Anthropometric Measures and Fuchs' Endothelial Corneal Dystrophy: The Women's Health Initiative Observational Study

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Purpose. Both genetic and environmental factors contribute to the development of Fuchs' endothelial corneal dystrophy (FECD), the most common indication for corneal transplantation in the United States. Prior studies have suggested an association of height, weight, or body mass index (BMI) with FECD. We examined the association between anthropometric measures and incident FECD in the Women's Health Initiative Observational Study (WHI-OS) of postmenopausal women (n = 22,983).

Methods. Medicare Part B claims data from the WHI-OS baseline visit (1993–1998) to 2019 were used to identify incident cases of FECD. At baseline and follow-up year 3, weight, height, waist circumference (WC), and hip circumference were measured. At baseline, women were asked to recall their historic weight at ages 18, 35, and 50 years. At follow-up years 1 and 4 to 8, the women were asked to self-report their weight. Height and weight were used to calculate BMI at each time point. Adjusted hazard ratios (HRs), 95% confidence intervals (CI), and p for trend for incident FECD were estimated by measures of historic BMI, baseline anthropometrics measures, and anthropometric measures that incorporated more than one baseline visit (time-varying). Anthropometric measures were parameterized as continuous and categorical in analyses.

Results. There were 1399 incident FECD cases with an annualized incidence rate of 5.06 per 1000 person-years (95% CI = 4.80–5.33) over 276,443 person-years of follow-up. No statistically significant associations were observed between baseline height and risk of FECD. Women with baseline BMIs ≥35 (obesity II) compared to <25 kg/m^2 (normal weight or underweight) had lower risk of incident FECD (HR = 0.68, 95% CI = 0.53–0.88) with a P value = 0.0373 for an ordinal trend analysis across BMI categories. Significant inverse associations were observed for continuous measures of WC (HR = 0.97, 95% CI = 0.95–0.99 per 5 cm increase) and waist-to-hip ratio (WHR; HR = 0.92, 95% CI = 0.86–0.99 per 0.1 unit increase). No statistically significant associations were observed for time-varying BMI, but time-varying WC and WHR has statistically significant inverse associations with risk for FECD (data not shown).

Conclusions. In this cohort of postmenopausal women, BMI, WC, and WHR were inversely associated with incident FECD. These findings generally support the potential role of anthropometric measures, particularly those indicative of abdominal obesity in FECD susceptibility in women.

Keywords: Fuchs' endothelial corneal dystrophy (FECD), eye diseases, ophthalmology, cohort studies, epidemiology, body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), anthropometry

Fuchs' endothelial corneal dystrophy (FECD) is a progressive ocular disease that affects the non-proliferative endothelial cells of the cornea, resulting in swelling and clouding of the cornea.[1] It is estimated that 4% to 11% of the adult population (>40 years) has FECD.[1] End-stage FECD is the leading indication for corneal blindness in the United States with more than 18,500 corneal transplants yearly for visually significant FECD.[2] However, corneal transplantation is limited by complications such as graft rejection, graft failure, glaucoma, and the availability of donor tissue.[3,4]

The prevalence and incidence of FECD in non-clinical settings are not well understood, and minimal research has been conducted to identify risk factors for the disease. Aging,[1] smoking,[5,6] female sex,[6–9] and genetics[10] have been shown to increase the risk for FECD. Anthropomorphic factors, such as height, weight, and body mass index (BMI), have also shown associations with FECD but are less well understood.[6,7,11–13]

Obesity has been identified as a risk factor for other age-related eye diseases, such age-related macular degeneration and cataract.[14] Increased risk of chronic eye diseases with obesity is hypothesized to be due to both increased systemic inflammatory load and associated metabolic changes in those with obesity.[14] Only a few published studies, all cross-sectional, have investigated the association between anthropometric measures and FECD prevalence yielding inconsistent results.[6,7,11–13] More evidence is needed to determine if meaningful associations exist between anthropometric measures and FECD risk.

Given the limited epidemiologic data available on FECD, we utilized data from the Women's Health Initiative Observational Study (WHI-OS) of postmenopausal women and examined the association among height, BMI, waist circumference (WC), and waist-to-hip ratio (WHR) on the risk of incident FECD identified using Medicare claims data. We hypothesized that, in postmenopausal women, the risk of FECD would significantly vary by level of these anthropometric measures.

Methods

Study Sample and FECD Ascertainment

The WHI-OS, launched in 1993, is a long-term, nationwide cohort study examining the main drivers of chronic disease among postmenopausal women.[15–18] With a diverse cohort of 93,676 women aged 50 to 79 years at baseline enrollment, WHI-OS recruited participants from 40 clinical centers across the United States. To identify our study sample and ascertain incident FECD cases, data from WHI-OS participants, who also had available records in the Centers for Medicare and Medicaid Services (CMS) fee-for-service claims, were accessed.

We required women to be enrolled in both the WHI-OS and Medicare part B at study baseline (1993–1998, n = 28,442). Additional inclusion criteria for this analysis required women to be 65 years of age or older and have stayed enrolled in both Medicare part B and WHI-OS for >1 year following baseline. Women with Medicare claims data indicative of endothelial corneal dystrophy (FECD), corneal transplants, or corneal failure/rejection/complications ≤1 year from WHI-OS enrollment were considered prevalent cases and excluded from the analytic sample. Cases were identified using the International Classification of Disease Ninth Revision (ICD)-9[19] and ICD Tenth Revision (ICD-10) codes[20]: endothelial corneal dystrophy (ICD-9 code = 371.57 and ICD-10 code = H18.51), and corneal transplant surgery or transplant failure/rejection/ complications (ICD-9 codes = V42.5 and 996.51 and ICD-10 codes = Z94.7, T86.840, T86.841, T86.842, and T86.848). Incident cases of FECD were determined from Medicare claims data reports through 2019. Women with incident claims data for corneal transplants or corneal failure/ rejection/complications without co-diagnosis of FECD were excluded leaving 24,355 women.

