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Racial Differences in the Effects of Hormone Therapy on Incident Open-Angle Glaucoma in a Randomized Trial

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Abstract

Purpose: We conducted a secondary analysis of a randomized, placebo-controlled trial to test if hormone therapy (HT) altered the risk of open-angle glaucoma (OAG), and if the risk reduction varied by race.

Design: Secondary analysis of randomized controlled trial data

Methods: We linked Medicare claims data to 25,535 women in the Women's Health Initiative. Women without a uterus were randomized to receive either oral conjugated equine estrogens (CEE 0.625mg/day) or placebo, and women with a uterus received oral CEE and medroxyprogesterone acetate (CEE 0.625mg/day+MPA 2.5mg/day) or placebo. We used Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence interval.

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Results: After excluding women with prevalent glaucoma or without claims for eye-care provider visits, the final analysis included 8,102 women (mean age=68.5±4.8 years). The OAG incidence was 7.6% (mean follow-up=11.5±5.2 years; mean HT duration=4.4±2.3 years). Increased age (p-trend=0.01) and African-American race (HR=2.69, 95%CI=2.13 to 3.42; Caucasian as a reference) were significant risk factors for incident OAG. We found no overall benefit of HT in reducing incident OAG (HR=1.01, 95%CI=0.79–1.29 in the CEE trial, and HR=1.05, 95%CI=0.85–1.29 in the CEE+MPA trial). However, race modified the relationship between CEE use and OAG risk (p-interaction=0.01), and risk was reduced in African-American women treated with CEE (HR=0.49, 95%CI=0.27–0.88), compared to placebo. Race did not modify the relation between CEE+MPA use and OAG risk (p-interaction=0.68).

Conclusions: Analysis suggests that HT containing estrogen, but not a combination of estrogen and progesterone, reduces the risk of incident OAG among African-American women. Further investigation is needed.

INTRODUCTION

Although a recent meta-analysis[1] suggested that men have a 36% greater risk of primary open angle glaucoma (POAG) than women, women comprise the majority of POAG cases in the United States, in part due to their longer lifespan.[1–3] POAG affects 1.44 million U.S. women, and with the rapid growth of the aging population it is projected to affect 3.66 million by 2050.[3] Additionally, gender disparities in POAG treatment may further increase the risk for visual impairment and blindness in older women. In certain regions, women have less access to eye care, and even in a developed nation, such as the U.S., women are 24% less likely to be treated for glaucoma than men.[2,4] Thus, it is important from a public health perspective to direct attention toward glaucoma screening and prevention in women.

Several lines of evidence indicate that menopause and sex steroid hormones influence the risk of POAG in women.[2,5] First, in a Mayo Clinic study of 1044 women, early menopause resulting from bilateral oophorectomy before age 43 was associated with a 1.6 increase in risk for POAG.[6] Second, intraocular pressure (IOP), the major and only proven modifiable risk factor for glaucoma, is affected by reproductive stage and sex steroid hormones. IOP is significantly higher in postmenopausal women compared to age-matched premenopausal women, with a difference of 1.5–2 mmHg.[7,8] Third, randomized trials and observational studies suggest that hormone therapy (HT) decreases IOP in postmenopausal women. In small randomized trials and observation studies, HT was associated with a 1–2 mmHg decrease following hormone therapy (HT) in postmenopausal women.[7–17] A post-hoc analysis of the Women's Health Initiative Sight Exam (WHISE), an ancillary study of a large randomized controlled trial of HT, treatment with estrogen alone, but not estrogen plus progestin, was associated with a small but significant decline in IOP (0.5 mmHg) in postmenopausal women, aged 65 years or older (n = 4347).[18] Similarly, a retrospective observational study using claims data from 152,163 enrollees, aged 50 years and older, showed that for each additional month of estrogen use, but not for each additional month of combination estrogen and progestin use, there was an associated 0.4% reduced risk for POAG over a 5-year period.[19]

The aim of this study was to determine the effects of HT on the incidence of OAG in a large, randomized trial with long-term follow-up. To achieve these aims, we utilized a Medicare-linked database from the WHI hormone trial (n = 27,347) with a 12-year follow-up period, making this the largest interventional study to date on this topic. In this study, we examined the effects of estrogen alone and estrogen plus progestin therapy on OAG risk. Furthermore, we tested whether the HT effects differed by age and race. Specifically, data from the WHI show that age is a strong modifier of the effects of HT on health outcomes, such as dementia and cardiovascular disease.[20,21] However, while the effect modification of age has been investigated, it is not known if the effect of HT differs by race. Compared to European-derived counterparts, African-derived populations not only have a higher prevalence and incidence of OAG,[1–3] but may also develop the condition a decade or more earlier.[22] In addition, African and African American women experience menopause at least 6–12 months sooner compared with women of European descent.[23] Given the fundamental racial differences in the risk profiles, it is therefore conceivable that the magnitude of HT effects on OAG might also vary by race.

METHODS

Data sources:

The WHI enrolled 161,808 women 50 to 79 years of age, nationwide, between 1993 and 1998 in a set of randomized clinical trials and an observational study, with ongoing longitudinal follow-up. Data from women enrolled in the WHI were linked to Medicare enrollment and utilization data from the Centers for Medicare and Medicaid Services (CMS) by social security number, birth or death date (or partial date), or zip code. CMS files used included the Medicare Provider and Analysis Review (MedPAR) file, which includes information for inpatient hospitalizations; carrier files containing information on physician charges, outpatient files containing billing information from outpatient providers, and the Denominator and Beneficiary Summary Files, which contain information about enrollment in a Medicare health maintenance organization (HMO), and information regarding coverage during the study period. More information about the Medicare files can be obtained from the Research Data Assistance Center (http://www.resdac.orq/cms-data).

