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Oral Contraceptive Use and Prevalence of Self-Reported Glaucoma or Ocular Hypertension in the United States

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Abstract

Objective—To investigate the association between oral contraceptive (OC) use and glaucoma prevalence in the United States.

Design—Cross-sectional study.

Participants—3406 female participants, 40 years of age or older, from the 2005–2008 National Health and Nutrition Examination Survey, who reported a presence or absence of glaucoma or ocular hypertension, completed both the vision and reproductive health questionnaires and underwent eye examinations.

Methods—Multivariate regression analysis was used to assess the correlation between OC use and self-reported glaucoma or ocular hypertension (n=231 cases), controlling for potential

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confounders including age, ethnicity, systemic comorbidities such as hypertension and stroke, ocular diseases such as cataract and diabetic retinopathy, reproductive health factors including age at menopause, age at menarche, history of hormone replacement therapy and gynecological surgical history.

Main Outcome Measures—The outcome variable was self-reported glaucoma or ocular hypertension.

Results—After adjusting for confounders, those with ≥3 years of OC use had greater odds (odds ratio= 1.94, 95% confidence interval=1.22–3.07) of self-reported glaucoma or ocular hypertension. Other factors associated with higher glaucoma or ocular hypertension prevalence included older age, African American race, and later age of menarche.

Conclusion—OC use may be associated with increased risk of self-reported glaucoma or ocular hypertension.

PRECIS

3 years or longer of oral contraceptive use was associated with an increased likelihood of self-reported glaucoma or ocular hypertension in women aged 40 years or older residing in the United States.

INTRODUCTION

Glaucomatous disease is a leading cause of bilateral blindness worldwide, second only to cataract (1). Known risk factors for glaucoma include family history, African American ethnicity, and older age (1). Women are also found to be more affected by this debilitating disease compared to their male counterparts (2). Currently, the only confirmed modifiable risk factor for glaucoma is intraocular pressure (IOP), and IOP lowering has been the target of all current medical and surgical therapies. Unfortunately, therapies aimed at lowering IOP are not always successful. Furthermore, due to the lack of highly effective treatment, little evidence exists to link early detection of glaucoma and preventable blindness or visual impairment. Identification of novel glaucoma risk factors may allow for earlier and more targeted screening of susceptible populations.

Estrogen is thought to play an important role in glaucoma pathogenesis (2, 3). While it has been hypothesized that early estrogen deficiency may increase the susceptibility to glaucomatous damage, the exact mechanism of how estrogen may protect the optic nerve remains unclear (2). Estrogen receptors (ERs) are expressed in a variety of ocular tissues including retinal ganglion cells (RGCs), lens epithelial cells, corneal epithelium, ciliary body and iris stroma (4–7). Some have theorized that estrogen enhances nitric oxide signaling within the trabecular meshwork and in the retinal vasculature that supplies the optic nerve to favorably modify outflow facility and retinal autoregulation, respectively. In support of this alternative hypothesis, the relation between postmenopausal hormone use and primary open angle glaucoma (POAG) was modified by nitric oxide synthase 3 single nucleotide polymorphisms in a case control group nested within the Nurses Health Study (8). Additionally, there is evidence suggesting that estrogen has direct beneficial effects on retinal ganglion cells. One study showed that 17-beta-estradiol eye drop treatment reduced

RGC and axon loss through inhibition of ganglion cell apoptosis in a rodent model of glaucoma (9). This study also demonstrated evidence of multiple, specific biochemical events that could account for estrogen-mediated RGC protection. Finally, it has been observed that estrogen and estrogen analogs are protective against insults in a mouse retinal photoreceptor cell line, suggesting that estrogen could emerge as a useful compound for neuroprotection of retinal cells (3).

Previous clinical studies have also shown an association between relative estrogen deficiency and glaucoma. In one study, early age of menopause was associated with an increased risk of POAG, whereas later age of onset of menopause was associated with a decreased risk of POAG (10). Five-year oral contraceptive (OC) use, which alters the physiological cycling of estrogen levels in women of reproductive age, was associated with a 25% increased risk of POAG in a prospective analysis of the Nurses Health Study (NHS) cohort (11).