Women were further excluded if they had missing data on baseline BMI, their baseline BMIs were <15 or >70 kg/m^2, or their baseline height was deemed unreliable. The range of heights at WHI baseline was from 100.8 to 189.8 cm and contained extremely short heights that showed a significant discrepancy with their recalled heights at 18 years old. Therefore, we excluded participants whose height was more than 4 standard deviations (SDs) below the mean baseline height (i.e. <141.6 cm), and those who had an extreme change in height from 18 years old to baseline exceeding 4 SD of the mean change (i.e. >16.9 cm), resulting in the exclusion of 19 women. We also excluded women missing relevant covariate data at baseline, except for the covariates of pack-years of smoking and recreational physical activity. A significant number of women were missing data on pack-years of smoking (n = 529). Women who were past or current smokers and had missing pack-years were assigned the median pack-years smoked among women in these categories (15 and 27.5 pack-years, respectively). A similar approach was used for the 157 participants missing recreational physical activity data. Women with missing data were given the median metabolic equivalent (MET)-hours/week of 10.13. Our final analytic sample consisted of 22,983 women. Participants gave written informed consent to participate in the WHI-OS.

Anthropometric Measures

At the WHI-OS baseline and the year 3 follow-up visit, women's weight, height, WC, and hip circumference were measured by trained WHI staff.[18,21,22] At baseline, women were also asked to recall their weight when they were 18, 35, and 50 years old.[21] At the year 1 follow-up visit, and at year 4 through year 8 follow-up visits, women were asked to self-report their current weight on questionnaires.[23,24] The height measurement taken at baseline, and the measured, recalled, or self-reported weight at baseline, year 1, year 3, and years 4 to 8 were used to calculate BMI, in kg/m^2, at each respective visit. Baseline and year 3 WHR was calculated by dividing the WC measurement (cm) by the hip circumference measurement (cm).

Demographic and Lifestyle Information

Covariates for all participants were ascertained at baseline.[18] Data collected included age at baseline, race, ethnicity, and education level. Also collected was information on baseline smoking status (current/former/non-smoker), pack-years of smoking at baseline, recreational physical activity, hormone therapy use (never/past/current), and self-reported dietary intake from a food frequency questionnaire (FFQ)[25] from which we estimated the Healthy Eating Index 2015 (HEI-2015).[26] In follow-up years 4 to 8, women were asked to update their current smoking status as well as their hormone therapy use, providing time-varying data on these variables.

Statistical Analyses

The annualized incidence rate (AIR) of FECD (per 1000 person-years) was described based on baseline characteristics including age, race, ethnicity, education, smoking status, pack-years of smoking, recreational physical activity (MET-hours/week), hormone therapy use, and the HEI-2015. The log rank test was used to compare incidence rates by level of characteristic. Mean anthropometric measures taken at WHI baseline were also compared by category of characteristic using *t*-tests and ANOVAs. The sample size is not shown for some of the characteristics by incidence of FECD in order to comply with the CMS cell size suppression policy.[27]

We used Cox proportional hazard models to estimate the hazard ratio (HRs) and 95% confidence intervals (CIs) for incident FECD with historic BMI (aged 18, 35, and 50 years) and baseline measures of height, BMI, WC, and WHR. All exposures were analyzed as both continuous and categorical variables. The P for trend analyses were also conducted (described below). Women were censored if they withdrew from WHI, died, or switched out of traditional fee-for-service.

Tertiles were created for height (tertile 1 = 133.7–158.0 cm, tertile 2 = 158.1–163.2 cm, and tertile 3 = 163.3–189.8 cm), with tertile 1 as the reference group. The BMI categories were underweight/normal (<25 kg/m^2), overweight (25 to <30 kg/m^2), obesity level I (30.0 to 34.9 kg/m^2), and obesity level II (35 to 35.9 kg/m^2) or III (≥40 kg/m^2), with underweight/normal serving as the reference group. Obesity levels II and III were combined to increase statistical power; however, in exploratory analyses, we examined the risk of FECD in those with obesity levels II and III separately. WC was defined using the World Health Organization (WHO) recommended groups of ≤80 cm, >80 to 88 cm, and >88 cm, with ≤80 cm as the reference group.[28] The WHR was categorized as ≤0.80, 0.81 to 0.84, and ≥0.85, suggested by the WHO, with ≤0.80 as the reference group.[28] The P for trend was calculated using ordinal values assigned to each anthropometric category with increasing numbers for increasing anthropometric measures (e.g. underweight/normal = 1, overweight = 2, obesity level I = 3, and obesity level II or III = 4). We constructed two adjusted models: model 1 adjusted for age group (age group in strata statement) and model 2 adjusted for education, smoking status, pack-years of smoking, 2015-HEI, hormone therapy use, and recreational physical activity; age group and race were included in the strata statement. The proportional hazards assumptions for all covariates in the models with baseline exposure measures were tested using weighted Schoenfeld residuals.[29,30]

We explored effect modification of continuous measures of baseline BMI by smoking exposure defined as (never smokers, ever smokers with pack-years <20, and ever smokers with pack-years ≥20 years). We examined stratified analyses and included a p for interaction term (smoking exposure variable* BMI) in the model. A p for interaction of <0.05 was considered statistically significant. We conducted sensitivity analyses with the baseline anthropometric measures. First, to minimize the possibility of prevalent disease in our sample, we restricted our analyses to include only women with claims data for incident FECD after 5 years from the baseline examination. Second, to reduce the possibility of false negatives in our analyses, we restricted the analysis to include only women who reported visiting an eye doctor within the last 2 years, based on questionnaire data collected in 2013 and 2018.

