



Cup-to-Disc Ratio Asymmetry in U.S. Adults

Prevalence and Association with Glaucoma in the 2005–2008 National Health and Nutrition Examination Survey

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Purpose: To describe the prevalence of vertical cup-to-disc ratio (vCDR) asymmetry in U.S. adults and assess the utility of vCDR asymmetry in the diagnosis of glaucoma.

Design: Cross-sectional study.

Participants: A total of 5359 subjects aged ≥ 40 years from the 2005–2008 National Health and Nutrition Examination Survey (NHANES).

Methods: Subjects completed retinal photography and had vCDR determined in both eyes, with vCDR asymmetry calculated as the absolute value of the difference between the 2 eyes. Frequency Doubling Technology perimetry was used to assess for visual field (VF) defects. Subjects were categorized as having “disc defined glaucoma” if either disc demonstrated glaucomatous features, and VF data were combined with optic disc grading to determine “disc plus field defined glaucoma.”

Main Outcome Measures: Association between vCDR asymmetry and disc plus field defined glaucoma.

Results: In U.S. adults without glaucoma, the 50th, 97.5th, and 99.5th percentiles of vCDR asymmetry are 0.05, 0.19, and 0.26, respectively. Vertical cup-to-disc ratio asymmetry ≥ 0.20 occurs in 2.1% of U.S. adults without glaucoma. The prevalence of vCDR asymmetry ≥ 0.20 among white, black, and Hispanic adults without glaucoma is 2.4%, 0.7%, and 1.8%, respectively. The odds of vCDR asymmetry ≥ 0.20 are 1.44 times higher per 10-year increase in age (odds ratio [OR], 1.44; 95% confidence interval [CI], 1.20–1.72; $P < 0.01$). Each 0.10 increase in vCDR asymmetry was associated with a 2.57 times higher adjusted odds of disc plus field defined glaucoma (OR, 2.57; 95% CI, 1.43–4.61; $P < 0.01$). The sensitivity and specificity of vCDR asymmetry ≥ 0.20 for disc plus field defined glaucoma are 22.7% and 97.7%, respectively, whereas the positive likelihood ratio is 9.9 and the positive predictive value (PPV) is 7.0%. At a higher vCDR asymmetry cutoff of ≥ 0.30 , the PPV increases to 37.7%.

Conclusions: Vertical cup-to-disc ratio asymmetry is predictive of prevalent glaucoma, but the PPV remains low even at high degrees of asymmetry. Vertical cup-to-disc ratio asymmetry should initiate a more comprehensive glaucoma workup, especially in individuals with additional risk factors, but it is not appropriate as a screening metric for glaucoma. *Ophthalmology* 2017; ■:1–8 © 2017 by the American Academy of Ophthalmology



Supplementary material available at www.aajournal.org.

Glaucoma, the leading cause of irreversible blindness worldwide,¹ is often an asymptomatic disease that goes undiagnosed until the patient reaches a moderate degree of visual field (VF) loss.² As such, it is important to develop methods to identify patients with signs of glaucoma or high-risk features for developing glaucoma, including elevated intraocular pressure, enlarged vertical cup-to-disc ratio (vCDR), vCDR asymmetry, disc hemorrhage, disc notching, and disc excavation.² Patients with these features should undergo a comprehensive glaucoma evaluation, particularly when found in the context of additional risk factors such as older age, African American race, and family history of glaucoma.

Significant vCDR asymmetry has been considered to be suggestive of glaucoma³ and has been shown to be a predictor for developing glaucomatous VF loss in patients with ocular hypertension and initially normal VFs.⁴ The International Society of Geographic and Epidemiologic Ophthalmology criteria require vCDR or vCDR asymmetry to be greater than the 97.5th or 99.5th percentile for a category 1 (structural and functional evidence) or category 2 (advanced structural damage with unproven field loss) glaucoma diagnosis.⁵ Population-based studies in countries including China, Japan, Thailand, Singapore, Mongolia, Bangladesh, India, and Tanzania, and regions in the United States, including

Wisconsin, Baltimore, and Los Angeles, have estimated the 97.5th and 99.5th percentiles for vCDR asymmetry to be approximately 0.20 and 0.30, respectively, and the prevalence of vCDR asymmetry ≥ 0.20 and ≥ 0.30 in those without glaucoma to be 2% to 7% and 0.5% to 3%, respectively.^{6–21} Although there is consensus about using vCDR as one of many parameters in the diagnosis and classification of glaucoma, it would be useful for clinicians to know the positive predictive value (PPV) of vCDR asymmetry for predicting glaucoma.

To our knowledge, there has been no large cross-sectional epidemiologic study investigating the prevalence of vCDR asymmetry in a representative sample of the entire U.S. adult population. The National Health and Nutrition Examination Survey (NHANES) is an ongoing population-based survey conducted in the United States by the Centers for Disease Control and Prevention with the purpose of estimating disease prevalence.²² This study was designed to use NHANES data to (1) describe the prevalence and distribution of vCDR asymmetry among U.S. adults; (2) identify whether there are any demographic predictors for vCDR asymmetry; and (3) explore the utility of vCDR asymmetry as a diagnostic test for glaucoma.