In this study, we aimed to assess the association of OC use and prevalence of self-reported glaucoma and/or ocular hypertension in the United States using the National Health and Nutrition Examination Survey (NHANES) (12).

METHODS

Sample and Population

Data from the 2005 to 2008 National Health and Nutrition Examination Survey (NHANES) (12), a cross-sectional series of interviews and examinations of the United States (U.S.) civilian, non-institutionalized population, were used to study the relationship between OC use and self-reported glaucoma and/or ocular hypertension.

NHANES is administered by the Centers for Disease Control (CDC) to provide U.S. health statistics of approximately 5000 persons per year. It uses a stratified multistage sampling design that requires a weighting scheme to provide optimal estimates of disease prevalence in the U.S. population. Our analysis included 3406 female participants in NHANES 2005–2008, who were 40 years of age or older, and underwent both the interview (including both eye health and reproductive health questionnaire) and examination portions of the study. There were 351 participants who were at least 40 years old that did not answer the questions regarding history of OC usage and/or self-reported history of glaucoma or ocular hypertension. These participants were excluded from analysis. As shown in Table 1 when compared with the excluded subjects, included women in this study were younger (57.4 years vs. 60.9 years, $p=0.0007$), had higher percentages of white participants ($p<0.0005$), reported overall better health ($p=0.01$), and had higher body mass index (BMI) (29 kg/m^2 vs. 28.2 kg/m^2, $p=0.04$). The percentage of participants with vertical CDR > 0.7 were not significantly different between the included and excluded participants ($p=0.89$). Included participants showed lower percentage of diabetic retinopathy ($p=0.006$), cataract surgery ($p=0.02$), FDT defects ($p=0.03$) in one or both eyes. However, this may be attributed to their significant younger age, and better general health conditions.

Measures

The primary exposure was self-reported OC use, categorized into the following three groups: denies OC use, less than three years of OC use, and three or more years of OC use. NHANES included a reproductive health questionnaire to be answered by women who were aged 12 years and older at the time of the survey. These questions were asked at the Mobile Examination Center (MEC), during the MEC Interview, using the computer-assisted personal interviewing system. Questions addressing age when first menstrual period occurred, age at last menstrual period, days since last period, history of pregnancy, number of total pregnancies, age at first live birth and a history of the following: breastfeeding, hysterectomy, bilateral oophorectomy, endometriosis or uterine fibroids, breast, uterine, or ovarian cancer, OC usage, and hormone replacement therapy use were included in the questionnaire.

The primary outcome was the presence or absence of self-reported glaucoma and/or ocular hypertension. Potential confounding variables included age, ethnicity, BMI, health-related behaviors such as smoking (current, past, or never); alcohol use (number of alcoholic drinks per day over the past year: greater than 1 drink per day, less than 1 drink per day); comorbid medical conditions such as self-reported history of hypertension, stroke; comorbid eye conditions such as a self-reported history of cataract extraction surgery and diabetic retinopathy; general health condition (self-rated as excellent or very good, fair, or poor or very poor); and reproductive health condition such as number of pregnancies, menopausal status, age at menarche, history of postmenopausal hormone use, history of hysterectomy or bilateral oophorectomy (including years since oophorectomy if answered yes), and history of breast, uterine, or ovarian malignancies.

Proportion of participants with a cup to disc ratio (CDR) greater than 0.7, as well as the proportion of participants with at least one visual field defect in either eye based on FDT abnormalities, between the “Yes glaucoma or ocular hypertension group” and the “No glaucoma or ocular hypertension group” were performed for internal validation of the self-reported glaucoma and/or ocular hypertension”. Both percentage of participants with CDR greater than 0.7, and percentage of participants with at least one FDT defect in either eye were higher in the “Yes” group compared to the “No” group (10.9% vs. 0.3%, $p<0.001$; 22.3% vs. 6.4%, $p<0.001$, respectively) Table 2.