We incorporated multiple anthropometric measurements from baseline and the follow-up visits, when possible, to examine our study associations allowing for time-varying anthropometric variables. For example, we allowed the BMI measures to change after baseline to measures of BMI at follow-up visits until a participant developed incident FECD or was censored.[31] For WC and WHR, women missing baseline measures, but having year 3 measures for WC or WHR, were included in the time-varying analyses. A Cox proportional hazard model was used to examine the association among time-varying BMI, WC, and WHR and FECD incidence. The two aforementioned multivariable models were used for this analysis, with the inclusion of time-varying smoking status and hormone therapy use exposure measures as well. All statistical analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Among 22,983 postmenopausal women, 1399 participants developed FECD, with an AIR of 5.06 (95% CI = 4.80–5.33) cases per 1000 person-years. Supplementary Table S1 describes the AIR of FECD by participant characteristics. There was a greater AIR of FECD in White women compared with women of other races, and in those whose education included only high school compared with college or post-graduate. The AIR was lowest in those with at least 20 pack-years of smoking compared with those with less pack-years, and lowest in those with recreational physical activity ≥12.5 MET-hours/week compared with those with less activity.

At baseline, 9572 (42%) women were underweight/normal (<25 kg/m^2), 8211 (36%) were overweight (25 to <30 kg/m^2), 3534 (15%) were obese level I (30 to <35 kg/m^2), and 1666 (7%) were obese level II or III (≥35 kg/m^2). Mean baseline BMIs were higher in younger women than older women, and they were highest in women of American Indian/Alaskan Native race followed by Black women, Native Hawaiian/Other Pacific Islander women, those with unknown/unreported race, those with more than one race, White women, and Asian women (Table 1). Those who were Hispanic/Latina had higher BMIs than women who were non-Hispanic/Latinas or those with unknown/not reported ethnicity. BMIs were also higher in those with less education, former smokers, those who smoked ≥20 pack-years, those with no self-reported recreational physical activity, those with poor diets, and those who never used hormone therapy, as compared with women in comparative groups for these characteristics.

No statistically significant associations were observed between continuous BMI or categorical BMI measures and incident FECD at the ages of 18 or 35 years (Table 2). A protective association was observed for risk of FECD in those with obese BMIs at age 50 of ≥30 to <35 kg/m^2 (obesity I) compared with those with underweight or normal BMIs at age 50 (<25 kg/m^2; HR = 0.75, 95% CI = 0.56–0.99). No other statistically significant findings were observed with historic anthropometric measures.

Height was not associated with the risk of FECD (Table 3). At baseline, women with BMIs ≥35.0 kg/m^2 (obesity levels II and III) had a decreased risk of incident FECD (HR = 0.68, 95% CI = 0.53–0.88) compared with women whose BMIs were underweight/normal weight (see Table 3). A significant decreased risk of FECD was observed for increasing categories of BMI (p for trend = 0.0373). In exploratory analyses, inverse associations remained when obesity II (BMI ≥35 to <40 kg/m^2) and III (BMI ≥40 kg/m^2) were

Table 1. Anthropometric Measures at WHI Baseline by Characteristics ($N = 22,983$)

