Metabolic Syndrome and Risk of Age-Related Cataract over Time: An Analysis of Interval-Censored Data Using a Random-Effects Model

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PURPOSE. To investigate whether the effect of metabolic syndrome (MetS) and its components on the incidence of different cataract subtypes (cortical, nuclear, and posterior subcapsular cataract [PSC]) change with time.

METHODS. A prospective cohort of persons 49 years of age and older were followed over 10 years in the Blue Mountains Eye Study, west of Sydney, Australia. MetS components as defined by the International Diabetes Federation criteria were measured at baseline (1992–1994), after 5 years (1997–1999), and after 10 years (2002–2004). The incidence of different cataract subtypes was obtained from standard photographic grading at these intervals (n = 1997). Using a random-effects complementary log–log regression model with time to cataract development in discrete time interval, we estimated the effect of MetS and its components on the incidence of different cataract subtypes at different time intervals.

RESULTS. After accounting for changes in MetS components over time and controlling for possible confounders, MetS was found to be associated with an increased 5-year incidence of cortical cataract (hazard ratio [HR] 1.48; 95% confidence interval [CI], 1.05–2.09) and PSC cataract (HR 1.75; 95% CI, 1.01–3.04). Among the five MetS components, high glucose and obesity predicted an increased 5-year incidence of cortical cataract. In addition, low high-density lipoprotein and high glucose were associated with an increased 10-year incidence of cortical and PSC cataracts, respectively.


Age-related cataract is a leading cause of blindness and poor vision and a major public health concern globally.1 Metabolic syndrome (MetS) represents a cluster of these metabolic abnormalities involving central obesity, dyslipidemia, hyperglycemia, and high blood pressure (BP).2 A few studies have investigated the association between cataract and MetS, and whether some individual components are more important risk factors than others for specific cataract subtypes. The Blue Mountains Eye Study (BMES) previously examined baseline MetS with glucose as a mandatory component based on the World Health Organization (WHO) criteria, in relation to 10-year cumulative incidence of the three principal cataract subtypes (i.e., cortical, nuclear, and posterior subcapsular [PSC]) and showed that MetS was associated with an increased risk of all three cataract subtypes.3 A recent cross-sectional study in Singapore confirmed the relation between baseline MetS, defined by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP-3) and cortical cataract, but not between MetS and either nuclear or PSC cataracts.4 Other studies have reported that baseline body mass index (BMI), high BP, or diabetes4,5 is associated with age-related cataracts, whereas elevated serum triglyceride (TG) was a predictor of cataracts among females in another study.5

However, there are a number of unanswered questions. First, previous studies used different definitions for MetS, that is, European Group for the Study of Insulin Resistance (EGIR), WHO, and ATP-3, and it has been reported that these definitions were not as successful in predicting diabetes, cardiovascular disease, and other health outcomes.6–9 Thus, in this study, we define MetS based on the International Diabetes Federation (IDF)10 criteria. This is a diagnostic tool for both research purposes and clinical practice, which can be used relatively easily in any country by any physician to identify patients at increased risk of developing health-related outcomes.2 Moreover, previous studies suggested that IDF provides more reliable criteria for diagnosing MetS in a predictive model for coronary clinical status in type 2 diabetes populations.11,12 Second, previous studies, including an earlier report of BMES,3 used only MetS data at baseline in the evaluation of its relationship with cataracts. However, experimental studies in rats and humans have shown that the effect...
of glucose and lipid abnormalities on cataract formation may change over time; therefore, this underscores the importance of collecting further information on glucose and lipid abnormalities beyond baseline measurements to better detect cataract formation.

To our best knowledge, this is the first study to have fully utilized the information on MetS and its components that were collected not only at baseline but also at subsequent follow-up visits (i.e., after 5 and 10 years) to examine the risk of different cataract subtypes. Further, since the outcome, different cataract subtypes, was measured in a discrete time interval, we implement the random-effect complementary log-log regression since it may be more appropriate for detecting stronger and more robust relationships between individual MetS components, than the logistic regression as used in previous studies. Thus, to evaluate the effect of MetS and its components on the incidence of different age-related cataract subtypes (i.e., cortical, nuclear, and PSC) more precisely, and to determine whether these associations changed with time, we utilized full information that was collected at each follow-up and implemented appropriate statistical models to better describe the relationships.