Design of the WHI Hormone Trial—The WHI hormone trial was a randomized, double-blind, placebo-controlled trial designed to test the effects of HT on incident coronary heart disease and invasive breast cancer.[24] Between 1993–1998, 27,347 postmenopausal women aged 50 to 79 years were recruited at 40 U.S. clinical centers. The WHI trial was conducted in accordance with Health Insurance Portability and Accountability Act regulations adhered to the tenets of the Declaration of Helsinki and was registered at clinicaltrials.gov (identifier is NCT00000611). Randomized treatment assignment was performed in the WHI hormone trial.[24] A total of 10,739 women who had previously undergone hysterectomy were randomized to receive either oral conjugated equine estrogens (CEE, 0.625 mg/day) or placebo; 16,608 women with a uterus were randomized to receive oral conjugated equine estrogens and medroxyprogesterone acetate (CEE 0.625 mg/day + MPA 2.5 mg/day) or placebo. Of note, women with a uterus received progestin in combination with estrogen, a practice known to prevent endometrial cancer.

Analysis of the effect of HT on incident OAG—The Institutional Review Board at the University of Illinois at Chicago waived the need for approval of a secondary analysis of this de-identified dataset.

Sample Selection—We utilized a Medicare-linked database from 25,535 women in the WHI Hormone Trial (1993 through 2014) and used a 4-year look-back period as an optimal approach to distinguish incident from non-incident cases of OAG in claims data.[25] Specifically, Stein et al. suggested that using look-back periods of 3–5 years yielded more accurate estimate of disease incidence.[25] In this analysis, for women in Medicare at WHI enrollment, the look-back began 4 years earlier. For women who became Medicare-eligible during follow-up, and while the HT intervention was still continuing, the look-back began at the time they enrolled in Medicare. Participants were excluded if they had not been seen by an eye care provider during the 4-year look-back period. Participants were included in the analysis if they met the following criteria:

1. Were enrolled in fee-for-service Medicare Part B at the time of randomization into the WHI hormone trial, or became eligible for and enrolled in Medicare Part B during the hormone trial.
2. Were continuously enrolled in fee-for-service Medicare Part B for >4 years (allowing a 4-year look-back period to exclude prevalent cases).
3. Made ≥ 1 visits to an eye-care provider (ophthalmologist or optometrist) based on documentation of ≥.1 International Classification of Diseases, Ninth Revision-Clinical Modification (ICD-9-CM) code for an eye-related diagnosis (360–379.9), or ≥1 Current Procedural Terminology (CPT) code for any eye-related visits, or diagnostic or therapeutic procedures (65091–68899 or 92002–92499).

OAG case ascertainment—Our analysis focused on primary OAG (ICD-9-CM 365.11) and excluded low-tension OAG (ICD-9-CM 365.12) or other forms of OAG, as previous research suggested the benefit of HT on high-tension OAG. Specifically, in a secondary analysis within the (Nurses' Health Study) NHS cohort, where detailed information on IOP among POAG cases was available, compared with never having used HT, current use of HT was associated with a reduced risk of POAG, characterized by IOP >21 mmHg before visual loss.[26] In contrast, no such association was demonstrated for POAG overall, when including both high-tension and POAG with IOP <21 mmHg subtypes. Lastly, in a candidate gene association study within the NHS,[27] four of five polymorphisms that tag the Nitric Oxide Synthase 3 (NOS3) gene showed significant interactions with HT use in relation to high-tension POAG subtype. By including only ICD-9-CM 365.11 without low-tension OAG (ICD-9-CM 365.12), as in the large healthcare claim by Newman-Casey et al.,[19] we believed that our outcome closely represented high-tension POAG.

The diagnosis of any OAG was identified by ICD-9-CM codes 365.1, 365.10, 365.11, 365.12, and 365.15. Participants with pre-existing OAG (≥ 1 diagnosis during a 4-year look-back period) were excluded. The main outcome was incident high-tension OAG (ICD-9-CM of 365.11) defined by: a) no diagnosis of any OAG during the 4-year look-back period and

b) a diagnosis of ICD-9-CM of 365.11 after the 4-year look-back period. Billing codes have been shown to be >90% accurate in identifying patients with OAG, as confirmed by chart review.[28] From this point on, our main outcome, high-tension OAG will be referred to as OAG.

Statistical Analysis—As a secondary data analysis of a clinical trial, we determined if demographic and clinical characteristics were statistically significantly different in the treatment vs. placebo groups in both the CEE and CEE/MPA arms of the subcohort that met our inclusion criteria. Chi-squared tests were used for categorical variables, whereas Wilcoxon Rank-Sum tests or t-tests were used for continuous variables. We then examined incident OAG by baseline characteristics and calculated age-adjusted p-values for the associations using logistic regression. Using time-to-event methods based on the intent-to-treat principle, we compared the incidence of OAG among the women during the periods of active intervention (through July 7, 2002 in the CEE/MPA trial and through February 29, 2004 in the CEE-only trial) as well as throughout the 12-year follow-up (from randomization to December 31, 2014, the last date for which Medicare data were available). Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for OAG. All models included strata for age group and randomization assignment in a concurrent intervention trial of a low-fat diet, high in fruits, vegetables, and grains.[29] During the intervention periods, event times were censored at the date of death, end date of the intervention, or date when the participant was no longer enrolled in fee-for-service Medicare Part B, whichever occurred first. For the analyses of cumulative follow-up, censoring was at the date of death, date no longer enrolled in fee-for-service Medicare Part B, or December 31, 2014, whichever occurred first. Several known risk factors for OAG were tested as potential confounders: race, age at menopause, diabetes, hypertension, alcohol consumption, cigarette smoking, and body mass index (BMI). Of note, bilateral oophorectomy was not a requirement for participation in the CEE hormone trial. A previous report shows 39.5% of the CEE assigned group with bilateral oophorectomy and 42.0% of the placebo group with bilateral oophorectomy. These percentages were similar in this study - 37.1% in the active CEE group and 41.9% in the placebo group.[20] We evaluated the importance of these covariates by comparing results from models that included the covariates to models that included only HT assignment. There were no important differences, and therefore we report the HRs for the overall results without additional adjustment. In pre-specified subgroup analyses, we tested modification of the effect of HT by age and race by including the variable and an interaction term in the model. We present HRs and 95% CIs for the subgroups defined by these factors and p-values for interactions.

