Weight status, abdominal adiposity, diabetes, and early age-related lens opacities\(^1-4\)

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ABSTRACT

Background: The association between weight status and the risk of lens opacities has received little attention.

Objective: We examined the cross-sectional relations of body mass index (BMI; in kg/m\(^2\)), waist circumference, and diabetes with the presence of age-related lens opacities.

Design: Eye examinations were conducted in 466 Boston-area women aged 53–73 y who were without previously diagnosed cataracts and were part of the Nurses’ Health Study cohort. Weight, height, waist, and hip measurements were obtained by self-report. Lens status was evaluated by using the Lens Opacification Classification System III (LOCS III). BMI and waist circumference were used as measures of overweight and abdominal adiposity, respectively. Nuclear, cortical, and posterior subcapsular (PSC) opacities were defined as LOCS III scores ≥ 2.5, ≥ 1.0, and ≥ 0.5, respectively. Diabetes was defined as a history of type 2 diabetes or as a fasting plasma glucose concentration ≥ 7.0 mmol/L.

Results: Women with diabetes were significantly more likely to have PSC opacities [odds ratio (OR): 4.1; 95% CI: 1.8, 9.4] than were women with fasting plasma glucose concentrations < 6.1 mmol/L. Women with a BMI ≥ 30 had a higher prevalence of PSC opacities than did women with a BMI < 25 (OR: 2.5; 1.2, 5.2), and women with a waist circumference ≥ 89 cm had a higher prevalence of PSC opacities than did those with a waist circumference < 80 cm (OR: 2.3; 1.0, 5.2). Diabetes and measures of adiposity were unrelated to the prevalence of cortical and nuclear opacities.

Conclusions: Diabetes is a strong risk factor for PSC opacities, and overweight and abdominal adiposity may be risk factors for PSC opacities. Am J Clin Nutr 2003;78:400–5.

KEY WORDS Aging, adiposity, blood glucose, body weight, cataract, diabetes mellitus, epidemiology, eye, lens, survey, waist-to-hip ratio

INTRODUCTION

Diabetes has long been considered a risk factor for cataracts, particularly cataracts in the posterior subcapsular region of the lens (1–3), and the role of weight and body composition as risk factors for type 2 diabetes is also well established (4, 5). Because of the relation between weight and diabetes, obesity was perceived as a potentially important cause of cataracts (2). However, the role of weight in the development of cataracts has only become the focus of epidemiologic investigations in the past several years (6–13). Most of these studies used body mass index (BMI; in kg/m\(^2\)) as a measure of weight status. Some studies also used waist-to-hip ratio (WHR) as a measure of abdominal adiposity (9, 11). The purpose of the present study was to examine the relation between diabetes and the risk of opacities in different regions of the lens and to determine whether overweight and abdominal adiposity are related to the prevalence of lens opacities.

SUBJECTS AND METHODS

Subjects and study population

In 1976, 121 700 female nurses aged 30–55 y who resided in 11 US states completed a mailed questionnaire on known and suspected risk factors for cancer and heart disease. These women formed the Nurses’ Health Study (NHS) cohort (14). Every 2 y since 1976, these women have been contacted by mail to update information on risk factors and disease status. In 1993, we identified 1707 NHS cohort members aged 54–73 y who resided in the Boston area, were free of diagnosed cancer other than non-melanoma skin cancer, had complete dietary data, and had both
lenses intact. The goal was to enroll 600 women into the Nutrition and Vision Project. To achieve that goal, all 1707 eligible NHS participants were contacted via a letter from the NHS and were requested to return an enclosed reply postcard indicating whether they would be willing to participate in the study. To preserve their participation in the NHS, the women who did not return the postcard received no further mailings or phone contacts. We received positive responses from 730 women (43%) with one mailing.