**METHODS**

**Study Design and Participants**

The BMES is a population-based prospective cohort study of vision, common eye diseases, and other health outcomes in a suburban Australian population west of Sydney, Australia. Between 1992 and 1994, noninstitutionalized permanent residents 49 years of age and older were invited to participate, and were requested to return for follow-up examinations after 5 (1997–1999) and 10 years (2002–2004). The recruitment details have been described elsewhere.3,16,17 The BMES, approved by the Human Research Ethics Committee of the University of Sydney, was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants at each examination.16 At each visit, trained interviewers completed a comprehensive questionnaire comprising demographic information, eye, and general medical history, including hypertension, diabetes, and preexisting diseases (i.e., angina, acute myocardial infarction [AMI], and stroke), as well as medication use. Height, weight, and seated BP were measured. Fasting pathology tests, including high-density lipoprotein (HDL) cholesterol, TG, and fasting blood sugar (FBS) were also measured within 2 months of each interview. In addition, information on smoking (never, former, and current smoker) and alcohol intake were collected. Moreover, history of eye diseases including cataract, age-related macular degeneration (AMD), myopia, glaucoma, as well as family history of eye disease or blindness were obtained and recorded.3 Eye iris color and skin sun-tanning characteristics were also estimated on a 4-point scale (always burn, never tan; usually burn, tan with difficulty; burn and tan above average; rarely burn, tan above average).21

**Cataract Grading**

Detailed cataract grading was performed according to definitions described previously.3 Briefly, the population at risk for cataract comprised participants who had at least one follow-up visit, but whose lens photographs were retrospectively shown not to show signs of cataract at baseline. They also had complete information to define MetS at baseline. Different subtypes of cataract were determined using standard photographic grading at each of the three examinations. The Wisconsin Cataract Grading System was used to perform masked grading of the lens photographs. A 5-point scale was used to assess the presence and severity of nuclear cataract. Nuclear cataract was defined as nuclear opacity worse than standard 3. The extent of cortical or PSC cataract was determined by estimating the lens area involved in segments of a circular grid overlaying the photographs. Cortical opacity involving at least 5% of the total lens area or the presence of any PSC opacity was used to define the presence of the respective cataract subtypes.3 Thus, distinct types of cataract were categorized and analyzed independently.

**Definition of Metabolic Syndrome**

Metabolic syndrome was defined according to IDF criteria as obesity (BMI > 30 kg/m²) plus any two of the following four factors: serum TG level ≥ 1.7 mM or specific treatment for this lipid abnormality; serum HDL cholesterol < 1.03 mM in males and <1.29 mM in females, or specific treatment for this lipid abnormality; systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension; or fasting plasma glucose ≥ 5.6 mM, or previously diagnosed type 2 diabetes.

In this study, the baseline MetS components were measured and recorded when the participant entered the study, and again at the 5- and 10-year examinations after first recruitment. Data are therefore available on how MetS and its components change in each subject throughout the study.

**Statistical Analysis**

The χ² test and independent sample t-test were used to determine the relationship between categorical and continuous covariates included in this study and the 10-year cumulative incidence of cataract, respectively.

Because an individual’s MetS status as well as cataract status were prospectively evaluated at predefined time intervals (i.e., baseline, 5-year, and 10-year), the exact time that cataract—the outcome of interest—developed was therefore not known. Such information was interval censored, and thus the effect of 10-year changes in MetS and its components on the incidence of each cataract subtype was modeled using a random-effects complementary log-log regression model. This statistical technique is readily available for survival analysis with discrete time and is one of the most frequently used discrete-time hazard functions.23 In this study, the outcomes of interest, that is, time to development of different cataract subtypes, were included in the model based on discrete time intervals (i.e., 0–5 years or 5–10 years), in accordance with the follow-up schedule. This approach includes indicator variables for the examination time interval (0–5 and 5–10 years) as covariates. The random-effects model accounts for possible intrasubject correlation in the assessment of MetS and its components, which were repeatedly measured at baseline, 5 years, and 10 years. Of note, when the dichotomous outcome is rare, the complementary log-log regression is more appropriate. However, Nelder (2001) and Hardin and Hilbe (2007) have suggested that when a binary outcome is common, the complementary log-log regression model may also fit the data well.