Analysis

We compared the distribution of possible confounding variables between participants with and without self-reported glaucoma using design-adjusted Rao-Scott Pearson-type Chi square and Wald tests for categorical and continuous variables, respectively (13). We used multiple imputation, a flexible, simulation-based statistical technique that is used to deal with missing data or survey nonresponse, which arises frequently in the NHANES dataset (14). Multiple imputation was conducted using the mice (*m*ultiple *i*mputation by *c*hained *e*quations) package, version 2.22. For each multiply imputed data set, OC use was always included in each statistical model, but backwards stepwise regression was used for regressors other than OC. Backwards stepwise regression on these other potential confounders was conducted by sequentially deleting the regressor (other than OC use with

the largest estimated P-value, and continuing until all remaining other regressors yielded P<0.25). Different values for the p-value for stepwise deletion have been used in the literature, and a value of p<0.1 is frequently used (15). However, we used a relatively conservative threshold (p<0.05), which favors inclusion of predictors other than OC use. OC use regressors were included in all models and were not subject to stepwise regression. The estimated regression coefficients for OC regressors, standard errors, and hypothesis tests for these coefficients were conducted using the standard Rubin procedure (16). Sixty-four multiple imputations were used. Computations were conducted in R v. 3.1 for MacIntosh (R Foundation for Statistical Computing, Vienna, Austria, using the procedure svyglm from the R package survey for survey weighted analysis, and the package mice for multiple imputation).

RESULTS

The 2005–2008 NHANES data yielded a total of 3406 female participants, aged 40 or older, who participated in both the interview and examination portions of the study, including the reproductive health questionnaire and all answered the question regarding whether or not they had ever been informed of a diagnosis of “glaucoma or high pressure in the eyes” (referred to as history of self-reported glaucoma in the following sections) by a health professional. Of all included participants, 231 self-reported a history of glaucoma, which comprised 6.8% of the total study population. Table 2 illustrates demographic information, comorbidities, health-related behaviors, as well as ocular health conditions for those with and without self-reported glaucoma. The mean age of those with and without self-reported glaucoma was 68.5 and 57.1 years respectively (p<0.0001). As shown in Table 2, the two groups (self-reported glaucoma vs. self-reported no glaucoma) differed significantly in many ways, including ethnic composition, general health condition, history of other comorbidities, and ocular health conditions. Differences between glaucoma self-reporters and those who did not report glaucoma were accounted for in multivariable analysis.

Results from the reproductive health questionnaire are shown in Table 3. A chi square analysis showed that the percentage of participants with self-reported glaucoma or ocular hypertension differed amongst participants of the three categories of OC use (p<0.0001). Of those who reported using OCs for less than three years, 6% reported a glaucoma diagnosis, while for those who had greater than 3 years of OC use, 5% reported a glaucoma diagnosis (p<0.0001). Those who self-reported a history of hormone replacement therapy (HRT) or more precisely postmenopausal hormone (PMH) use had a greater likelihood of self-reported glaucoma versus those who did not receive any HRT (7% vs. 6%, respectively; p<0.0001). Similarly, 8% of those who had reached menopause at the time of the survey had self-reported glaucoma, and 3% of those who had not reached menopause had self-reported glaucoma (p<0.0001). Participants with or without self-reported glaucoma had a mean number of 3.7 and 3.4 pregnancies, respectively (p<0.0001, Table 3). Age at menarche was greater amongst those with self-reported glaucoma (13.3 vs. 12.8 years old, p<0.0001, Table 3). Among women who answered yes to history of hysterectomy (p=0.0001) or bilateral oophorectomy (p=0.0003), there was also a higher percentage of self-reported glaucoma when compared to those who had not undergone these gynecological surgeries. Further, the

number of years since either hysterectomy (p<0.0001) or oophorectomy (p<0.0001) also positively correlated with a greater likelihood of self-reported glaucoma.