	Anthropometric Measures at Baseline							
	Height, cm		BMI, kg/m^2		WC, cm		WHR, *100	
Sub-Group	***N* (%)**	**Mean, ± SD**	***N* (%)**	**Mean, ± SD**	***N* (%)**	**Mean, ± SD**	***N* (%)**	**Mean, ± SD**
Entire samples	22,983 (100.0%)	160.6 ± 6.2	22,983 (100.0%)	26.9 ± 5.4	22,921 (100.0%)	84.7 ± 12.8	22,900 (100.0%)	81.4 ± 8.0
Age at baseline, y								
65–69	11,016 (47.9%)	161.4 ± 6.1	11,016 (47.9%)	27.1 ± 5.5	10,983 (47.9%)	85.1 ± 13.3	10,970 (47.9%)	81.1 ± 8.0
70–74	8,349 (36.3%)	160.3 ± 6.1	8,349 (36.3%)	26.8 ± 5.3	8,332 (36.4%)	84.6 ± 12.4	8,327 (36.4%)	81.5 ± 7.7
≥74	3,618 (15.7%)	159.0 ± 6.2	3,618 (15.7%)	26.3 ± 4.9	3,606 (15.7%)	84.0 ± 12.0	3,603 (15.7%)	82.0 ± 8.3
P value*	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
Race								
American Indian/Alaska Native	>49 (>0.2%)‡	160.1 ± 6.7	>49 (>0.2%)‡	29.8 ± 6.9	>49 (>0.2%)‡	93.5 ± 18.0	>49 (>0.2%)‡	84.6 ± 9.3
Asian	510 (2.2%)	153.3 ± 5.5	510 (2.2%)	24.1 ± 3.9	510 (2.2%)	77.4 ± 9.9	510 (2.2%)	81.9 ± 7.2
Native Hawaiian/Other Pacific Islander	<11 (<0.1%)‡	159.8 ± 8.8	<11 (<0.1%)‡	29.0 ± 6.7	<11 (<0.1%)‡	88.1 ± 14.6	<11 (<0.1%)‡	82.9 ± 8.1
Black	1,201 (5.2%)	161.1 ± 6.1	1201 (5.2%)	29.7 ± 6.1	1,197 (5.2%)	89.5 ± 12.9	1,195 (5.2%)	82.6 ± 7.5
White	20,823 (90.6%)	160.8 ± 6.1	20,823 (90.6%)	26.8 ± 5.2	20,766 (90.6%)	84.6 ± 12.7	20,747 (90.6%)	81.3 ± 7.9
More than one race	168 (0.7%)	160.2 ± 6.2	168 (0.7%)	27.3 ± 4.7	168 (0.7%)	85.6 ± 12.5	168 (0.7%)	82.1 ± 6.8
Unknown/not reported	221 (1.0%)	157.2 ± 6.7	221 (1.0%)	28.7 ± 7.0	220 (1.0%)	87.1 ± 13.3	220 (1.0%)	83.1 ± 13.9
P value*	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
Ethnicity								
Not Hispanic/Latina	22,335 (97.2%)	160.7 ± 6.1	22,335 (97.2%)	26.9 ± 5.3	22,274 (97.2%)	84.7 ± 12.8	22,253 (97.2%)	81.4 ± 7.9
Hispanic/Latina	472 (2.1%)	156.9 ± 5.9	472 (2.1%)	28.0 ± 6.3	471 (2.1%)	85.2 ± 12.4	471 (2.1%)	82.2 ± 11.7
Unknown/not reported	176 (0.8%)	156.0 ± 6.8	176 (0.8%)	26.1 ± 5.7	176 (0.8%)	83.4 ± 14.4	176 (0.8%)	82.8 ± 7.1
P value*	**<0.0001**		**<0.0001**		**0.2785**		**0.0038**	
Education								
High school or lower	7,891 (34.3%)	159.9 ± 6.2	7,891 (34.3%)	27.7 ± 5.6	7,870 (34.3%)	86.6 ± 13.4	7,862 (34.3%)	82.2 ± 8.3
College	8,554 (37.2%)	160.9 ± 6.0	8,554 (37.2%)	26.6 ± 5.2	8,529 (37.2%)	84.1 ± 12.6	8,519 (37.2%)	81.1 ± 7.7
Post-graduate	6,538 (28.4%)	161.1 ± 6.3	6,538 (28.4%)	26.3 ± 5.1	6,522 (28.5%)	83.3 ± 12.1	6,519 (28.5%)	80.7 ± 7.9
P value*	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
Smoking status								
Never	12,252 (53.3%)	160.2 ± 6.2	12,252 (53.3%)	26.9 ± 5.3	12,227 (53.3%)	84.2 ± 12.6	12,218 (53.4%)	80.9 ± 7.9
Former	9,694 (42.2%)	161.1 ± 6.1	9,694 (42.2%)	27.0 ± 5.4	9,663 (42.2%)	85.5 ± 13.0	9,653 (42.2%)	81.9 ± 8.0
Current	1,037 (4.5%)	161.2 ± 6.2	1,037 (4.5%)	25.6 ± 5.0	1,031 (4.5%)	84.0 ± 12.5	1,029 (4.5%)	82.6 ± 7.1
P value*	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	

Table 1. Continued

	Anthropometric Measures at Baseline							
	Height, cm		BMI, kg/m^2		WC, cm		WHR, *100	
Sub-Group	***N* (%)**	**Mean, ± SD**	***N* (%)**	**Mean, ± SD**	***N* (%)**	**Mean, ± SD**	***N* (%)**	**Mean, ± SD**
Pack-years of smoking								
Missing†	529 (2.3%)	160.8 ± 6.0	529 (2.3%)	26.8 ± 5.2	528 (2.3%)	84.9 ± 13.0	527 (2.3%)	81.5 ± 8.0
Never smoker	12,252 (53.3%)	160.2 ± 6.2	12,252 (53.3%)	26.9 ± 5.3	12,227 (53.3%)	84.2 ± 12.6	12,218 (53.4%)	80.9 ± 7.9
<5 y	2,878 (12.5%)	161.0 ± 6.2	2,878 (12.5%)	26.7 ± 5.3	2,871 (12.5%)	84.3 ± 12.6	2,868 (12.5%)	81.0 ± 7.5
5 to <20 y	2,975 (12.9%)	161.1 ± 6.2	2,975 (12.9%)	26.7 ± 5.2	2,964 (12.9%)	84.5 ± 12.6	2,961 (12.9%)	81.5 ± 8.3
≥20 y	4,349 (18.9%)	161.3 ± 6.1	4,349 (18.9%)	27.2 ± 5.6	4,331 (18.9%)	86.8 ± 13.4	4,326 (18.9%)	83.0 ± 7.9
P value*	**<0.0001**		**0.0002**		**<0.0001**		**<0.0001**	
Recreational physical activity, MET-h/wk								
Missing†	157 (0.7%)	160.7 ± 6.0	157 (0.7%)	27.3 ± 5.8	157 (0.7%)	87.2 ± 13.8	157 (0.7%)	82.8 ± 7.5
0	2,899 (12.6%)	160.4 ± 6.2	2,899 (12.6%)	28.9 ± 6.3	2,888 (12.6%)	89.8 ± 14.1	2,882 (12.6%)	83.2 ± 8.1
<12.5	10,161 (44.2%)	160.5 ± 6.2	10,161 (44.2%)	27.4 ± 5.4	10,132 (44.2%)	85.9 ± 12.9	10,124 (44.2%)	81.8 ± 8.1
≥12.5	9,766 (42.5%)	160.8 ± 6.1	9,766 (42.5%)	25.8 ± 4.7	9,744 (42.5%)	81.9 ± 11.5	9,737 (42.5%)	80.4 ± 7.6
P value*	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
HEI-2015								
"Poor" <51	1,397 (6.1%)	160.3 ± 6.3	1,397 (6.1%)	28.7 ± 6.2	1,396 (6.1%)	89.5 ± 14.3	1,395 (6.1%)	83.2 ± 8.7
"Need Improvement" 51–80	19,627 (85.4%)	160.6 ± 6.2	19,627 (85.4%)	26.9 ± 5.3	19,569 (85.4%)	84.8 ± 12.7	19,550 (85.4%)	81.4 ± 7.9
"Good" >80	1,959 (8.5%)	161.0 ± 6.3	1,959 (8.5%)	25.2 ± 4.6	1,956 (8.5%)	80.3 ± 10.8	1,955 (8.5%)	79.6 ± 7.5
P value*	**0.0063**		**<0.0001**		**<0.0001**		**<0.0001**	
HT use ever								
Never	8,175 (35.6%)	160.4 ± 6.3	8,175 (35.6%)	27.7 ± 5.8	8,148 (35.5%)	86.7 ± 13.6	8,140 (35.5%)	82.3 ± 8.0
Former	5,787 (25.2%)	160.4 ± 6.1	5,787 (25.2%)	27.0 ± 5.4	5,772 (25.2%)	85.4 ± 12.8	5,763 (25.2%)	81.9 ± 8.2
Current	9,021 (39.3%)	161.0 ± 6.1	9021 (39.3%)	26.0 ± 4.7	9001 (39.3%)	82.5 ± 11.7	8,997 (39.3%)	80.3 ± 7.6
P value*	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	

