The degree of agreement on the readings of the fundus photographs between preliminary grading and detailed grading was estimated at 94.1% for the right eye and 95.0% for the left eye. The degree of agreement between the detailed grading and the final grading was estimated at 96.2% for early AMD and 99.7% for late AMD.

Statistical Analysis

All estimates were derived using sample weights statistically adjusted for response rate, extraction rate, and distribution of the Korean population in 2008 to 2009. Prevalence was expressed as mean values with 95% confidence intervals (CIs) or in age- and sex-stratified tables. Continuous variables were expressed as means ± standard error or mean with 95% CIs. Categorical and continuous variables were examined as risk factors through calculating odds ratios (ORs) with 95% CIs. Risk factors for the presence of any AMD, including early and late types, and those for the presence of late AMD were examined using a two-step multidimensional approach. During the first step, potential risk factors were individually subjected to age-adjusted univariate logistic regression analysis, and the risk factors with a P value <0.1 were selected as candidates for further analysis. Among these, variables with high variance inflation factors were excluded to avoid multicollinearity. During the second step, the candidate risk factors with a P value <0.1 were included in a multivariate logistic regression analysis with a stepwise selection method. To determine the order of entry, previously reported information was used to validate the rationale of the regression model. Risk factors suggested in previous studies were included first, and other risk factors were included and excluded from the model in a stepwise manner. The concentration of heavy metals was the last factor included in the model. With the final set of selected covariates, multivariate logistic regression was performed again to build a final model for the presence of any AMD type or late AMD. Statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL) for Windows (Microsoft, Redmond, WA).

RESULTS

Study Participants

From 2010 to 2011, 16,528 of 21,527 total eligible subjects (76.8% response rate) participated in the Health Interview
Survey and the Health Examination Survey, which involved ophthalmologic examinations (Figure). Of these participants, 8714 (52.7%) subjects who were aged ≥40 years were included. The response rate among those aged ≥40 years was 79.6% (8714 of 10,953). Among them, 7899 (90.6%) had a gradable fundus photograph for at least 1 eye and were ultimately involved in this study. The mean age of the study participants was 55.2 ± 0.2 years (range, 40–97 years) and 3419 (47.9%) of the participants were men. The study participants were younger by 7.6 years than those without any gradable fundus photograph (P < 0.001), but the sex distribution was not different (P = 0.579). The proportion of ever-smokers was lower (44.0%) in the study participants than in those without gradable fundus photographs (48.6%; P = 0.046). The proportion of subjects who had only 1 eye imaged was 3.5% of all study participants, 6.7% of participants with early AMD, and 8.2% of participants with late AMD.

### Prevalence of AMD

The prevalence rates of early and late AMD are presented by age and sex in Table 1. The overall prevalence of early AMD among the study participants was estimated at 6.7% (95% CI, 6.1–7.4), and the overall prevalence of late AMD was estimated at 0.7% (95% CI, 0.5–0.9), including a prevalence of 0.5% (95% CI, 0.4–0.8) for neovascular AMD and 0.2% (95% CI, 0.1–0.3) for geographic atrophy (GA). Bilateral presence of any AMD type was detected in 5.3% (95% CI, 2.9–3.8), and bilateral presence of late AMD was detected in 0.2% (95% CI, 0.1–0.3) of all participants. When analyzed by sex, the prevalence of early AMD was estimated at 5.4% (95% CI, 4.6–6.3) in male participants and 0.4% (95% CI, 0.2–0.7) in female participants. Among participants aged ≥65 years, the prevalence rates of early and late AMD increased to 16.9% (95% CI, 15.1–18.9) and 1.8% (95% CI, 1.3–2.6), respectively; the prevalence rates of neovascular AMD and GA also increased to 1.3% (95% CI, 0.8–2.0) and 0.6% (95% CI, 0.4–1.2), respectively. The prevalence of early AMD increased with age, from 1.4% in participants aged 40 to 49 years to 18.1% among participants aged ≥70 years (P for trend, <0.001). The prevalence rates of late AMD, neovascular AMD, and GA followed a similar trend.