We investigated the possible independent association between OC use and the prevalence of self-reported glaucoma and ocular hypertension, while taking into consideration the potential confounders that are known to be associated with glaucomatous disease. We performed a multivariate logistic regression analysis to control for these potential confounding variables including age, ethnicity, general health conditions, tobacco and alcohol consumption behavior, systemic and ocular comorbidities, reproductive health conditions including number of pregnancies, history of hormone replacement therapy, menopausal status, and age at menarche; and gynecological history including history of hysterectomy, bilateral oophorectomy, history of breast cancer or gynecological malignancies. We found that after adjusting for confounders, women who had 3 or more years of cumulative OCs use were significantly more likely to self-report glaucoma or ocular hypertension (Odds Ratio (OR) =1.94, Confidence Interval (CI) =1.22–3.07; p=0.007) when compared to those with no prior history of OC use.

Additionally, this regression model found older age (OR=1.08, CI=1.05–1.1, p<0.0001), African American ethnicity (OR=2.07, CI=1.41–3.06, p=0.0005), history of retinopathy (OR=2.41, CI=1.40–4.13, p=0.002) and older age at menarche (OR=1.13, CI=1.03–1.22, p=0.008) to all be significantly associated with higher odds of self-reported glaucoma (Table 4). Every addition year menarche was delayed was associated with a 13% increased risk of self-reported glaucoma and ocular hypertension.

DISCUSSION

This population-based study finds an association between OC use and self-reported glaucoma and/or ocular hypertension. We found that 3 or more years of OC use to be associated with increased odds of self-reported glaucoma (OR =1.94, CI =1.22–3.07; p=0.007) after adjusting for potential confounding variables (Table 4). Our finding is supported by results from the Nurses' Health Study reported by Pasquale et al. In that longitudinal prospective study, the researchers found an 25% increased risk of developing POAG among participants who took OC for five years or longer (MVRR=1.25; 95% CI, 1.02, 1.53; P for linear trend=0.04) (11).

Prior studies have found evidence supporting the hypothesis that estrogen plays an important protective role in the pathogenesis of glaucoma with expression in multiple ocular tissues (4–7). Estrogen is also thought to decrease the risk of glaucoma and other ocular diseases through a favorable impact on blood flow regulation (17). However, the concentration or mode of estrogen delivery that is needed to be protective in the human eye has yet to be defined. Additionally, PMH use may help reduce the risk for POAG (18). Clinical studies have shown hormone therapy supplementation to be associated with modest reduction in IOP as well as some evidence supporting a potential protective effect on RGCs (4, 19–24).

Estrogen is primarily released by the ovaries and plays an essential role in menstrual cycle regulation. The very low serum estradiol and progesterone concentration during the early

follicular phase results in an increase in the serum follicle-stimulating hormone (FSH) concentration via negative feedback (25). This subsequently leads to increased serum estradiol level, and decreased serum FSH and LH levels. Peaking of the serum estradiol concentration just before ovulation leads to a serum LH surge which then results in ovulation (26). In the mid-luteal phase of the menstrual cycle, progesterone concentration increases and results in a gradual fall in progesterone and estradiol levels. This natural cycle can be interrupted by OC use, which block ovulation by inhibiting the mid-cycle LH surge.

Among the two forms of OCs including combined estrogen-progestin, or progestin-only pills, the latter are typically prescribed for lactating women, or those who cannot take estrogen. While we did not distinguish participants based on types of OCs used, it is noteworthy that most OC us in the U.S. employs combination products of which there are several different formulations (25). The majority of combination pills are monophasic, which contain a constant level of estrogen and progesterone, whereas biphasic and triphasic OCs contain varying hormone levels. More importantly, none of the existing OCs on the market act exactly like the physiological hormones during the menstrual cycle. We therefore hypothesize that OC use significantly changes the natural daily, or even hourly, variations in hormone levels which may be important in the pathogenesis of glaucomatous diseases (26).