In addition, we conducted additional analyses to explore the impact of lack of adherence to study medications. Non-adherence was defined as any of the following: discontinued study medications or below 80% compliance based on pill counts (active arm) or began using postmenopausal hormones (placebo arm).[24] For the adherence analysis, we defined three distinct time periods during the cumulative follow-up:

1. Time during which the participant was adherent to the intervention, ending at the point she became non-adherent, was no longer in follow-up, or the end of the intervention (whichever was first).

2. Time during which the participant was non-adherent (if applicable), defined from first non-adherence to the time at which the participant was no longer in follow-up or to the end of intervention period (whichever was first).

3. Post-intervention period (for women who were still in follow-up at this time) to December 31, 2014.

We included this variable as a time-dependent stratum variable, allowing the baseline hazard to vary within strata. The variable of interest is still the intent-to-treat hormone trial assignment, but including the stratum variable adjusts for the different time periods and where the incident OAG event occurs.

Power calculation for subgroup analyses—The power analysis was based on the following assumptions:

1. The sample sizes of 8,102 women: 3,510 in the CEE trial and 4,592 in the CEE +MPA trial.

2. Annual incidence rate of OAG in the placebo arms: 0.65% in all women, 0.57% in Caucasians, and 1.92% in African Americans.

3. A power of 0.80 and two-sided alpha level of 0.05.

4. The effect size of 30% risk reduction or higher (HR of 0.7 or lower).

In the CEE trial, the study had the statistical power to detect a significant risk reduction of 30%, 40%, and 50% in the overall group, the subgroup for Caucasian women, and the subgroup of African American women, respectively. In the CEE+MPA trial, the study had the statistical power to detect a significant risk reduction of 30%, 30%, and 63% in the overall group, the subgroup for Caucasian women, and the subgroup of African-American women, respectively. All statistical analyses were conducted using SAS software version 9.4 and statistical tests were considered to be significant at p=0.05.

RESULTS

Study sample

The final analysis included 8,102 women. Of 27,347 women in the WHI hormone trial, we excluded 1,813 women who had no link to Medicare data through 12/31/2014, 4,294 women who had no fee-for-service Medicare Part B coverage, 4,126 women for whom there were no 4-year look-back data, 2,074 women who had not visited eye-care providers, and 6,276 women who became eligible for Medicare after the hormone trials ended. Figure 1 shows the flow chart of inclusion in the study and the number of women who received glaucoma diagnoses during follow-up. Women included in the analysis were older (68.5 ± 4.8 years) than women not included (61.3 ± 7.0 years; $p < 0.001$), reflecting the criterion that women had at least four years of continuous enrollment in Medicare. Compared to excluded women, included women were more likely to be Caucasian (88.7% versus 77.1%, $p < 0.001$) or having been treated for hypertension (29.6% versus 23.0%, $p < 0.001$), less likely to be current smokers (7.1% versus 11.9%, $p < 0.001$), and less likely to be obese (BMI ≥30) (35.6% versus 39.3%, $p < 0.001$). Table 1 shows the baseline characteristics of women

included in the final analysis. There were 3,510 women in the CEE trial and 4,592 in the CEE/MPA trial. Age at screening, age at menopause, race, randomization for the concurrent dietary intervention, treated diabetes, history of hypertension, alcohol intake, smoking status, and BMI were similar across the active and placebo arms of the trials (all, P > 0.2).

Primary endpoint OAG Incidence Outcomes

The incidence of OAG was 3.3% during the intervention phase (mean ±standard deviation (SD) of 4.4 ± 2.3 years) and 5.0% during the cumulative follow-up (mean ± SD of 11.5 ± 5.2 years). The baseline characteristics that were associated with incident glaucoma after adjusting for age included older age at HT randomization, African-American race, and non-smoker status (Table 2). Increased age (p-trend = 0.01) and African-American race (HR 2.69, 95% CI = 2.13 to 3.42; Caucasian as a reference) were significant risk factors for incident OAG.

During the intervention period, the incidence of OAG did not differ significantly by HT treatment. Figure 2 shows the cumulative numbers, annualized incidence of OAG, and HRs across the treatment group for the cumulative follow-up. Similarly, during the cumulative follow-up, the incidence of OAG did not differ by HT treatment for the CEE trial (HR 1.01, 95%CI = 0.79 to 1.29, mean ±SD = 11.1 ±5.3 years) or the CEE/MPA trial (HR 1.05, 95%CI = 0.85 to 1.29, mean ±SD = 11.9 ±5.2 years). In analyses stratified by age at initiation, no effect of HT on the incidence of OAG was evident. However, in analyses stratified by race, a significant risk reduction was shown in the follow-up period among African-American women treated with CEE (HR 0.49, 95% CI = 0.27 to 0.88, p-interaction = 0.01), but not with CEE/MPA (HR 0.82, 95%CI = 0.40 to 1.68, p-interaction = 0.68), compared to placebo.