HT, menopausal hormone therapy.
Boldface entries indicate *P* values <0.05.
* ANOVA-F-tests were used to examine the difference in group mean adiposity measures by other characteristics.
† Missings are not included in ANOVAs.
‡ Exact *N* for Medicare data not shown due to small cell counts and compliance with the Centers for Medicare and Medicaid Services (CMS) cell size suppression policy.[27]

Table 2. HRs and 95% CIs for FECD by Historical BMI at Ages of 18, 35, and 50 Y

	N	Person-Years of Follow-Up × 1,000	AIR (95% CI)*	Model 1†	Model 2‡
Age 18, y (*N* = 22,769)					
BMI (pre 1 kg/m^2)				1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
BMI strata					
Underweight/ Normal (<25 kg/m^2)	20,980	253.88	5.08 (4.81, 5.37)	Ref.	Ref.
Overweight (25 to <30 kg/m^2)	1,528	17.48	4.69 (3.78, 5.82)	0.94 (0.75, 1.17)	0.94 (0.75, 1.17)
Obesity level I (30 to <35 kg/m^2)	206	2.38	5.46 (3.17, 9.40)	1.10 (0.64, 1.90)	1.07 (0.62, 1.85)
Obesity levels II and III (≥ 35 kg/m^2)	55	0.56	1.79 (0.25, 12.68)	0.37 (0.05, 2.66)	0.36 (0.05, 2.58)
p for trend‖				0.5339	0.4836
Obesity level II (35 to <40 kg/m^2)	39	0.43	2.31 (0.33, 16.38)	0.47 (0.07, 3.34)	0.46 (0.06, 3.25)
Obesity level III (≥40 kg/m^2)	16	0.13	NA	NA	NA
p for trend‖				0.5102	0.461
Age 35, y (*N* = 22,745)					
BMI (per 1 kg/m^2)				1.00 (0.98, 1.02)	0.99 (0.97, 1.01)
BMI strata					
Underweight/ Normal (<25 kg/m^2)	18,809	230.5	5.15 (4.86, 5.45)	Ref.	Ref.
Overweight (25 to <30 kg/m^2)	3,308	36.73	4.52 (3.88, 5.26)	0.91 (0.77, 1.07)	0.87 (0.74, 1.03)
Obesity level I (30 to <35 kg/m^2)	487	5.19	6.16 (4.36, 8.71)	1.26 (0.88, 1.79)	1.17 (0.82, 1.66)
Obesity levels II and III (≥35 kg/m^2)	141	1.41	1.41 (0.35, 5.66)	0.30 (0.07, 1.18)	0.28 (0.07, 1.10)
p for trend‖				0.3614	0.1488
Obesity level II (35 to <40 kg/m^2)	103	1.02	0.98 (0.14, 6.95)	0.20 (0.03, 1.44)	0.19 (0.03, 1.36)
Obesity level III (≥40 kg/m^2)	38	0.39	2.55 (0.36, 18.12)	0.54 (0.08, 3.82)	0.49 (0.07, 3.46)
p for trend‖				0.3461	0.1415
Age 50, y (*N* = 22,765)					
BMI (per 1 kg/m^2)				1.00 (0.98, 1.01)	0.99 (0.97, 1.01)
BMI strata					
Underweight/ Normal (<25 kg/m^2)	14,521	179.95	5.05 (4.73, 5.39)	Ref.	Ref.
Overweight (25 to <30 kg/m^2)	6,610	76.66	5.28 (4.79, 5.82)	1.07 (0.95, 1.20)	1.02 (0.91, 1.15)
Obesity level I (30 to <35 kg/m^2)	1,251	13.56	3.83 (2.92, 5.03)	0.80 (0.60, 1.05)	**0.75 (0.56, 0.99)**
Obesity levels II and III (≥35 kg/m^2)	383	3.97	4.53 (2.85, 7.19)	0.95 (0.60, 1.52)	0.87 (0.55, 1.39)
p for trend‖				0.7295	0.2497
Obesity level II (35 to <40 kg/m^2)	270	2.80	4.29 (2.44, 7.55)	0.90 (0.51, 1.59)	0.83 (0.47, 1.46)
Obesity level III (≥40 kg/m^2)	113	1.18	5.10 (2.29, 11.35)	1.08 (0.48, 2.41)	0.99 (0.44, 2.20)
p for trend‖				0.749	0.2639

* AIR (95% CI): Annualized Incidence Rate (per 1,000 person-years) with its 95% confidence interval.
† Model 1 age group in the strata statement.
‡ Model 2 adjusted for education level, smoking status, pack-years of smoking, HEI-2015, hormone therapy use and physical activity (MET-hour/week). Age group and race are included in the strata statement.
‖ The p for trend across anthropometric categories as ordinal variable.
The figures in bold represent confidence intervals that do not include 1.0 or where *P* values are <0.05.

analyzed as separate groups, but the statically significant association only remained among those who were obesity level II.