Our hypothesis is further supported by the fact that inclusion of history of hysterectomy, bilateral oophorectomy, years since oophorectomy (years since hysterectomy were not included due to high co-linearity with years since oophorectomy), and history of breast, uterine or ovarian cancers, in addition to demographic and reproductive health factors showed a significantly increased risk of self-reported glaucoma amongst women with 3 or more years of OC use (Table 4). Studies have shown an increased risk for overall mortality, cardiovascular disease in women who undergo bilateral oophorectomy inducing premature menopause (before age of 40) or early menopause (before age of 51). Estrogen replacement proximate to bilateral oophorectomy is thought to be particularly important for reducing premature coronary heart disease and death in this group of women (27–29). Estrogen replacement therapy is recommended for women with premature menopause or premature ovarian failure by professional organizations including the North American Menopause Society, the British Menopause Society, and the International Menopause Society (30, 31). In these women, hormones are usually also delivered at a constant dosage, different from what would have happened physiologically. Furthermore, similar to our findings, results from the Mayo clinic cohort study of oophorectomy and aging (32) found that for women who underwent oophorectomy before the age of 43 years had a significantly increased risk of glaucoma with a hazard ratio of 1.6, after controlling for multiple confounders.

Other female reproductive parameters have been found to increase risk of glaucoma. As with our study, Hulsman et al (10) found an association between open-angle glaucoma (OAG) and early menopause in the Rotterdam study. Women who experienced menopause before age 45 had increased risk (OR=2.6, CI=1.5–4.8) of OAG compared to those with later menopause. Similar findings were also reported by Lam et. al based on the Singapore Malay Eye Study where women who had menopause at earlier than 52 years old were found to be 3.5 times more likely to have glaucoma (p=0.02) when compared to women who reached menopause after 52 years of age (33). In the Blue Mountains Eye Study (BMES), the

increased odds of OAG in women with early natural menopause was not found to be statistically significant (34). Further work from the BMES reported by Lee et al. showed, in concordance with our findings, that later years of menarche (age > 13 years) and greater parity are both linked to a significantly greater OAG risk relative to those with early menarche and less parity, respectively (34).

The percentage of participants who have self-reported glaucoma or ocular hypertension in our study was about 6.8%, which appears to be higher than reported prevalence of glaucoma. This might be attributed to the fact that more participants with ocular hypertension without glaucomatous visual field changes than true glaucoma patients were included in the NHANES study. The lack of confirmation of self-reported glaucoma diagnosis was a limiting factor of NHANES that could not be addressed in this study and will require further prospective work to assess our hypotheses relating to OC use and glaucoma risk. Another potential limitation of our study was the exclusion of women with incomplete eye exams, or incompletion of their reproductive health or ophthalmic health surveys, as well as those who did not answer the question regarding a history of glaucoma. The 351 women excluded had significantly older age, higher percentage of African American ethnicity, poorer general health conditions, and higher percentage of diabetic retinopathy and history of cataract surgery when compared to the included counterparts. Inclusion of these participants should they have answered the glaucoma or reproductive questionnaire may result in changes in our outcomes. However, the number of excluded participants is relative small (10%) when compare to the study population. The mean BMI of our study population was high (Table 2), indicating a possible higher rate of metabolic syndrome than the general population. Therefore, our results, though in line with the NHS study which has a lower average BMI with all participants being health professionals, may not be widely applicable across the spectrum of BMI, which hinders extrapolation of our study results to the general population.

Based on our initial univariate analysis, 19% of all included participants with self-reported glaucoma reported three years or more of OC use, while 27.7% of all participants without glaucoma reported more than 3 years of OC use. Yet, the relationship between OC use and self-reported glaucoma was reversed after our multivariate analysis, most likely due to confounding effects. A higher percent of African Americans, women with poor or worse general health conditions, positive hypertensive or stroke history, women who have diabetic retinopathy and history of cataract surgery reported glaucoma (Table 2). Interestingly, a higher percentage of these women were found to be OC non-users. Specifically, we found 38.8% of women with “poor or worse general health condition” vs. 32.7% with “fair general health condition” or better ($p=0.001$) to be non-OC users. Women who reported a history of stroke or hypertension, also tended to report OC non use (48.1% vs 31.1%, $p=0.01$; and 37.7% vs. 27.4%, $p<0.001$ respectively) when compared to their counterparts, respectively. Additionally, women who had cataract surgery or who had reached menopause, were also found to have higher percentage of OC never-use (all $p<0.0001$). African American women also reported a higher percentage of OC non-users when compared to their non-African American counterparts, although this difference was not found to be statistically significant ($p=0.09$).