In adherence analysis, the risk estimates were similar, without the adherence stratum variable. There was no overall benefit of HT on incident OAG in the CEE trial (HR 1.03, 95%CI = 0.80 to 1.32) or in the CEE/MPA trial (HR 1.04, 95%CI = 0.84 to 1.28) overall and when stratified by age at initiation. When stratified by race, a significant risk reduction was found in the follow-up period among African-American women treated with CEE (HR 0.52, 95% CI = 0.28 to 0.94, p-interaction = 0.01), but not with CEE/MPA (HR 0.81, 95%CI = 0.39 to 1.67, p-interaction = 0.68), compared to placebo.

DISCUSSION

Consistent with previous reports, our study revealed that the incidence of OAG increases with age, as well as findings showing that the risk is higher in African-American women compared to Caucasian women. For the primary focus on HT, we found no overall effect of CEE or CEE/MPA on the incidence of OAG. Race, but not age at HT initiation, significantly modified the risk. Specifically, CEE alone, not CEE/MPA, decreased the risk of incident OAG by half among African-American women during the 12-year follow up. These findings are notable because African-American women showed the highest overall annual incidence of OAG (1.56%) compared to approximately 0.60% in women of other ethnicities (based on all women in the active and placebo groups). This secondary analysis is unique in that the WHI Hormone Trial provided an opportunity to examine the effect of CEE and CEE/MPA

on the incidence of OAG in a large randomized placebo controlled trial during active treatment and over a 12-year longitudinal follow-up. The large sample size provided sufficient power to examine effect modification by race. In addition, the 12-year follow up is the longest among randomized trials published to date. These findings suggest that hysterectomized African-American women may derive the greatest benefit from estrogen alone HT on reducing incident POAG.

The effect of estrogen alone versus estrogen plus progestin has been studied in several observational studies, yielding inconsistent findings.[19,26,30,31] In observational studies, the "healthy user bias," the tendency for women who were receiving HT to be healthier and better educated than women not receiving HT, can influence results. Analysis of a large claims database of 152,163 enrollees aged over 50 years showed that an additional month of estrogen HT alone, not the combination of estrogen and progestin HT, was associated with a 0.4% reduced risk for POAG (HR = 0.996).[19] Compared to that claims database analysis,[19] as expected, our annual incidence of OAG was higher (0.66% vs. 0.3%). This is likely because our study included older women (Medicare eligible 65+ in the present study vs. 50+ in the claims database) and had a longer follow-up duration (12-year follow up vs. 6-year follow up). Concerning race, African-American race was consistently found to be a significant risk factor for developing *de novo* OAG, compared to Caucasian (2.67-time in the present study vs. 1.72-time in the claim database). Of note, there was 9% missing information on race and the effect modification by race was analyzed in the claims database. Overall, it is not feasible to directly compare the outcomes reported in the present study vs. those reported in the claims database. Specifically, we used an intent-to-treat analysis, in which we followed women long after the intervention and after hormone usage should have stopped for nearly all women. In contrast, the claims database results were based on HT use as a time-dependent covariate. In addition, other epidemiologic studies have investigated the protective effects of HT on OAG with mixed results. Two cross-sectional population-based studies, the Rotterdam Study (3,078)[31] and the Blue Mountain Eye Study (n = 2,072)[30] found no significant association between HT and the risk for OAG, but they did not differentiate between estrogen alone versus estrogen plus progestin. The NHS[26] with a 22-year follow-up (n = 56,703) suggested no overall benefit of HT use on incident OAG.[26] However, significant risk reduction was only found in women with ocular hypertension; HT containing both estrogen and progestin, not estrogen alone, was associated with a statistically significantly 42% reduction in the risk for OAG. In addition to the healthy user bias, differences in study design, sample size, and follow-up period can influence results of observational studies. Generally, most studies may not have been powered to detect a small risk reduction as demonstrated in the claims database. However, our results generated from a randomized trial involving of 8,102 women over a 12-year follow-up in part support the results of these observational studies in that our analyses suggested no overall effect of HT on incident glaucoma, but we found a moderate risk reduction for OAG among African-American CEE users.

Female sex hormones have been linked to the pathophysiology of glaucoma.[2,5] Particularly, a shorter duration of estrogen exposure is associated with an increased risk of developing glaucoma, whereas a longer exposure appears to be protective. For instance, surrogates for a lifetime decrease in estrogen exposure were measured in several population-based studies,

which showed that late menarche[30] and early menopause (natural[31] or surgical[6]) were associated with an increased likelihood of OAG. HT use in postmenopausal women extends the duration of female sex hormone exposure, and may mitigate the risk. In the present study, age at menopause was not a significant risk factor in the overall model or the model with race and CEE interaction. While the reason is unclear, it is possible that the relationship between incident OAG and age at menopause might be different for women who have reached age 65. Furthermore, although a significant percentage of African American women (55%) entered menopause before 45 in the CEE trial (vs. 41% Caucasians, $p < 0.01$), including age at menopause in the final model did not change the HRs for CEE vs. placebo. Hence, age at menopause was not a confounder in these analyses.