Inverse associations were observed between risk of FECD and increasing continuous measures of WC (HR = 0.97, 95% CI = 0.95–0.99 per 5 cm increase) and WHR (HR = 0.92, 95% CI = 0.86–0.99 per 1 unit increase). For both WC and WHR, participants in the highest categories for these exposures had a statistically significant decreased risk of FECD when compared with those in the lowest categories. The p for trends across categories of WC and WHR were also both statistically significant ($P < 0.05$).

Further adjustment of the models in Table 3 for diabetes status did not change the findings. When the baseline anthropometric analyses were restricted to the subset of women who reported visiting an eye doctor in the past 2 years, or when the analyses excluded women diagnosed with FECD within 5 years of WHI-OS, inverse associations with BMI, WC, and WHR remained, but were only statistically significant for BMI (data not shown). No effect modification by smoking exposure was observed (data not shown).

In analyses using time-varying measures for BMI throughout 8 years of follow-up, the reduced risk of incident FECD in those with BMIs ≥35.0 (obesity levels II and III) compared to normal/underweight remained but was no longer statistically significant (Table 4). Time-varying measures for WC and WHR that included measures from baseline and year 3, still showed an inverse association between increasing continuous units of WC and WHR and decreased risk of incident FECD.

Discussion

In this cohort of postmenopausal women, we observed a decreased risk of incident FECD in women with a baseline BMI of ≥35 kg/m^2 (obesity levels II and III) compared to <25 kg/m^2 (underweight/normal weight), a significant trend for decreasing risk of FECD by increasing category of BMI, and an inverse association between WC and WHR and incident FECD. No statistically significant associations were observed with women's height or self-reported historic BMI at ages 18 or 35 years, although HRs for incident FECD were less than 1.0 in women with BMIs ≥35 kg/m^2 at these ages.

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Table 3. HR and 95% CIs for FECD by Body Anthropometric Measures at Baseline.

	N	Person-Years of Follow-Up (× 1,000)	AIR (95% CI)*	Model 1†	Model 3‡
Height (n = 22,983)					
Height (per 1 cm)				1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Height					
Tertile 1 (133.7–158.0)	7,777	90.47	5.01 (4.57, 5.49)	Ref.	Ref.
Tertile 2 (158.1–163.2)	7,492	90.47	5.36 (4.90, 5.86)	1.06 (0.94, 1.21)	1.04 (0.91, 1.18)
Tertile 3 (163.3–189.8)	7,714	95.51	4.83 (4.41, 5.29)	0.95 (0.83, 1.08)	0.93 (0.82, 1.06)
p for trend‖				0.3901	0.2817
BMI (n = 22,983)					
BMI (per 1 kg/m^2)				0.99 (0.98, 1.01)	0.99 (0.98, 1.00)
BMI strata					
Underweight/ normal (<25 kg/m^2)	9,572	118.85	5.23 (4.83, 5.65)	Ref.	Ref.
Overweight (25 to <30 kg/m^2)	8,211	99.08	4.98 (4.56, 5.44)	0.96 (0.85, 1.08)	0.93 (0.83, 1.05)
Obesity level I (30 to <35 kg/m^2)	3,534	40.15	5.41 (4.73, 6.17)	1.06 (0.91, 1.24)	1.00 (0.85, 1.17)
Obesity levels II and III (≥35 kg/m^2)	1,666	18.37	3.70 (2.92, 4.69)	**0.74 (0.57, 0.95)**	**0.68 (0.53, 0.88)**
p for trend‖				0.2495	**0.0373**
Obesity level II (35 to <40 kg/m^2)	1,142	12.73	3.54 (2.64, 4.74)	**0.70 (0.52, 0.95)**	**0.65 (0.48, 0.88)**
Obesity level III (≥40 kg/m^2)	524	5.64	4.07 (2.71, 6.13)	0.82 (0.54, 4.25)	0.76 (0.50, 1.16)
p for trend‖				0.2284	**0.0373**
Waist circumference (n = 22,921)					
Waist circumference (per 5 cm)				0.98 (0.96, 1.00)	**0.97 (0.95, 0.99)**
Waist circumference strata					
≤80	9,459	118.11	5.33 (4.93, 5.77)	Ref.	Ref.
>80 to ≤88	5,567	68.04	5.10 (4.59, 5.67)	0.96 (0.84, 1.10)	0.93 (0.82, 1.07)
>88	7,895	89.54	4.67 (4.24, 5.14)	0.90 (0.80, 1.02)	**0.85 (0.75, 0.97)**
p for trend‖				0.1119	**0.0131**
Waist-hip ratio (n = 22,900)					
Waist-hip ratio (per 0.1)				0.93 (0.87, 1.00)	**0.92 (0.86, 0.99)**
Waist-hip ratio strata					
≤0.80	10,528	132.25	5.35 (4.97, 5.76)	Ref.	Ref.
0.81 to 0.84	5,863	69.88	5.08 (4.58, 5.64)	0.96 (0.85, 1.10)	0.95 (0.83, 1.08)
≥0.85	6,509	73.33	4.53 (4.07, 5.04)	0.88 (0.77, 1.00)	**0.86 (0.75, 0.98)**
p for trend‖				0.0515	**0.0245**

* AIR (95% CI): Annualized Incidence Rate (per 1,000 person-years) with its 95% confidence interval.
† Model 1 age group in the strata statement.
‡ Model 2 adjusted for education level, smoking status, pack-years of smoking, HEI-2015, hormone therapy use, and physical activity (MET-hour/week). Age group and race are included in the strata statement.
‖ The p for trend across anthropometric categories as ordinal variable.
The figures in bold represent confidence intervals that do not include 1.0 or where P values are <0.05.