Age, sex, smoking, preexisting disease (i.e., angina, AMI, and stroke), family history of eye disease (i.e., cataract, AMD, myopia, glaucoma, and blindness), history of eye disease (i.e., AMD, myopia, and glaucoma), eye iris color, and skin sun-tanning characteristics were considered as possible confounders in the model building. Furthermore, we included interactions between MetS (as well as its components) and the time interval to evaluate whether its relationship with the different cataract subtypes varied according to time interval (i.e., 5- and 10-years). We further explored possible interaction between age and sex with MetS and its components. It should be noted that for each cataract subtype, the control group included participants without the same cataract subtype. All statistical evaluations were made assuming a two-sided test based on a 5% level of significance (STATA, version 11; StataCorp, College Station, TX).
### Table 1. Baseline Characteristics of Study Population according to 10-Year Cumulative Incidence of Age-Related Cataract

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n = 1997</th>
<th>No Cataract n = 1140</th>
<th>Cataract n = 857</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean age (SD)</td>
<td>63.9 (8.3)</td>
<td>62.3 (8.3)</td>
<td>65.9 (7.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>844 (42.5)</td>
<td>517 (45.3)</td>
<td>327 (38.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1153 (57.7)</td>
<td>623 (54.7)</td>
<td>530 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Family history of blindness (%)</td>
<td>83 (4.2)</td>
<td>39 (3.4)</td>
<td>44 (5.1)</td>
<td>0.058</td>
</tr>
<tr>
<td>Family history of any eye disease (%)</td>
<td>643 (32.2)</td>
<td>366 (32.1)</td>
<td>277 (32.5)</td>
<td>0.918</td>
</tr>
<tr>
<td>History of any eye disease at baseline (%)†</td>
<td>400 (20.0)</td>
<td>221 (19.4)</td>
<td>179 (20.9)</td>
<td>0.407</td>
</tr>
<tr>
<td>Preexisting disease (%)‡</td>
<td>308 (15.4)</td>
<td>161 (14.1)</td>
<td>147 (17.2)</td>
<td>0.064</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1046 (52.4)</td>
<td>601 (52.7)</td>
<td>445 (51.9)</td>
<td>0.416</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>698 (34.9)</td>
<td>387 (33.9)</td>
<td>311 (36.3)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>253 (12.7)</td>
<td>152 (13.3)</td>
<td>101 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Eye iris color (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>978 (49.0)</td>
<td>565 (49.5)</td>
<td>413 (48.2)</td>
<td>0.897</td>
</tr>
<tr>
<td>Hazel/green</td>
<td>572 (28.6)</td>
<td>323 (28.3)</td>
<td>249 (29.0)</td>
<td></td>
</tr>
<tr>
<td>Tan/brown</td>
<td>251 (12.6)</td>
<td>144 (12.6)</td>
<td>107 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Dark brown</td>
<td>196 (9.8)</td>
<td>108 (9.5)</td>
<td>88 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Sun skin-burned (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always burn, never tan</td>
<td>271 (13.6)</td>
<td>152 (13.3)</td>
<td>119 (13.9)</td>
<td>0.927</td>
</tr>
<tr>
<td>Usually burn, tan with difficulty</td>
<td>496 (24.8)</td>
<td>288 (25.3)</td>
<td>208 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Burn and tan above average</td>
<td>784 (39.3)</td>
<td>448 (39.4)</td>
<td>336 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Rarely burn, tan above average</td>
<td>446 (22.3)</td>
<td>251 (22.0)</td>
<td>194 (22.7)</td>
<td></td>
</tr>
<tr>
<td>MetS (%)</td>
<td>246 (12.3)</td>
<td>119 (10.4)</td>
<td>127 (14.8)</td>
<td>0.744</td>
</tr>
<tr>
<td>BMI &gt; 30 (%)</td>
<td>346 (17.3)</td>
<td>173 (15.2)</td>
<td>173 (20.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>High glucose (%)§</td>
<td>306 (15.3)</td>
<td>149 (13.1)</td>
<td>157 (18.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low-HDL (%)§</td>
<td>591 (29.6)</td>
<td>318 (27.9)</td>
<td>273 (31.9)</td>
<td>0.055</td>
</tr>
<tr>
<td>High TG (%)§</td>
<td>815 (40.8)</td>
<td>461 (40.4)</td>
<td>354 (41.5)</td>
<td>0.713</td>
</tr>
<tr>
<td>High BP (%)§</td>
<td>1689 (84.6)</td>
<td>941 (82.5)</td>
<td>748 (87.3)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* Includes family history of cataracts, glaucoma, macular, and blindness.
† Includes history of age-related macular degeneration, myopia, and glaucoma at baseline.
‡ Includes history of angina, stroke, and acute myocardial infarction at baseline.
§ Fasting plasma glucose ≥ 5.6 mM, or previous diagnosis or specific treatment for type 2 diabetes.
¶ Serum HDL cholesterol < 1.03 mM in males and <1.29 mM in females, or specific treatment for this lipid abnormality.
‖ Serum TG level ≥ 1.7 mM or specific treatment for this lipid abnormality.
# Systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension.