Estrogens have protective effects against OAG. Particularly, estrogen can influence IOP by multiple mechanisms; it lowers IOP by reducing aqueous humor production, improving outflow facility, and reducing venous pressure through estrogen receptors in the ciliary epithelium, trabecular meshwork, and blood vessels.[9] Interventional and observational studies have shown that HT significantly reduces IOP by 0.5 to 2 mmHg.[7,8,10–13,16–18,32] Furthermore, human[15,33] and animal studies[15,34,35] have shown that estrogen can further protect the optic nerve by preserving ganglion cells and improving blood flow through receptors in the retinal ganglion cells and blood vessels.[9] For instance, an observational study suggested that postmenopausal women using HT had preserved retinal nerve fiber thickness[15] and enhanced blood flow[33] compared with controls.

Our analysis suggests racial differences in the incidence of OAG and the effect of HT on incident OAG in African Americans—we found that estrogen alone significantly decreased the risk of OAG among African-American women compared to placebo. While a biological mechanism for the inverse relation between CEE use and OAG among African Americans is unknown, we hypothesize that it is related to racial differences in endothelial dysfunction, [36,37] and the neuroprotective effects of estrogens through the NOS 3 pathway.[38]Specifically, endothelial dysfunction has been demonstrated in patients with POAG, as evidenced by impaired flow mediated vasodilation[39] and marked nailfold capillary morphological abnormalities.[40] These findings imply abnormal nitric oxide (NO) signaling, which could be improved by estrogens—Kang et al. found that HT use modified the relation between NOS3 genotypes and high-tension OAG in a large cohort of predominately Caucasian postmenopausal women.[27] Compared to Caucasians, African Americans inherently have attenuated endothelial function, which might explain their predisposition to endothelium-function disorders, such as hypertension, diabetes and POAG.[37] For instance, young healthy African-Americans, compared to age-matched Caucasians exhibit a sign of endothelial impairment, as demonstrated by attenuated cutaneous microvascular function in response to local heating.[36] In addition, based on electrochemical experiments, African American endothelial cells exhibited a decrease in NO bioavailability, compared to endothelial cells from Caucasians.[37] Given the racial differences in endothelial function and NO signaling, women of African descents may benefit from estrogen-related NOS 3 microvascular rescue that translates into the greater risk reduction of OAG, compared to Caucasians observed in this cohort.

Strengths and limitations

Conducted in the context of a randomized, placebo controlled trial for HT, this investigation offered many advantages, including control for the healthy user bias, documentation of the exact type, dosage, duration and adherence to HT; and a rich data set on associated factors that may influence the development of OAG. The Medicare-linked database allowed for long-term monitoring of OAG incidence. Importantly, even though the WHI trials were not originally designed to assess OAG as an outcome, the final analysis had well-balanced clinical characteristics between the active and placebo arms. Lastly, adherence to HT was taken into account in the ITT analyses.

Despite the many strengths, this study has some limitations. First, based on stringent inclusion and exclusion criteria, a significant number of WHI participants were not included in the final analysis, and the included women differed from excluded women on age at screening, race, hypertension treatment, and smoking status. Nevertheless, the clinical characteristics of participants in the active and placebo arms were similar. Second, given the nature of the study, which focused only on incident cases, we included a small number of cases. This especially highlights the importance of having a large sample size with long-term follow up. Specifically, we were able to demonstrate a significant risk reduction in African-American women during the cumulative follow-up of 11.7 years, but not during the intervention period of 5.5 years, despite that period having a similar magnitude of difference. Furthermore, with a mean age of 65.8 years and a mean follow-up of 11.5 years, mortality is a competing risk factor in developing OAG and other age-related conditions.

Third, our main outcome relied on ICD-9 coding, which could potentially be prone to selection bias and misclassification. Specifically, the Medicare data relies on ICD coding of diagnoses, and HCPCS/CPT codes to define conditions and procedures. The ICD-9 codes for glaucoma were included in a range of ICD codes that define a visit to an eye care provider, so by definition, all glaucoma cases had seen an eye care provider. While the lack of eye care provider claims did not mean that the woman did not have glaucoma, it was not possible to identify these women with the Medicare billing data. The randomization however remained balanced on race, even with the exclusion of women without an eye care provider visit. Comparing the incidence rates, our annual incidence rate is in line with that reported in other observational and population-based studies; as expected, we found a high incidence of OAG in women aged 65 years or older. Based on a population-based study in Australia (the Visual Impairment Project), there is a sharp increase in incident OAG as a function of age. Specifically, the 5-year incidence of possible, probable, and definite OAG increases from 0.5% of participants aged 40 to 49 years to 11% of participants aged 80 years and older.[41] In our study, the annual incidence rates in the placebo arm (averaged age of 68 years) was 0.57% in Caucasians (vs. 2.3% in women aged 70 years based on a 5-year incidence of probable and definite OAG in the Rotterdam Study),[42] and was 1.92% in Africans (vs. 13.6% in women aged 70 years based on a 9-year incidence of probable OAG in the Barbados Study).[43] Notably, population-based studies followed set criteria for probable and/or definite OAG diagnoses, whereas in clinical practice, eye care providers might utilize ICD-9 365.11 coding for definite OAG, pre-perimetric glaucoma and/or glaucoma suspects. In addition, although we used ICD-9-CM 365.11 (primary OAG) and excluded ICD-9-CM

365.12 (low-tension OAG), some eye care providers might use 365.11 coding for low-tension OAG. Nevertheless, the non-differential ICD coding misclassification in this study would have likely resulted in an underestimation of the hypothesized relationship between exposure and outcome (a bias toward null).