Of these 730 women, 603 were ultimately examined as part of the Nutrition and Vision Project between April 1993 and August 1995. Scheduling conflicts (because of work and travel) were the most common reasons for the failure to examine the 127 women who agreed to participate but were never seen. There were few notable differences between the participants and the nonparticipants (15). They were similar in age, alcohol consumption, BMI, reported summertime sunlight exposure, prevalence of hypertension, and vitamin C and multivitamin supplement use between 1980 and 1994. Compared with the nonparticipants, the participants reported fewer pack-years of smoking and were also more likely to have taken vitamin E supplements between 1980 and 1994. Written informed consent was obtained from all study participants, and the Human Investigations Review Committee at the New England Medical Center and the Human Research Committee at the Brigham and Women’s Hospital approved all study procedures.

Measurement of diabetes, weight status, and adiposity

Fasting plasma glucose concentrations in samples obtained at the time of the eye examination were measured by using a coupled enzymatic procedure (16) on a Cobas Mira Clinical Chemistry Analyzer (Roche Diagnostics, Indianapolis). Diabetes was defined on the basis of 1 of the 2 following criteria: 1) a confirmed history of type 2 diabetes before the Nutrition and Vision Project examination, as determined from information collected as part of the NHS (17); or 2) a fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) (18). Impaired fasting glucose was defined as a fasting glucose concentration between 6.1 and 6.9 mmol/L (110–125 mg/dL) (18). The women were divided into 3 categories of fasting glucose concentrations: < 6.1 mmol/L (normoglycemia), 6.1–6.9 mmol/L (impaired fasting glucose), and ≥ 7.0 mmol/L (unconfirmed diabetes). For some analyses, the women with fasting glucose concentrations ≥ 7.0 mmol/L were combined with the women who had a confirmed diagnosis of diabetes.

Overweight was assessed by using BMI. Central adiposity was estimated by using waist circumference and WHR. Adult weight change was calculated by using recalled weight at 18 y of age. Weight and adiposity measurements from 1986 were used for these analyses because this was the only time point before the Nutrition and Vision Project examination for which the waist and hip circumferences were available. For women with missing body weight data in 1986 (n = 10), weights from the 1984 and 1988 questionnaires were averaged and used for these analyses. Height reported in 1976 was included as a covariate in all weight-status analyses. All of the weight, height, and circumference data were self-reported. Ascertainment of waist and hip circumferences was an optional component on the 1986 questionnaire. The women were provided with detailed instructions on measuring circumferences and were asked to report circumferences only if they were measured with the use of a tape measure. Estimates of overweight and abdominal adiposity were categorized for analyses by using previously recommended cutoffs (19), but when sufficient numbers of subjects were available, we subdivided the categories to better assess trends with increasing weight or adiposity. BMI was categorized as < 25.0, 25.0–27.9, 28.0–29.9, and ≥ 30; weight change from 18 y of age was categorized as < 2, 2–4.9, 5–11.9, and ≥ 12 kg; waist circumference was categorized as < 80, 80–88, and ≥ 89 cm; and WHR was categorized as < 0.8, 0.8–0.84, and ≥ 0.85.

Assessment of lens status

All Nutrition and Vision Project participants received a detailed eye examination in which standardized techniques were used as previously described (15). Color film images were taken with a Zeiss photo-slitlamp (Zeiss, Oberkochen, Germany) and Ektachrome 200 film (Kodak, Rochester, NY) to assess the degree of nuclear opalescence. Two digital retroillumination black-and-white images were taken with a Nidek EAS 1000 camera (Nidek, Hiroishi, Japan), one with an anterior image focus (focused on the pupillary plane) to assess the degree of cortical and posterior subcapsular (PSC) opacification. The Lens Opacity Classification System III (LOCS III) was used to measure the degree of nuclear, cortical, and PSC opacification, with possible grades ranging from 0.1 to 5.9 for cortical and PSC opacities and from 0.1 to 6.9 for nuclear opacities (20, 21). Because of the difficulty in using images to assess certain features of the PSC region of the lens, grading of the extent of PSC opacification was also done in vivo at the slit-lamp with the use of LOCS III. We used this in vivo measurement to grade PSC opacification in the present study. We considered eyes to have nuclear, cortical, or PSC opacities if the associated LOCS III grade was ≥ 2.5, ≥ 1.0, or ≥ 0.5, respectively. These thresholds represent early stages of opacification and are not usually associated with symptoms such as reduced vision.