### Results

#### Description of Study Population

A total of 1997 subjects with complete information for the study factors at baseline contributed to the analysis of age-related cataract. Of these, 1820 individuals contributed information for the analysis of cortical cataract, 1357 for nuclear cataract, and 197 for PSC cataract. Table 1 presents the baseline characteristics for the study subjects according to the cumulative incidence of cataract at 10 years. Over the 10-year follow-up, 857 persons (42.9%) with incident cataract were detected. Of these, 455 (25.0%) were cortical cataract, 436 (22.3%) were nuclear cataract, and 135 (7.0%) were PSC cataract. The Figure shows the changes in MetS and its components at baseline, 5-year, and 10-year follow-up among individuals with different cataract subtypes. Generally, a lower proportion of individuals with nuclear cataract had MetS or its components as compared with cortical or PSC cataract. MetS increased from baseline to 5-year follow-up, and was 12.8% (95% CI, 11.1%–13.8%) at baseline, and 12.3% (95% CI, 10.9%–13.8%) at 5-year follow-up, 16.6% (95% confidence interval [CI], 14.9%–18.3%) after 5 years follow-up from 12.3% (95% CI, 10.9%–13.8%) at baseline, and 12.8% (95% CI, 11.1%–14.6%) after 10 years (Table 2).
MetS and Its Components and the Incidence of Age-Related Cataract

We found MetS (hazard ratio [HR] 1.48; 95% CI, 1.05–2.09), BMI > 30 (HR 1.59; 95% CI, 1.16–2.17), and elevated glucose (HR 1.60; 95% CI, 1.15–2.23) to be associated with increased 5-year incidence of cortical cataract, whereas low-HDL cholesterol (HR 1.57; 95% CI, 1.10–2.24) was associated with an excess in incidence of cortical cataract at 10-year follow-up (Table 3).

However, there was no association between MetS or any of its components with the incidence of nuclear cataract at either 5 or 10 years, even after accounting for information on MetS and its components at baseline and follow-up visits as well as controlling for confounders.

Conversely, MetS was associated with an increase in 5-year incidence of PSC cataract (HR 1.75; 95% CI, 1.01–3.04), whereas elevated glucose was associated with an increase in 10-year incidence of PSC cataract (HR 1.90; 95% CI, 1.01–3.61) (Table 3).

**DISCUSSION**

In this prospective cohort study of an Australian white population participating in the BMES, we found the following: First, after accounting for baseline and further follow-up information on MetS and its components as defined by the IDF criteria, MetS, elevated glucose, and BMI levels >30 contributed to an increase in 5-year incidence of cortical cataract, whereas low-HDL cholesterol was linked to an increase in 10-year incidence of cortical cataract. Second, MetS and elevated glucose were positively associated with the incidence of PSC cataract at 5- and 10-year follow-up, respectively.

The association between elevated glucose and incidence of cortical and PSC cataract at different time intervals suggests that FBS levels best predicted late incidence of PSC cataract and early incidence of cortical cataract. Mechanisms connecting hyperglycemia with cataract include advanced glycation of lens proteins,28 hyperosmotic effects of sorbitol on lens fibers via the aldose reductase pathway,29 with induction of apoptosis in lens epithelial cells leading to the development of cataract.30

Additionally, our study demonstrated that BMI levels >30 predicted the 5-year incidence of cortical cataract, suggesting...
that the contribution of obesity to cortical cataract formation may reduce over time. In the Singapore Malay Eye Study and another study by Lim et al., baseline BMI levels have been shown to contribute to a higher risk of cortical cataract and PSC cataract. The underlying mechanism behind the relationship between obesity and cataract is unclear. To date, there has not been any study that examined how changes in BMI over time would affect cataract formation. However, it has been suggested that obesity was related to cataract by its associated complications such as diabetes, glucose intolerance, insulin resistance, and hyperlipidemia. Moreover, it has been shown that the relationship between glucose and cholesterol with cataract formation changed over time. Therefore, this may partly explain why the relationship between obesity and incidence of cataract may also change with time.

Moreover, our finding has shown an association between low-HDL cholesterol and an excess in 10-year incidence of cortical cataract, suggesting that it takes a longer observation time for low-HDL cholesterol to be confirmed as a predictor of cortical cataract. A previous BMES report, which considered only baseline information using logistic regression, failed to detect such a relationship. This finding thus suggests the importance of full utilization of baseline and follow-up data, to better describe the discrete time to development of cataract and its importance of fully accounting for the data on MetS components at each follow-up visit for physicians to better predict the risk of different cataract subtypes in older persons at varying time intervals.

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References