Fourth, multiple comparisons were performed in subgroup analysis. The presented study, however adhered to guidelines in reporting subgroup analyses in clinical trials proposed by Wang et al.[44] In particular, our analyses met their criteria—pre-specified subgroups, no post-hoc analyses, tests of interaction and p-values for effects within subgroup categories presented, and a cautious interpretation of significant findings. Based on our hypothesis, we pre-specified subgroup analyses to test the effect modification of age and race—we found statistically significant effects of race ($p = 0.02$ for African Americans, p-interaction = 0.01), not age (p-interaction > 0.05) on the HT against incident OAG. Given the number of comparisons made in the subgroup analyses (classified by age and race) for two treatment arms (treatment vs. placebo) in each trial, one must be cautious in the interpretation of these results, as multiple comparisons are subjected to increased false positive rates. Based on the number of comparisons (4 comparisons in each trial), there is a 20% probability that one of the significant interaction tests ($p < 0.05$) would be expected on the basis of chance alone.

Finally, the protective effect of HT may vary by the status of uterus, types and form/dosage. Our analyses suggest that CEE alone was associated with a decreased risk of OAG in hysterectomized women, particularly African American, whereas CEE/MPA was not associated with a decreased risk of OAG in women with a uterus. The effects of CEE alone were tested only in women with a uterus because CEE alone is contraindicated in women with a uterus due to increased risk of endometrial cancer associated with estrogen alone therapy. The administration of a progestogen counteracts that risk. The reason why CEE alone, but not CEE/MPA are beneficial is unclear. One possibility is that the absolute risk of OAG is higher in women in the CEE arm because they are more likely to have had an oophorectomy before the typical age of menopause, and early menopause is associated with an increased risk of OAG. In that view, perhaps CEE was beneficial because the absolute rate of OAG would be higher in the CEE arm. However, that explanation is not supported because rates of OAG did not differ between the CEE placebo group and the CEE/MPA group. Specifically, during the cumulative follow-up the annualized percent incident OAG was 0.65% in the CEE placebo group and 0.64% in the CEE/MPA placebo group; during the intervention periods, the annualized percent incident OAG was 0.73% in the CEE placebo group and 0.74% in the CEE/MPA placebo group. The other possibility is that progesterone might antagonize the beneficial effects of estrogens. Based on our published work, CEE, not CEE/MPA significantly reduced IOP.[18] Similarly, breast cancer, cardiovascular disease, Alzheimer's disease, and other WHI outcomes differed by CEE versus CEE/MPA, with more favorable outcomes with CEE alone.[45] Consistent with other studies in the WHI and the claim database, the present study demonstrated the protective effect of CEE alone (oral CEE, 0.625 mg/day) in hysterectomized women, but not CEE/MPA in women with a uterus. Whether the benefits of CEE alone generalize to women with a uterus is therefore unknown. The combination of CEE with bazedoxifene is FDA approved for the treatment of vasomotor symptoms in women with a uterus, but its effect on the eye is unknown.

In conclusion, this investigation suggests that intervention with CEE for 4 years was associated with lower risk of OAG in postmenopausal African-American women post hysterectomy by half during 12 years of follow-up. Our findings further suggest that the sex-hormone related pathophysiology of glaucoma and may guide individualized assessments of the risks and benefits of HT in older menopausal women. Further investigations are warranted.

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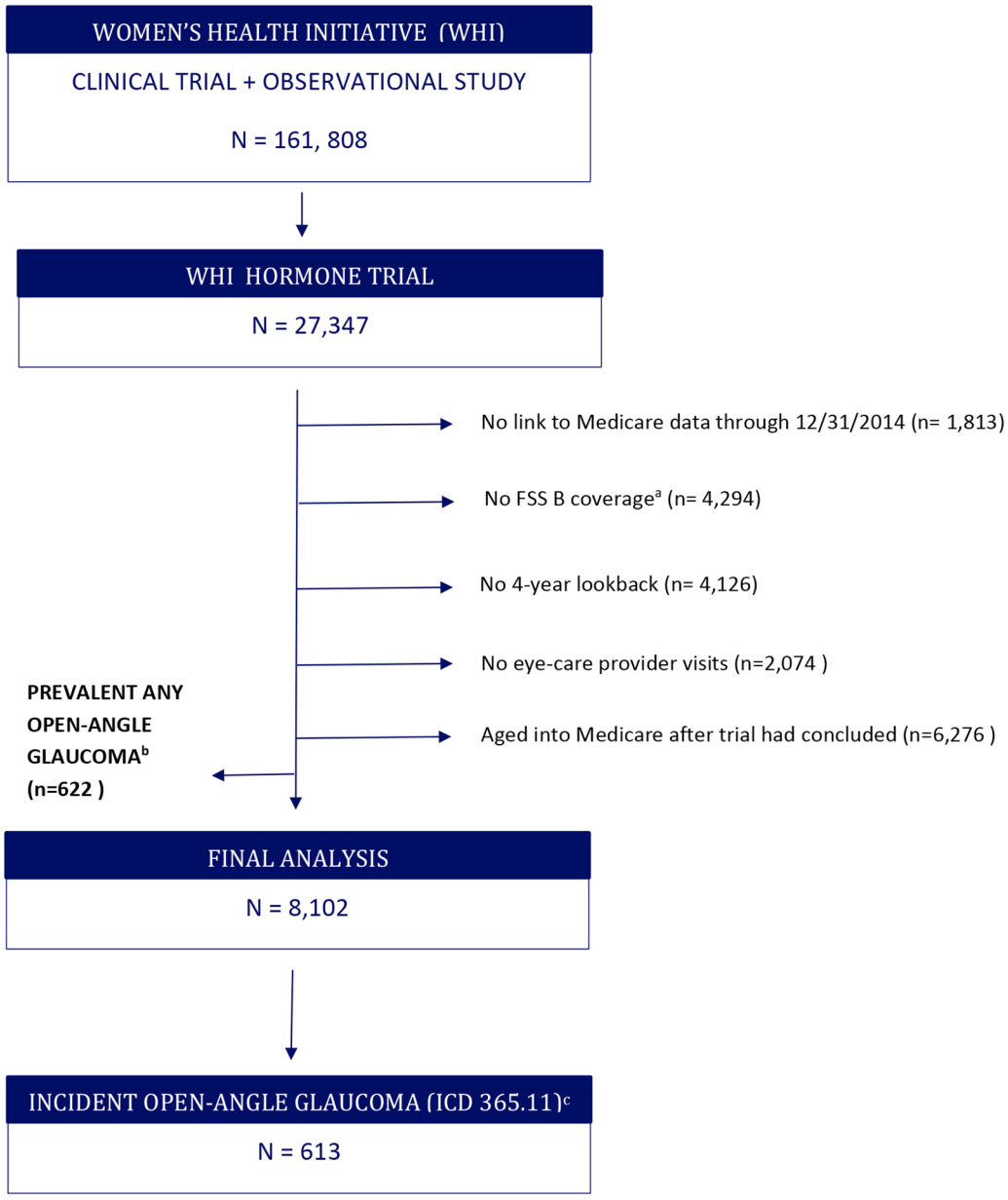