While NHANES provides a large, robust database, the small proportion of subjects with certain characteristics combined with missing data may have led to less than optimal power to achieve our study objectives. For example, in this study, we did not study the relationship between structural and functional parameters indicative of glaucomatous disease such as cup to disc ratio or FDT abnormalities, and OC use. In our dataset, there were more than 400 missing FDT tests amongst all participants included in this study, resulting in a small number of participants who have both self-reported glaucoma diagnosis and abnormal FDT findings, which limited the power of such an analysis. More importantly, the NHANES 2-2-1 algorithm for FDT N-30-5 had a previously demonstrated sensitivity of 54.8% and specificity of 91.9% in detecting subjects with glaucoma based on previous publications (35). The low sensitivity of FDT to detect glaucoma precluded it from being a possible end point. Similarly, the number of participants with vertical cup to disc ratio greater than 0.7 was also small, precluded the use of a structural optic nerve endpoint. Furthermore, due to data availability, we were not able to separate the OCs included in the study into the different subtypes by hormone composition or mode of hormone delivery (monophasic vs. triphasic). A larger study that allows detailed separation as described above can better elucidate the role of female hormones, especially estrogen. Finally, our study uses cross-sectional information limited to a 4-year period.

In summary, we found that after adjusting for numerous potential confounding variables including age, gender, systemic comorbidities, ocular disease and reproductive factors including gynecological surgical history and PMH use, ≥ 3 year OC use was significantly associated with increased odds of self-reporting glaucoma and/or ocular hypertension in women who were 40 years or older in this nationally representative sample of the U.S. population. These data further confirm that female reproductive health has an impact on glaucoma risk and carefully performed studies that assess OC usage or more precisely alterations in endogenous estrogen level in women with and without glaucoma are indicated.

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Table 1

Comparison of Demographic, General and Ocular Health Factor for Included and Excluded Participants

	Included* **(N=3,406)**	**Excluded**** **(N=351)**	**P values**
Age (years)±SEM	57.4±0.45	60.9±1.06	***0.0007***
Ethnicity			***0.0005***
Mexican	5.2%	5.3%	
Other Hispanic	3.1%	5.1%	
African American	10.8%	14.0%	
White	76.1%	65.8%	
Other/Multiracial	4.7%	9.8%	
General Health Condition			***0.01***
Good	41.3%	26.4%	
Fair	38.3%	34.6%	
Poor	20.5%	39.1%	
Body Mass Index (kg/m^2)±SEM	29.0±0.17	28.2±0.4	***0.04***
Hypertension-Yes	43.8%	37.9%	0.11
hypertension-No	56.2%	62.1%	
Stroke-Yes	5.1%	7.2%	0.1 5
Stroke-No	94.9%	92.8%	
Ocular Health Condition			
Retinopathy-Yes	2.6%	5.8%	***0.006***
Retinopathy-No	97.4%	94.2%	
Cataract Surgery-Yes	12.8%	18.0%	***0.0 2***
Cataract Surgery-No	87.2%	82.0%	
Any FDT Defect (one or both eye)-Yes	6.9%	13.8%	***0.03***
Any FDT Defect (one or both eye)-No	93.1%	86.2%	
Vertical CDR ≥0.7	0.78%	0.86%	0.89
Vertical CDR <0.7	99.2%	99.1%	

*Women Age ≥40 who answered both the oral contraceptive (OC) use AND glaucoma questions

**Women Age ≥40 who did not respond to whether they have history of OC use question OR who did not respond to whether or not they have glaucoma question. Numbers in bold and italic style denote statistical significance ($p<0.05$). For results presented as proportion, chi square test was performed. For continuous data, student-t test was performed. Discrepancies in total number of participants in certain categories are due to missing data. SEM=standard error for means. FDT= Frequency doubling perimetry. FDT defect is defined as any abnormal FDT findings in one eye or both. CDR= cup-disc ratio.