### Risk Factors for AMD

According to univariate binary logistic regression analysis, age was strongly associated with the prevalence of any AMD type.
TABLE 1. Weight-Adjusted Prevalence of Early and Late Age-Related Macular Degeneration (AMD) in Korea Based on the KNHANES 2010–2011

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Unweighted Count of Eyes at Risk</th>
<th>% of Early AMD (SE)</th>
<th>% With Any Late AMD (SE)</th>
<th>% With Neovascular AMD (SE)</th>
<th>% With GA (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥40</td>
<td>7899</td>
<td>6.7 (0.3)</td>
<td>0.7 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>Male</td>
<td>3419</td>
<td>5.4 (0.4)</td>
<td>1.0 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>Female</td>
<td>4480</td>
<td>7.9 (0.5)</td>
<td>0.4 (0.1)</td>
<td>0.3 (0.1)</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>≥65</td>
<td>2483</td>
<td>16.9 (1.0)</td>
<td>1.8 (0.3)</td>
<td>1.3 (0.3)</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>Male</td>
<td>1070</td>
<td>13.6 (1.2)</td>
<td>2.9 (0.7)</td>
<td>1.8 (0.6)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>Female</td>
<td>1413</td>
<td>19.2 (1.5)</td>
<td>1.1 (0.3)</td>
<td>0.9 (0.3)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>40–49</td>
<td>2161</td>
<td>1.4 (0.3)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>50–59</td>
<td>2257</td>
<td>5.1 (0.5)</td>
<td>0.6 (0.2)</td>
<td>0.5 (0.2)</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>60–69</td>
<td>1897</td>
<td>12.0 (0.9)</td>
<td>1.2 (0.3)</td>
<td>0.9 (0.3)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>70–79</td>
<td>1357</td>
<td>18.2 (1.4)</td>
<td>1.3 (0.3)</td>
<td>0.7 (0.2)</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>≥80</td>
<td>247</td>
<td>17.3 (3.2)</td>
<td>3.8 (1.4)</td>
<td>2.9 (1.3)</td>
<td>1.8 (1.1)</td>
</tr>
</tbody>
</table>

P value for trend* <0.001 <0.001 <0.001 <0.001

GA, geographic atrophy; SE, standard error.
* Binary logistic regression analysis.

and late AMD (P < 0.001, respectively). A 1-year increment in age was associated with an 8% increase in the risk for any AMD type (odds ratio [OR], 1.08; 95% CI, 1.07–1.09) and a 7% increase in the risk for late AMD (OR, 1.07; 95% CI, 1.05–1.10).

The association between AMD and other potential risk factors is described in Table 2. In age-adjusted univariate logistic regression analysis, factors with a P value < 0.1 for the presence of any AMD type included body mass index (BMI), waist circumference, white blood cell count, platelet count, hepatitis B surface antigen (HBsAg) serum positivity, as well as glycosylated hemoglobin, HDL, aspartate transaminase (AST), GGT, blood urea nitrogen, creatinine, lead, and urine bilirubin levels. Factors with a P value of < 0.1 for late AMD included male sex, current smoking, ever-smoking history of 100 or more cigarettes, BMI, systolic blood pressure (SBP), diastolic blood pressure, as well as hemoglobin, glycosylated hemoglobin, AST, GGT, creatinine, cadmium, lead, and mercury levels. All the variance inflation factors of these variables were less than 5, and multicollinearity was verified to be low. Among the variables, HDL level and smoking status, which have been consistently identified as risk factors for AMD in previous studies,8,17–19 were selected as forced-in variables in final regression models. Of the two smoking status variables, ever-smoking was chosen as it has the higher OR and the greater statistical significance.

The final logistic regression model for any AMD type included age, HDL level, GGT level, and HBsAg serum positivity as risk factors (Table 3). All these factors were positively associated with the presence of any AMD type. In the final regression model for late AMD, age, ever-smoking history, GGT level, and SBP were identified as risk factors. All these variables were also positively associated with the presence of late AMD. Ever-smoking was associated with the highest OR value of 2.18 (95% CI, 1.09–4.53). Each 5-mm Hg increase in SBP was associated with a 12% increase in the risk for late AMD. Gamma-glutamyltransferase level was significantly correlated with late AMD, as well as with any AMD type (OR: 1.02 and OR: 1.01 per 5 IU/L increment, respectively). Following adjustment, the remaining factors that were initially identified yielded insignificant correlations.