Methods

Study Design

The NHANES uses a complex stratified, multistage sampling design to select a nationally representative sample of noninstitutionalized U.S. civilians to participate in a series of comprehensive health-related interviews and examinations every 2 years. Recruitment and testing are performed in counties across the United States, 15 of which are visited each year. The NHANES purposely oversamples persons aged 60 years and older, Hispanics, and African Americans to acquire more detailed health-related information about the aging population and these racial minority groups. The NHANES protocols were approved by the National Center for Health Statistics research ethics review board, and informed consent was obtained from all participants. The research adhered to the tenets of the Declaration of Helsinki.

Demographics

Subjects' age, sex, and race/ethnicity were collected in a demographic questionnaire. Age was categorized into decades for this analysis. The NHANES categorizes race and ethnicity into 5 categories: Mexican American, other Hispanic, non-Hispanic black, non-Hispanic white, and non-Hispanic other, or multiracial. For this analysis, race was classified as white, black, Hispanic, and other.

Retinal Photography and Vertical Cup-to-Disc Ratio Grading

In the 2005–2008 NHANES, retinal photographs were obtained from subjects aged 40 years and older unless they were unable to see light with both eyes open or had an eye infection. Two 45° nonmydriatic digital images were obtained from both eyes using a Canon CR6-45NM nonmydriatic camera (Canon, Tokyo, Japan). The first image was centered on the macula, and the second image was centered on the optic nerve. Common reasons for not completing retinal photography included insufficient time (47.2%),

physical limitations (16.8%), refusal to participate (11.4%), and eye-specific limitations (9.0%).

The images were initially graded at the University of Wisconsin Fundus Photograph Reading Center using standardized methods for assessing vCDR as a continuous numeric variable from 0.00 to 1.00. The vCDR asymmetry was calculated as the absolute value of the difference between the vCDR of the 2 eyes.

Visual Field Defects

The 2005–2008 NHANES administered frequency doubling technology (FDT) perimetry to subjects aged 40 years and older unless they were unable to see light with both eyes open or had an eye infection, as described previously.²³ Briefly, subjects underwent a 19-point supra-threshold screening test in both eyes using the N-30-5 test on the Matrix FDT perimeter (Carl Zeiss Meditec, Dublin, CA). A successful FDT test for a given eye required a subject to complete the test twice, with reliable results. Examinations were considered unreliable if either of the 2 tests on each eye had at least 2 of 3 false-positive or fixation errors, or the technician administering the test noted lack of fixation.

A subject was categorized as having a VF defect in a particular eye if at least 2 test points in the first and second tests were abnormal at the 1% level, and at least 1 of the abnormal points was the same point on both tests (2-2-1 algorithm).²³ For this analysis, subjects were categorized as having VF defects overall if they had VF defects in either eye according to the 2-2-1 algorithm. Subjects with no VF defects in 1 eye but with unreliable VF data in the other eye were deemed to have an unknown overall VF defect status and excluded from subanalyses using this variable.

Disc Defined Glaucoma

In 2012, ophthalmologists at the Wilmer Eye Institute re-read the retinal images of both eyes from 548 subjects with vCDR ≥ 0.60 in at least 1 eye, as well as 180 randomly selected subjects with vCDR < 0.60 in both eyes, with attention to features relevant to glaucoma.²⁴ In brief, disc defined glaucoma in each eye was graded as “no, possible, probable, definite, or unable to assess.” If at least 2 of 3 graders provided the same grade and the third grader was within 1 level, then that grade was assigned to the image. If at least 2 of the graders did not agree or if the third grader was off by 2 or more levels, then the image was re-read in the presence of all 3 graders to achieve consensus. Subjects were categorized as having disc defined glaucoma if they had probable or definite glaucoma in either eye. Subjects with unknown disc defined glaucoma status in both eyes or with no disc defined glaucoma in 1 eye but unknown disc defined glaucoma status in the other eye were deemed to have an unknown overall disc defined glaucoma status and excluded from subanalyses evaluating this outcome. Boland et al²⁵ previously reported that the prevalence of disc defined glaucoma in 1 or both eyes was 1.6% among the 180 randomly selected subjects with vCDR < 0.60 in both eyes compared with 31.4% among the 548 subjects with vCDR ≥ 0.60 in at least 1 eye.

Disc Plus Field Defined Glaucoma

For this analysis, an additional variable was created to define glaucoma by both anatomic optic disc appearance and functional VF loss. Eyes with disc defined glaucoma (as defined earlier) and a VF defect (as defined earlier) in the same eye were deemed to have “disc plus field defined glaucoma.” Subjects with disc plus field defined glaucoma in at least 1 eye were classified as having disc plus field defined glaucoma overall. Finally, subjects with neither disc defined glaucoma nor VF defects in either eye were defined as having no glaucoma.

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