Defining potential confounders

Data on known or suspected determinants of cataract risk were obtained from the biennial NHS questionnaires. For the present study, we considered the following potential confounders: age on the date of the eye examination, cigarette pack-years smoked through the biennial questionnaire returned before the eye examination, reported summertime sunlight exposure (≥ 8 h/wk) as reported on the 1980 questionnaire, and alcohol use based on the average responses from 5 food-frequency questionnaires.

Statistical methods

We estimated the odds ratios relating the prevalence of each type of opacity to measures of weight status and fasting glucose or diabetes from logistic regression analyses performed with the SAS GENMOD procedure (22). This procedure allowed the individual eyes to be the unit of observation. This generalized estimating equation approach for estimating logistic regression models adjusts the standard errors of the model parameters for the correlated data resulting from repeated measurements on the same individual.

Measures of weight status and fasting glucose or diabetes were categorized as described above, and the categories were modeled with indicator variables by using women in the lowest category as the reference group. Odds ratios for the prevalence of opacities in the categories for weight status and fasting glucose or diabetes were calculated as the antilogarithm of the logistic regression coefficient for each of these categories. All odds ratios were adjusted for age and the other potential confounders described...
RESULTS

Of the 603 women examined as part of the Nutrition and Vision Project, we excluded 76 women who had a history of cataract or cataract extraction, 15 women who had questionable lens data, 23 women who had incomplete lens data for both eyes, 1 woman who had confirmed type 1 diabetes, 15 women for whom glucose concentrations were missing, 4 women for whom height or weight measurements were missing, and 3 women for whom data on potential confounders were missing. Of the 932 eyes from these 466 women, complete data for all lens sites were available and which had an opacity in ≥1 lens site. The distribution of opacities in these 397 eyes is shown in Figure 1. Many lenses had opacities in ≥1 site. The remaining 11 eyes, for which data for ≥1 lens site were missing, were included in the analyses for the lens site for which data were available. All analyses were based on the 466 women who had complete data, except for analyses involving WHR (n = 355) and waist circumference (n = 359).

Selected characteristics of the study sample are shown in Table 1. The women with PSC, cortical, or nuclear opacities were significantly older than were the women with no opacities and had significantly higher WHR values than did the women with no opacities. The women with either PSC or nuclear opacities had significantly higher plasma glucose concentrations than did the women with no opacities, and the women with PSC opacities also had a significantly higher prevalence of diabetes and significantly higher waist circumference and BMI and consumed significantly less alcohol than did the women with no opacities.

The relation between lens opacities and fasting glucose concentrations among the women either including or excluding those who had previously diagnosed diabetes is shown in Table 2. The women who were classified as diabetic on the basis of either a previous diagnosis or a fasting plasma glucose concentration ≥7.0 mmol/L had a significantly higher prevalence of PSC opacities than did the women with normal fasting glucose concentrations. Relative to the women with normal fasting glucose concentrations, the odds ratio for PSC opacities among the diabetic women was 4.1 (95% CI: 1.8, 9.4). This association remained after exclusion of the women who had a prior diagnosis of diabetes. The prevalence of PSC opacities among the women with impaired fasting glucose was not significantly higher than that among the women with normal fasting glucose concentrations, and opacities in the lens nucleus and cortex were not associated with diabetes and impaired fasting glucose.