At age 50 years, the participants with BMIs ≥35 compared to <25 kg/m^2 had a statistically significant decreased risk of FECD, similar to what we observed with the baseline BMI data. Observations with BMI, WC, and WHR were supported by study using time-varying covariates. Sensitivity analyses did not influence the study conclusions.

Several studies have investigated the association between anthropometric measures and FECD.[6,7,11–13] We observed no statistically significant associations between height and FECD outcomes in women, similar to other studies that examined height.[6,7,11] Studies have found associations with weight and BMI. Zoega et al.[6] conducted a study with 775 participants from Reykjavik, Iceland, and found that the odds of having corneal guttata, a hallmark of FECD, was inversely associated with BMI and weight. After adjusting for age and sex, the inverse, statistically significant association remained with BMI but not weight. The Kumejima Study,[7] which involved 3060 residents of a Southwestern Island in Japan, reported inverse associations between height, weight, BMI and risk of corneal guttata, but these associations were not statistically significant. Furthermore, in a study of 156 individuals from the Tangier Island of Virgina,[11] individuals with FECD tended to have lower weight, but this difference was only significant in men and the analyses were unadjusted for covariates. In a previous clinical study of FECD cases from the Mayo Clinic, we observed a greater severity of FECD in women (but not men) with higher BMIs compared with those with lower BMIs[12] even after adjustment for age and genetics (CTG18.1 expansion in the *TCF4* gene). Similarly, another analysis of only FECD cases, from the Fuchs genetic Database of the University of Cologne (Cologne, Germany), observed an earlier age of diagnosis in cases with BMIs ≥30 compared to <30 kg/m^2, but no statistically significant differences were seen in disease grade, central corneal thickness, or visual acuity by BMI group.[13] Analyses were minimally adjusted for age. Together, these studies suggest that individuals with higher BMIs are less likely to have FECD. However, when studies are limited to just cases of FECD, the association of BMI to FECD severity may be the opposite.

Obesity is often associated with increasing risk for other age-related eye diseases,[14] so it seems paradoxical that it would be a protective factor for FECD. In a previous analysis in the same cohort of women,[32] we observed that current

Table 4. HRs and 95% CIs for FECD by Time-Varying Anthropometric Measures[*]

	No. of Records	Person-Years of Follow-Up (× 1,000)	AIR[†]	Model 1[‡]	Model 2[§]
BMI (n = 22,983)					
BMI (per 1 kg/m^2)				1.00 (0.98, 1.01)	0.99 (0.98, 1.00)
BMI strata					
Underweight/normal (<25 kg/m^2)	64,110	132.04	5.03 (4.66, 5.43)	Ref.	Ref.
Overweight (25–30 kg/m^2)	48,925	96.77	5.16 (4.72, 5.63)	1.08 (0.96, 1.21)	1.04 (0.92, 1.18)
Obesity level I (30.0–34.9 kg/m^2)	19,610	37.47	4.94 (4.27, 5.70)	1.06 (0.90, 1.26)	1.00 (0.84, 1.19)
Obesity levels II and III (≥35 kg/m^2)	8,015	14.81	3.44 (2.62, 4.53)	0.82 (0.61, 1.10)	0.76 (0.57, 1.02)
p for trend[‖]				0.9231	0.3603
Obesity level II (35 to <40 kg/m^2)	5,724	10.87	3.77 (2.78, 5.12)	0.87 (0.63, 1.19)	0.81 (0.58, 1.12)
Obesity level III (≥40 kg/m^2)	2,291	3.94	2.54 (1.36, 4.71)	0.68 (0.36, 1.27)	0.62 (0.33, 1.17)
p for trend[‖]				0.8018	0.2853
Waist circumference (n = 22,965)					
Waist circumference (per 5 cm)				0.98 (0.96, 1.01)	**0.97 (0.95, 0.99)**
Waist circumference strata					
≤80	16,725	114.78	5.22 (4.82, 5.65)	Ref.	Ref.
>81 to ≤88	10,093	69.50	5.05 (4.55, 5.61)	0.95 (0.82, 1.09)	0.92 (0.80, 1.06)
>88	14,205	95.71	4.67 (4.26, 5.12)	0.91 (0.80, 1.04)	**0.86 (0.75, 0.99)**
p for trend[‖]				0.1767	**0.0289**
Waist-hip ratio (n = 22,958)					
Waist-hip ratio (per 0.1)				**0.92 (0.85, 0.99)**	**0.90 (0.84, 0.98)**
Waist-hip ratio strata					
≤0.80	18,500	127.61	5.37 (4.98, 5.79)	Ref.	Ref.
0.81 to 0.84	10,606	72.65	4.93 (4.44, 5.47)	0.93 (0.81, 1.06)	0.91 (0.79, 1.05)
≥0.85	11,894	79.61	4.45 (4.01, 4.93)	0.88 (0.77, 1.01)	**0.86 (0.75, 0.99)**
p for trend[‖]				0.0597	**0.0309**

[*] Available BMI data from baseline through year 8 follow-up were used. BMIs were calculated from measured height at baseline with measured weight at baseline and year 3, and self-reported weight at follow-up years 1 and 4 to 8. WC and WHR at baseline and year 3 were used from measured WC and hip circumferences at baseline and year 3. For WHR measures included some women with missing baseline WHR at baseline but available at year 3.