**DISCUSSION**

The present study examined the prevalence of AMD in the adult Korean population, based on the KNHANES V through grading fundus photographs. The estimated prevalence rates of early and late AMD in Korea were 6.7% and 0.7%, respectively, among participants aged ≥40 years. Accordingly, approximately 1.4 million people have early AMD in at least 1 eye, and approximately 140,000 people have late AMD in 1 or both eyes, respectively, in Korea. Among elderly subjects, aged ≥65 years, the prevalence rates of early and late AMD were estimated at 16.9% and 1.8%, respectively; this translates to 770,000 people with early AMD and 82,000 people with late AMD, respectively, in Korea. The prevalence of early AMD increased steadily from the age of 40, approaching a plateau after the age of 70, while the prevalence of late AMD suddenly increased between the ages of 70 and 80, as observed in other studies.3,5,20,21 This might suggest that cumulative senile changes are associated with the development of late AMD, but no clear explanations for this trend have been attained yet. Our estimates in this study were slightly higher than previous estimates of South Korean population in health screenings, which were reported as 2.3% for early AMD and 0.2% for late AMD among healthy individuals aged ≥40 years22 or 5.07% for early AMD and 0.34% for late AMD among individuals aged 50 to 92 years.23 This might be possibly due to the selection bias of those studies, which recruited participants in health check-ups and might have excluded the very elderly or ill people.

The United States National Health and Nutrition Examination Survey of 2005 to 2008, which targeted the noninstitutionalized population aged ≥40 years, estimated the prevalence of any AMD type at 6.5% and that of late AMD at 0.8%.24 In other Western countries, early and late AMD were detected in 7.2% and 1.9%, respectively, among individuals aged ≥49 years.4 As for Asia, the prevalence of early AMD and late AMD was reported as 5.1% and 0.3% among individuals aged ≥40 years in the Beijing Eye Study25 and was estimated at 3.5% and 0.5% in the Japanese population aged ≥35 years.12 The estimated prevalence rates of early AMD and late AMD in this study (6.7% and 0.7%, respectively) were similar to those estimated for the pooled Asian population (6.8% and 0.56%, respectively)6 and the pooled Indian population (6.27% for...
early AMD), as well as those for the United States population in 2005 to 2008 (6.5% and 0.8%, respectively), after adjusting for a population aged ≥40 years. For the elderly population aged ≥65 years, the prevalence rates of early and late AMD in this study were comparable to the rates reported in Taiwan (10.2% and 2.1%, respectively). Several studies, including a recent meta-analysis, have shown that women have a higher prevalence rate than men for late AMD. Whereas other studies reported no significant association between sex and early or late AMD after controlling for age, male sex has not been significantly associated with late AMD after controlling for age only, but the association was not significant after adjusting for age and smoking. Although, there have been hormonal or cerebrovascular explanations for the higher AMD prevalence in women.
women,29 the sex differences in AMD have not been clearly elucidated yet. On the other hand, cigarette smoking has been considered a strong risk factor for late AMD in many large studies.7,12,28,30 While some studies have observed an association between smoking and early AMD (OR, 1.4),30 this association has been mainly established with late AMD.8,12,28,32 In this study, both ever-smoking history of 100 or more cigarettes and current smoking were associated with late AMD after adjusting for age, but ever-smoking history was more highly correlated with the prevalence of late AMD. This might imply a cumulative effect of smoking for the development of late AMD.