BMI and waist circumference measured in 1986, which was 7–9 y before the eye examination, were positively associated with the prevalence of PSC opacities (Table 3). The odds ratio for PSC opacities was 2.5 (95% CI: 1.2, 5.2) for women with a BMI ≥30 compared with women with a BMI <25 (P for trend = 0.02), and the odds ratio for PSC opacities was 2.3 (95% CI: 1.0, 5.2) for women with a waist circumference ≥89 cm compared with women with a waist circumference <80 cm (P for trend = 0.06). Weight change from 18 y of age to 1986 was weakly related to the prevalence of PSC opacities (P for trend = 0.09). None of the measures of weight status or abdominal adiposity was related to cortical or nuclear opacities. We further adjusted all of the associations listed in Table 3 for the presence of opacities in other regions of the lens, but this adjustment had no effect on the odds ratios (data not shown).

DISCUSSION

Our results showed that the prevalence of PSC opacities was significantly higher among the women classified as diabetic than among the women with normal fasting glucose concentrations. However, the prevalence of PSC opacities was not higher among the women with impaired fasting glucose. We also observed a higher prevalence of PSC opacities among the women who were classified as obese on the basis of their BMI values and among the women classified as having excess visceral fat on the basis of their waist circumference. The prevalence of PSC opacities also appeared to increase with increasing weight change and WHR, but these trends were not significant. It is possible that the lack of significance for these associations was the consequence of our limited statistical power to detect associations with odds ratios of ≤2.3 for PSC opacities. There were no significant associations between diabetes or weight status and the prevalence of either cortical or nuclear opacities. We also had limited statistical power at these lens sites to detect significant odds ratios of <2.0 for the weight-status measures and of <2.5 for diabetes, but there were no consistent trends and all of the observed odds ratios for nuclear and cortical opacities were <2.0.

Interpretation of the results from the present study is subject to some additional caveats. Although we controlled for the most likely known or suspected determinants of cataract risk, it is also...
possible that we did not adequately control for some of these or that the observed associations may have been the result of confounding by other unmeasured factors. Another potential limitation is that the participants in the study where not representative of all eligible women from the NHS cohort. This may have laid the foundation for potential bias but did not by itself cause bias. For bias to have occurred in the present study, the women who did not participate would have to have done so on the basis of the knowledge of their lens status. Although it is possible that women may have preferentially participated because of knowledge of their lens status. The availability of waist- and hip-circumference data from a nonrepresentative subset of women may also have introduced bias. Several earlier studies of lens opacities and diabetes were conducted (3, 7, 9, 12, 25–29), but these studies provide no consistent pattern, they did not observe any association between fasting blood glucose concentrations and PSC opacities among subjects without a history of diabetes. For subjects without a history of diabetes, Rowe et al (3) reported a weak, positive trend between fast- ing blood glucose concentrations and the risk of cortical opacities in women but not in men. However, in contrast to our observations, they did not observe any association between fasting blood glucose concentrations and PSC opacities among subjects without a history of diabetes. Several epidemiologic studies examined the association between weight status, typically measured as BMI, and the risk of lens opacities (6–12, 25, 29–31), but these studies provide no consistent pat-
tern of relations between weight status and lens opacities. Some retrospective studies (10, 25, 31) reported that a lower BMI was associated with a higher risk of nuclear cataracts, whereas other studies did not (12). Some studies also reported a positive association between BMI and cortical cataracts (10), whereas others did not (12, 25, 31), but none of these cross-sectional studies observed an association with PSC cataracts. Prospective studies also fail to provide insight into the relation between BMI and lens opacification. In the NHS, BMI was positively associated with the risk of cataract extraction (30). Hiller et al (8) reported that baseline BMI was related to the development of cortical, but not PSC, opacities over a follow-up of 13 years in the Framingham Study cohorts. In contrast, they observed that average BMI over follow-up and increasing BMI over time were associated with PSC, but not cortical, opacities. They observed no associations between any measures of BMI and nuclear opacities. In the Beaver Dam Eye Study, BMI was associated with the incidence of PSC opacities but not with the incidence of nuclear or cortical opacities (7), and in the Physician’s Health Study cohort after 5 years of follow-up (6), BMI was associated with the incidence of nuclear and PSC opacities and cataract extraction but not with the incidence of cortical opacities. With an additional follow-up of 9 years in this same cohort, Schaumberg et al (11) confirmed the positive associations between BMI and incident nuclear and PSC opacities and cataract extraction but again observed no association with incident cortical opacities. This latter study also reported that WHR was positively associated with nuclear and PSC cataracts and cataract extraction. The WHR association appeared to be independent of the BMI association. Leske et al (9) also examined the relation between WHR and cataracts in a cross-sectional study of cataracts in a disproportionately overweight black population and observed a positive association between WHR and the prevalence of cortical cataracts, but WHR was not significantly associated with nuclear or PSC cataracts.