Table 2

Distribution of Demographic, General and Ocular Health Factor for Females > 40yrs Who Completed NHANES Vision and Reproductive Health Questionnaire and Underwent Eye Exams

	Self-Reported Yes Glaucoma* (n=231)	**Self-Reported No Glaucoma* (n=3175)**	**P value**
Age (years) ± SEM	68.5±1.11	57.1±0.42	***<0.0001***
Ethnicity			***0.049***
Mexican	25 (10.8%)	508 (16%)	
Other Hispanic	20 (8.7%)	235 (7.4%)	
African American	68 (29.4%)	685 (21.6%)	
White	111 (48.1%)	1626 (51.2%)	
Other/Multiracial	7 (3.0%)	121 (3.8%)	
General Health Condition			***<0.0001***
Good	57 (22%)	957 (20.5%)	
Fair	59 (25.5%)	1154 (36.3%)	
Poor	93 (40.3%)	811 (25.5%)	
Mean Body Mass Index (kg/m^2) ± SEM	28.6±0.41	29±0.17	***<0.0001***
Hypertension-Yes	150 (64.9%)	1499 (47.2%)	***0.003***
Hypertension-No	80 (34.6)	1669 (52.6%)	
Stroke-Yes	21 (9.1%)	187 (5.9%)	***0.026***
Stroke-No	209 (90.5%)	2979 (93.8%)	
Ocular Health Condition			
Retinopathy-Yes	29 (12.6%)	99(3.1%)	***<0.0001***
Retinopathy-No	200 (86.6%)	3066 (96.6%)	
Cataract Surgery-Yes	88 (38.2%)	457 (14.4%)	***<0.0001***
Cataract Surgery-No	143 (61.9%)	2718 (85.6%)	
Any FDT Defect (one or both eye)-Yes	50 (21.6%)	233 (7.3%)	***<0.0001***
Any FDT Defect (one or both eye)-No	114 (49.4%)	2259 (7.1%)	
Vertical CDR ≥ 0.7	25 (10.8%)	9 (0.3%)	***<0.0001***
Vertical CDR <0.7	206 (89.2%)	3166 (99.7%)	

Numbers in bold and italic style denote statistical significance (p<0.05). For proportional data, results presented as proportion, chi square test was performed. For continuous data, student-t test was performed.

*Self-reported Glaucoma represents self-reported glaucoma and/or ocular hypertension. Discrepancies in total number of participants in certain categories are due to missing data. SEM= standard error for means. FDT= Frequency doubling perimetry. FDT defect is defined as any abnormal FDT findings in one eye or both. CDR= cup-disc ratio.

Table 3

Distribution of Reproductive Health Factor and History of Gynecological Surgeries/Malignancy for Females > 40yrs Who Completed NHANES Vision and Reproductive Health Questionnaire and Underwent Eye Exams