Gamma-glutamyltransferase, which is a widely used marker for alcohol abuse and liver dysfunction, is an enzyme that is located in the cell membranes of many tissues including the kidney, bile duct, gallbladder, heart, and brain.33,34 Gamma-glutamyltransferase plays a role in the intracellular antioxidant-protective mechanisms by mediating the transmembranous transport of extracellular glutathione which protects cells against oxidants.34 An increase in the intracellular levels of free radicals leads to the depletion of intracellular glutathione and induces GGT production.35 Thus, it has been suggested that a high GGT level indicates a response to persistent oxidative stress.36 Additionally, GGT has been closely associated with C-reactive protein,37 and elevated serum GGT level was suggested as an independent marker for the activation of systemic inflammation.34 Several recent studies have demonstrated a strong association between GGT and cardiovascular disease or metabolic syndrome.50,56 With respect to the eye, elevated serum GGT levels are suggested to be a risk factor for senile cataract formation,59 but no association between GGT and AMD has been previously reported. In this study, serum GGT level was strongly associated with AMD regardless of the type of AMD. Increased GGT levels may reflect chronic oxidative stress or inflammation in the RPE or choroid or might contribute to drusen deposition by atheromatous plaque formation.34 However, the pathophysiology in this association should be further explored.

The association between hypertension and AMD was observed in some studies26,40 but not in others.27,41 The Rotterdam study suggested elevated SBP is a risk factor for AMD, with an OR of 1.08 per 10-mm Hg increase.18 In the current study, SBP was associated with late AMD (OR, 1.12 per 5-mm Hg increase), whereas hypertension was not. Several hypotheses suggesting that atherosclerosis causes accumulation of lipids and an increase in choroidal vascular resistance as well as the functional impairment of the retinal pigment epithelium have been proposed for this association.18 Additionally, high serum HDL level was associated with the presence of any AMD type in the present study. Many previous studies have reported similar association.17–19,22 but the underlying pathophysiology is still unclear. Additionally, a previous study conducted in Korea identified hepatitis B infection as a significant risk factor for AMD with an OR of 2.736,22 and we observed similar results in our study. This may result from the molecular mimicry between hepatitis viral antigen and retinal S-antigen.22 Hyperopia was also associated with AMD, as reported in many previous studies.3,11,26 Although one study specifically identified short axial length as a risk factor,26 this association is not readily explained. Whereas alcohol consumption and sun exposure were associated with AMD in some studies,10,49 neither was correlated with the prevalence of AMD in this study.

The present study has some limitations. First, this study was cross-sectional in nature and therefore did not allow causality assessment. Hence, in the future, a prospective study is needed to confirm the causal relationship. Second, individuals who did not participate in the survey or who did not have photographs could be graded for AMD were also excluded from our analyses. This might have led to selection bias. Subjects who did not have gradable fundus photographs were older and more likely to have ever smoked than those with a gradable fundus photograph. Considering that old age and ever-smoking were identified as risk factors for AMD in this study, the exclusion of these patients might have led to the underestimation of the prevalence of AMD. Moreover, the exclusion of institutionalized individuals in the survey might influence the results in the same direction. However, despite these limitations, this study used national representative data that involved a large study sample, which enabled us to determine the prevalence of AMD in the general adult population in Korea. This study was conducted by both the KOS and the KCDC and has a reliable quality. The use of a standardized protocol and the periodical training of examiners helped control the quality and validity of the results. Additionally, a high degree of agreement in the grading of AMD lesions was achieved, and the reproducibility of AMD grading was satisfactory.

<table>
<thead>
<tr>
<th>AMD Type</th>
<th>Risk Factor</th>
<th>Unit of Increment</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AMD</td>
<td>Age</td>
<td>1 y</td>
<td>1.10</td>
<td>1.09–1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>5 mg/dL</td>
<td>1.09</td>
<td>1.02–1.18</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>GGT</td>
<td>5 IU/L</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.006</td>
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<tr>
<td></td>
<td>HbsAg</td>
<td>Positive</td>
<td>2.26</td>
<td>1.20–4.27</td>
<td>0.012</td>
</tr>
<tr>
<td>Late AMD</td>
<td>Age</td>
<td>1 y</td>
<td>1.08</td>
<td>1.05–1.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Ever smoking*</td>
<td>Yes</td>
<td>2.18</td>
<td>1.09–4.35</td>
<td>0.027</td>
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<tr>
<td></td>
<td>GGT</td>
<td>5 IU/L</td>
<td>1.02</td>
<td>1.01–1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>SBP</td>
<td>5 mm Hg</td>
<td>1.12</td>
<td>1.03–1.22</td>
<td>0.010</td>
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</tbody>
</table>

* Smoking history of ≥100 cigarettes during the course of one’s life.
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References