The most likely mechanisms for an increased risk of opacities among diabetic persons include modification of lens proteins from either oxidative stress or glycation (1, 32). The lack of any association between diabetes and nuclear opacities, despite the fact that the nuclear constituents are the oldest in the lens, may indicate that higher metabolic activity, as present in the outer lens zones, is required in lens cells for diabetes-related damage to occur. The basis for the elevated risk of opacities among obese persons is less certain. Obesity is an established determinant of diabetes, and diabetes is acknowledged as a risk factor for PSC lens opacities and may also increase the risk of cortical opacities. Therefore, it is possible that obesity is related to the risk of opacification as a metabolic consequence of diabetes. Obesity, particularly central obesity, is associated with insulin resistance, which is a strong predictor of type 2 diabetes, and weight reduction improves insulin resistance (33). The strong association between overweight and insulin resistance would certainly imply a high prevalence of insulin resistance among the overweight women in our sample. As a consequence of diabetes or prediabetic endocrine dysfunction, lens cells in obese persons may be exposed to higher glucose concentrations, which may be cataractogenic by the mechanisms mentioned above. This would be consistent with the concurrent lower risk of advanced cataract and lower glucose concentrations in calorie-restricted animals than in animals fed control diets (34).

### Table 3: Odds ratios (ORs) and 95% CIs for prevalent lens opacities by weight status and abdominal adiposity category