Figure 1: The flow chart of inclusion in the study and the number of women who received glaucoma diagnoses during follow-up.

[a]Excluded because the only FSS B coverage was prior to WHI enrollment; [b]Having ≥ 1 ICD codes for any open-angle glaucoma during look-back period; [c]ICD-9 code of 365.11

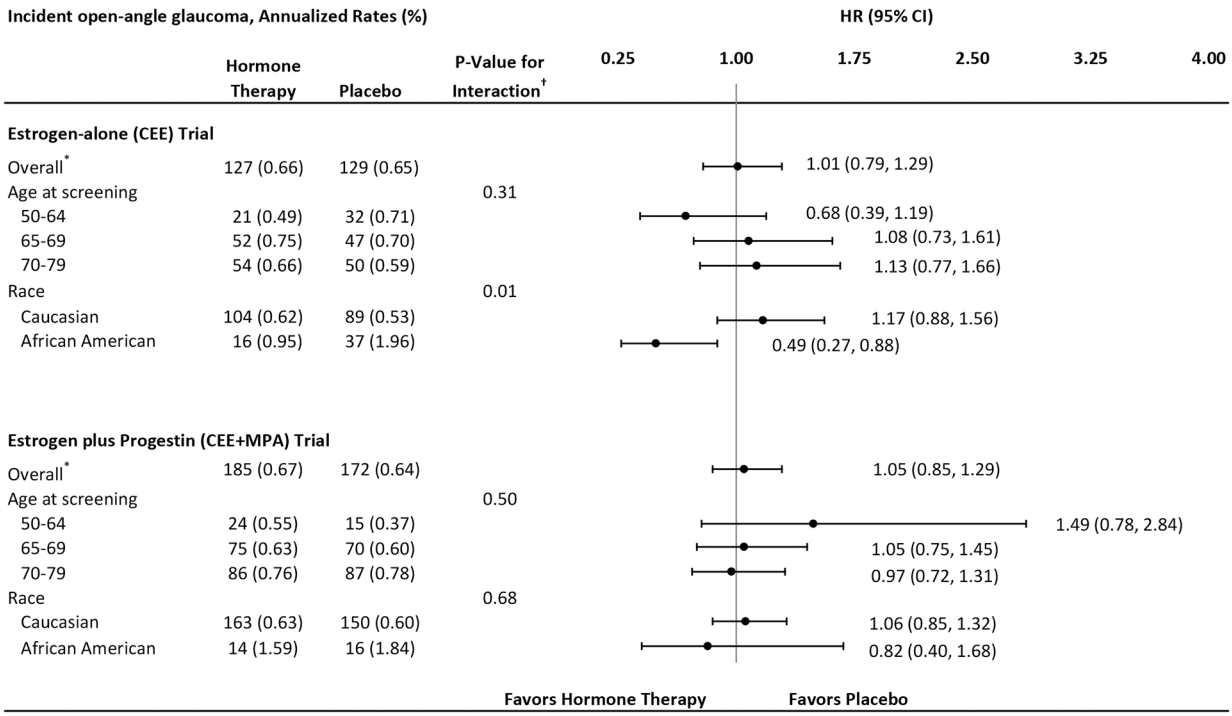

Figure 2: The forest plot of hazard ratios from intent-to-treat analyses of hormone therapy compared to placebo.

Abbreviations: CEE, conjugated equine estrogen; MPA, Medroxyprogesterone acetate; HR, hazard ratio; Cl, confidence interval.

* Results are from intent-to-treat analyses of hormone therapy compared to placebo. HRs, 95% CIs, and P-values were calculated in Cox proportional hazards models, stratified according to age and enrollment status in a low-fat diet Dietary Modification trial.

† P-value obtained from an interaction term between treatment assignment and the factor of interest in Cox proportional-hazards models. For subgroup analyses, models included the factor of interest, treatment assignment, and the interaction term, and were stratified according to age and enrollment status in a low-fat diet Dietary Modification trial. Estimation of HRs for race subgroups shown only for Caucasian and African American participants.