Reproductive Health Condition	Self-Reported Yes Glaucoma** (n=231)	Self-Reported No Glaucoma** (n=3175)	P value
Oral Contraceptive (OC) Use			***<0.0001***
Never	109 (47.2%)	1111 (35%)	
OC <3 years	52 (22.5%)	876 (27.6%)	
OC >3 years	44 (19.0%)	881 (27.7%)	
Replacement Hormone-Yes	70 (30.3%)	958 (30.2%)	***<0.0001***
Replacement Hormone-No	134 (58.0%)	1938 (61.0%)	
Menopause-Yes	193 (83.5%)	2116 (66.6%)	***<0.0001***
Menopause-No	38 (16.5%)	1059 (33.4%)	
Number of Pregnancy			***<0.0001****
Mean ± SEM	3.7±0.1	3.4±0.2	
Age at Menarche (years)			***<0.0001****
Mean (years) ± SEM	13.3±0.05	12.8±0.13	
Hysterectomy-Yes	98 (42.4%)	982 (30.9%)	***0.0001***
Hysterectomy-NO	131 (56.7%)	2189 (68.9%)	
Years since Hysterectomy			***<0.0001****
Mean (years) ± SEM	27.1±0.58	20.4±1.57	
Bilateral Oophorectomy-Yes	55 (23.8%)	508 (16.0%)	***0.0003***
Bilateral Oophorectomy-No	173 (74.9%)	2634 (83.0%)	
Years since Oophorectomy			***<0.0001****
Mean (years)± SEM	26.6±0.86	18.6±1.33	***0.0003***
Breast, Uterine or Ovarian Cancer-Yes	22 (9.5%)	188 (5.9%)	0.064
Breast, Uterine or Ovarian Cancer-No	209 (90.5%)	2987 (94.1%)	

Numbers in bold and italic style denote statistical significance ($p<0.05$). For proportional data, results presented as proportion, chi square test was performed. For continuous data, student-t test was performed.

* denotes p values calculated while factors were calculated as continuous.

** Self-reported Glaucoma represents self-reported glaucoma and/or ocular hypertension. Discrepancies in total number of participants in certain categories are due to missing data. SEM= standard error for means.

Table 4

Multivariate Logistic Regressions Analysis of Associations between Three Years or Longer Oral Contraceptive Use and Self-Reported Glaucoma and/or Ocular Hypertension Adjusting for Demographic, General, Ocular Comorbidities, Reproductive Health and Gynecological Cancer/Surgery Factors

	Odds Ratio	95% Confidence Interval	P
Oral Contraceptive (OC) Use (Reference= Never use)			
OC <3 years use	1.56	0.88 – 2.78	0.136
OC >=3 years use	**1.94**	1.22–3.07	***0.006***
Age	**1.08**	1.05–1.1	***<0.0001***
Ethnicity (Reference= White)			
Mexican	1.00	0.57–1.74	0.99
Other Hispanic	1.45	0.78–2.69	0.25
African American	2.07	1.41–3.06	***0.0005***
Other	1.08	0.43–2.66	0.88
General Health Condition (Reference = Good)			
Fair	0.81	0.49–1.33	0.40
Poor	1.48	0.93–2.34	0.10
Lifestyle Behavior (Reference=Never use)			
Smoking: Current	1.19	0.81–1.78	0.38
Smoking: Past	0.89	0.49–1.33	0.72
Alcohol: <1 drink per day	0.91	0.62–1.35	0.65
Alcohol: >1 drink per day	0.51	0.31–0.86	***0.01***
Other Comorbidity			
Body Mass Index	0.99	0.97–1.02	0.52
History of Hypertension	0.81	0.51–1.27	0.36
History of Stroke	1.00	0.45–2.24	1.00
Ocular History			
History of Diabetic Retinopathy	2.41	1.40–4.13	***0.002***
History of Cataract Surgery	1.42	0.85–2.38	0.19
Reproductive Health Condition			
Number of Pregnancy	0.98	0.91–1.07	0.70
Hormone Replacement Therapy	0.75	0.55–1.04	0.08
Menopause (Yes/No)	0.98	0.50–1.90	0.94
Age at Menarche	1.13	1.03–1.22	***0.007***
Hysterectomy (Yes/No)	1.08	0.67–1.73	0.76
Bilateral Oophorectomy (Yes/No)	1.19	0.74–1.92	0.47
Years since Bilateral Oophorectomy	1.00	0.98–1.03	0.76
History of Breast/Uterine /Ovarian Cancer	1.20	0.67–2.14	0.54

Numbers in bold and italic style denote the association is statistically significant ($p<0.05$). For oral contraceptive use, default comparison was no history of OCP use; for ethnicity, default comparison was Caucasian; for general health condition, default comparison was good. For smoking or alcohol consumption, default comparison was never use.