<table>
<thead>
<tr>
<th>Weight and adiposity measurements</th>
<th>Type of lens opacity</th>
<th>PSC (OR 95% CI)</th>
<th>P</th>
<th>Cortical (OR 95% CI)</th>
<th>P</th>
<th>Nuclear (OR 95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>BMI in 1986</strong></td>
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<td></td>
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<tr>
<td>&lt; 25.0 (n = 269)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.2 (0.7, 2.0)</td>
<td>1</td>
<td>1.1 (0.6, 2.0)</td>
<td>1</td>
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<tr>
<td>25.0–27.9 (n = 87)</td>
<td>1.0 (0.5, 2.2)</td>
<td>0.98</td>
<td></td>
<td>1.2 (0.7, 2.0)</td>
<td>1</td>
<td>1.1 (0.6, 2.0)</td>
<td>1</td>
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<tr>
<td>28.0–29.9 (n = 48)</td>
<td>1.9 (0.7, 5.1)</td>
<td>0.20</td>
<td></td>
<td>1.1 (0.6, 2.1)</td>
<td>1</td>
<td>0.5 (0.3, 1.1)</td>
<td>1</td>
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<tr>
<td>≥ 30.0 (n = 62)</td>
<td>2.5 (1.2, 5.2)</td>
<td>0.02</td>
<td></td>
<td>1.4 (0.8, 2.4)</td>
<td></td>
<td>1.0 (0.5, 1.8)</td>
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<tr>
<td><strong>P for trend</strong></td>
<td>0.02</td>
<td>0.27</td>
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<tr>
<td><strong>Weight change from 18 y of age to 1986</strong></td>
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<tr>
<td>&lt; 2.0 kg (n = 74)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.1 (0.4, 3.3)</td>
<td>1</td>
<td>1.1 (0.6, 2.1)</td>
<td>1</td>
</tr>
<tr>
<td>2.0–4.9 kg (n = 71)</td>
<td>1.1 (0.4, 3.3)</td>
<td>1.8 (1.0, 3.2)</td>
<td></td>
<td>1.8 (1.0, 3.2)</td>
<td>1</td>
<td>1.1 (0.6, 2.1)</td>
<td>1</td>
</tr>
<tr>
<td>5.0–11.9 kg (n = 156)</td>
<td>1.8 (0.7, 4.7)</td>
<td>1.4 (0.8, 2.4)</td>
<td></td>
<td>1.4 (0.8, 2.4)</td>
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<td>1.1 (0.6, 2.1)</td>
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<tr>
<td>≥ 12 kg (n = 165)</td>
<td>2.1 (0.8, 5.3)</td>
<td>1.2 (0.7, 2.1)</td>
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<td>1.2 (0.7, 2.1)</td>
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<td>1.3 (0.7, 2.4)</td>
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<tr>
<td><strong>P for trend</strong></td>
<td>0.09</td>
<td>0.88</td>
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<td><strong>WHR in 1986</strong></td>
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<tr>
<td>&lt; 0.8 (n = 207)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.6 (1.0, 2.5)</td>
<td>1</td>
<td>1.4 (0.8, 2.5)</td>
<td>1</td>
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<tr>
<td>0.8–0.84 (n = 94)</td>
<td>1.1 (0.5, 2.4)</td>
<td>1.6 (1.0, 2.5)</td>
<td></td>
<td>1.6 (1.0, 2.5)</td>
<td></td>
<td>1.4 (0.8, 2.5)</td>
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<tr>
<td>≥ 0.85 (n = 54)</td>
<td>2.1 (0.9, 5.0)</td>
<td>1.3 (0.7, 2.5)</td>
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<td>1.3 (0.7, 2.5)</td>
<td></td>
<td>1.0 (0.5, 1.9)</td>
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<tr>
<td><strong>P for trend</strong></td>
<td>0.15</td>
<td>0.14</td>
<td></td>
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<tr>
<td><strong>Waist circumference in 1986</strong></td>
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<tr>
<td>&lt; 80 cm (n = 214)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.6 (0.4, 1.0)</td>
<td>1</td>
<td>1.4 (0.8, 2.5)</td>
<td>1</td>
</tr>
<tr>
<td>80–88 cm (n = 90)</td>
<td>1.3 (0.6, 2.9)</td>
<td>0.6 (0.4, 1.0)</td>
<td></td>
<td>0.6 (0.4, 1.0)</td>
<td></td>
<td>1.4 (0.8, 2.5)</td>
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<tr>
<td>≥ 89 cm (n = 55)</td>
<td>2.3 (1.0, 5.2)</td>
<td>1.2 (0.6, 2.2)</td>
<td></td>
<td>1.2 (0.6, 2.2)</td>
<td></td>
<td>0.9 (0.4, 1.8)</td>
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<tr>
<td><strong>P for trend</strong></td>
<td>0.06</td>
<td>0.99</td>
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</table>

1 Adjusted for age, smoking (pack-years), summertime sunlight exposure (≥8 h/wk), alcohol intake, and height. PSC, posterior subcapsular; WHR, waist-to-hip ratio.

2 n = the number of women in each category. Analyses were based on eyes.

3 Adjusted for age, smoking (pack-years), summertime sunlight exposure (≥8 h/wk), alcohol intake, height, and weight at 18 y of age.
In summary, overweight and elevated adiposity, whether as risk factors for diabetes or by other mechanisms, appear to be strong determinants of PSC opacities. Although less common than other types of opacities, PSC opacities are more likely to result in visual disability and are highly overrepresented among extracted cataracts (35, 36); therefore, they represent a potentially preventable public health burden. Although much remains to be learned about the risk factors for age-related cataracts, our results and those of earlier studies strongly suggest that overweight and elevated adiposity aremodifiable risk factors for PSC opacities.

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REFERENCES