[†] AIR: Annualized Incidence Rate (per 1,000 person-years).

[‡] Model 1 age group in the strata statement.

[§] Model 2 adjusted for education level, smoking status, pack-years of smoking, HEI-2015, hormone therapy use and physical activity (MET-hour/week). Age group and race are included in the strata statement.

[‖] The p for trend across anthropometric categories as ordinal variable.

The figures in bold represent confidence intervals that do not include 1.0 or where P values are <0.05.

hormone therapy use was associated with a decreased risk of FECD. We know that BMI can be a proxy measure (determinant) of endogenous estrogen levels,[33–35] especially in postmenopausal as compared with premenopausal women. We observed a Spearman correlation coefficient of 0.23 (P < 0.0001) between circulating serum estradiol and BMI in a subsample (n = 2174) of this cohort with estradiol concentrations, supporting this hypothesis. In our previous analysis, we also observed inverse but not statistically significant associations between serum estradiol and incident FECD in women in the WHI (HR = 0.67, 95% CI = 0.35–1.29 for quintile 5 vs. 1). Perhaps this association between BMI and FECD is reflecting protective associations between estrogen, because of a higher BMI, and corneal dystrophy development in older women. At the same time, we did not see a decreased risk of FECD in those with baseline BMIs ≥30 to <35 kg/m^2, but only in those with more extreme BMIs (≥35 kg/m^2). It is possible that there is a bias occurring with inadequate screening of individuals with obese body habitus due to difficulty positioning them at the slit lamp biomicroscope for proper evaluation of the cornea and identification of signs of FECD. This could lead to underestimation of the incidence of FECD in those with high BMIs (e.g. ≥35 kg/m^2).

Another possible explanation is that individuals at higher genetic risk for FECD may also be genetically prone to lower weight. Polymorphisms within introns in the transcription factor 4 gene (*TCF4*)[36,37] are more likely in persons with than without FECD. One polymorphism is a microsatellite region comprised of CTG trinucleotide repeats (TNRs) in intron 4 of the *TCF4* gene (CTG1.1). Individuals with FECD are more likely to have longer TNRs[10,12,37] than those without FECD. Other diseases are also associated with TNR expansion, such as Huntington's disease, which has an expanded number of CAG TNRs.[38] The CAG repeat length has been positively associated with weight loss[38] and is hypothesized to be related to a cellular hypermetabolic state.[38] In individuals with the TNR expansion disorder Spinocerebellar ataxia type 3, a progressive movement disorder, the length of the TNR is inversely associated with BMI.[39] It is possible that individuals who are more prone to genetic risk of FECD are also genetically less susceptible to gaining weight. However, in a previous cross-sectional study of only individuals with FECD,[12] we observed no statistically significant associations between the CTG18.1 TNR length and BMI. However, that study was cross-sectional and limited to only individuals with FECD.

Our paper also highlights some interesting findings that deserve further attention in future research on this cohort. We observed a statistically significant association between smoking pack-years and incident FECD. Women with ≥20 pack-years of smoking had the lowest incidence. It is possible that individuals with the highest pack-years died of other

causes prior to developing FECD. These analyses could be confounded by other factors. Previous research on smoking and FECD is rather limited, and not all show positive associations.[5–7,11] It is possible that smoking influences FECD progression or severity rather than risk, or that genetics are more influential on risk of FECD than some modifiable risk factors, We also observed a novel association suggesting a protective effect of recreational physical activity on FECD. Adjustment or recreational physical activity strengthened the protective associations. This observes further investigation as well.

Unfortunately, among the limitations of our study, we did not have data on genetic risk factors for FECD. Another limitation is the use of Medicare claims data for the identification of incident FECD cases. The claims data does not stratify FECD by disease severity. Most likely early cases of FECD, which are asymptomatic, were missed, especially among women who did not report seeing the eye doctor on a regular basis (at least every 2 years). In addition, we did not restrict our follow-up to women continuously enrolled in Medicare and we chose to exclude women <65 years of age as many of them were not enrolled in Medicare at WHI-OS baseline. Women could have exited Medicare or the WHI-OS, again adding to the possible lack of identification of incident cases. Other than the measured height and weight taken at WHI-OS baseline and year 3, BMI data from other periods of time used in this analysis were based on self-reported past or current weights from participants. These data are subject to some degree of measurement error, however, the validity of self-reported weight in WHI has been shown to be quite high.[40] There may also be residual confounding that we were unable to adjust for adequately.

Our study has several strengths. Its large size is well powered to examine our hypothesized associations and we were able to look at incident disease development over approximately 12 years of follow-up. Our study was designed prospectively so that we could examine exposure measures in women prior to disease development, in addition to examining the varying levels of some of these exposure over time such as with BMI, WC, and WHR, as well as historic measures of BMI at earlier ages. We were able to develop multivariable models controlling for possible confounding factors that could also explain associations between BMI and FECD risk, and we were able to explore effect modification of our associations by smoking exposure. As FECD is more prevalent in older women than older men,[6–9] we were able to restrict our analysis to the study of just women removing any potential confounding due to sex.

Conclusions

In conclusion, women with extremely obese BMIs (>35 kg/m^2), and women with increasing WC and WHR, were at a decreased risk of incident FECD. We cannot say whether this association is causal or a consequence of genetic traits that increase both risk for FECD and weight loss (or limitations to weight gain). Nevertheless, our data support a potential association of anthropometric factors, specifically those associated with central adiposity, such as WC and WHR, with FECD risk.

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