Table 1:

Baseline characteristics of participants in the Women's Health Initiative Hormone Trials (n = 8102)

	CEE (n = 3510)				CEE+MPA (n = 4592)			
	CEE (n = 1724)		Placebo (n = 1786)		CEE+MPA (n = 2326)		Placebo (n = 2266)	
	N	%	N	%	N	%	N	%
Age at screening, years								
50–64	438	25.4	459	25.7	407	17.5	373	16.5
65–69	598	34.7	602	33.7	967	41.6	954	42.1
70–79	688	39.9	725	40.6	952	40.9	939	41.4
Age at screening, years (Mean ± SD)	68.0 ± 5.1		68.2 ± 5.2		68.7 ± 4.6		68.9 ± 4.5	
Race								
Caucasian	1467	85.1	1491	83.5	2144	92.2	2084	92.0
Black	175	10.2	207	11.6	86	3.7	95	4.2
Other	82	4.8	88	4.9	96	4.1	87	3.9
Age at menopause, years (Mean ± SD)	44.9 ± 7.7		45.3 ± 7.6		50.2 ± 5.0		50.1 ± 4.9	
Menopausal hormone therapy use status								
Never user	919	53.3	953	53.4	1811	77.9	1755	77.5
Past user	646	37.5	681	38.1	444	19.1	449	19.8
Current user *	159	9.2	152	8.5	70	3.0	60	2.7
T reated diabetes (pills or injections)	133	7.7	155	8.7	102	4.4	109	4.8
History of hypertension **								
Never hypertensive	869	56.1	874	56.0	1346	65.9	1336	64.0
Untreated hypertensive	151	9.8	157	10.1	163	8.0	202	9.7
Treated hypertensive	528	34.1	529	33.9	535	26.2	550	26.3
Alcohol intake								
Non-drinker/past drinker	664	38.9	665	37.7	705	30.5	667	29.7
< 7 drinks per week	901	52.8	956	54.1	1311	56.7	1265	56.4
7+ drinks per week	140	8.2	145	8.2	295	12.8	311	13.9
Smoking status								
Never	905	53.0	954	54.1	1217	52.8	1171	52.5
Past	664	38.9	681	38.6	937	40.6	912	40.9
Current	138	8.1	129	7.3	153	6.6	148	6.6
Body-mass index (kg/m2), baseline (categories)								
< 25	387	22.5	398	22.4	708	30.6	725	32.3
25 - < 30	631	36.8	654	36.8	848	36.6	834	37.1
>= 30	699	40.7	723	40.7	759	32.8	688	30.6
Body-mass index (kg/m2), baseline ** (Mean ± SD)	29.5 ± 5.7		29.5 ± 5.8		28.2 ± 5.5		28.0 ± 5.5	
Enrollment in Dietary Modification trial								
Not enrolled	1230	71.3	1279	71.6	1750	75.2	1744	77.0
Assigned to intervention	185	10.7	192	10.8	235	10.1	219	9.7
Assigned to control	309	17.9	315	17.6	341	14.7	303	13.4

[*] Required a 3-month washout period before randomization.

[**] $p < 0.20$ difference between arms in CEE+MPA trial

Abbreviations: CEE, conjugated equine estrogen; MPA, Medroxyprogesterone acetate; SD, standard deviation; kg, kilograms; m, meters.

Table 2:

Incident open-angle glaucoma by baseline characteristics of participants in the Women's Health Initiative Hormone Trials (n = 8102)

	Open-Angle Glaucoma (OAG) ICD-9 365.11				
	No (n=7489)		Yes (n=613)		P-Value*
	N	%	N	%	
Age at screening, years					0.001
50–64	1585	94.5	92	5.5	
65–69	2877	92.2	244	7.8	.
70–79	3027	91.6	277	8.4	.
Race					<.001
Caucasian	6680	93.0	506	7.0	
Black	480	85.3	83	14.7	
Other	329	93.2	24	6.8	
Age at menopause, years					0.84
< 45	1617	92.7	128	7.3	
45–49	1603	92.1	138	7.9	
50+	3384	92.4	279	7.6	
Menopausal hormone therapy use status					0.51
Never user	5038	92.6	400	7.4	
Past user	2041	91.9	179	8.1	
Current user†	408	92.5	33	7.5	
Treated diabetes (pills or injections)					0.50
No	7025	92.5	572	7.5	
Yes	458	91.8	41	8.2	
History of hypertension					0.88
Never hypertensive	4095	92.5	330	7.5	
Untreated hypertensive	625	92.9	48	7.1	
Treated hypertensive	1975	92.2	167	7.8	
Alcohol intake					0.55
Non-drinker/past drinker	2510	92.9	191	7.1	
< 7 drinks per week	4090	92.3	343	7.7	
7+ drinks per week	820	92.0	71	8.0	
Smoking status					0.04
Never	3909	92.0	338	8.0	
Past	2954	92.5	240	7.5	
Current	542	95.4	26	4.6	
Body-mass index (kg/m2)					0.08
< 25	2024	91.3	194	8.7	
25 - < 30	2760	93.0	207	7.0	
>= 30	2662	92.8	207	7.2	
Enrollment in Dietary Modification trial					0.78

	Open-Angle Glaucoma (OAG) ICD-9 365.11				
	No (n=7489)		Yes (n=613)		P-Value*
	N	%	N	%	
Not enrolled	5552	92.5	451	7.5	
Assigned to intervention	765	92.1	66	7.9	
Assigned to control	1172	92.4	96	7.6	

*Age-adjusted association

†Required a 3-month washout period before randomization.

Abbreviations: OAG, open angle glaucoma; CEE, conjugated equine estrogen; MPA, Medroxyprogesterone acetate; SD, standard deviation; kg, kilograms; m, meter