Relationship of Fuchs Endothelial Corneal Dystrophy Severity to Central Corneal Thickness

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**Objective:** To define the relationship between Fuchs endothelial corneal dystrophy (FECD) severity and central corneal thickness (CCT).

**Methods:** We examined 1610 eyes from a subset of index cases, family members, and unrelated control subjects with normal corneas from the FECD Genetics Multi-Center Study. To estimate the association between FECD severity grade (7-point severity scale based on guttae confluence) and CCT measured by ultrasonographic pachymetry, a multivariable model was used that adjusted for eye, age, race, sex, history of glaucoma or ocular hypertension, diabetes mellitus, contact lens wear, intraocular pressure, and familial relationship to the index case. An interaction between FECD severity grade and edema (stromal or epithelial) on slitlamp examination findings was used to investigate whether the effect of FECD severity grade on CCT differed between those with and without edema.

**Results:** Average CCT was thicker in index cases for all FECD grades compared with unaffected controls \( (P < .003) \) and in affected family members with an FECD grade of 4 or greater compared with unaffected family members \( (P < .04) \). Similar results were observed for subjects without edema. Average CCT of index cases was greater than that of affected family members with grades 4, 5, and 6 FECD \( (P < .02) \). Intraocular pressure was also associated with CCT \( (P = .01) \).

**Conclusions:** An increase in CCT occurs with increasing severity of FECD, including at lower FECD grades in which clinically observable edema is not present. Monitoring CCT changes serially could be a more sensitive measure of disease progression with surgical therapeutic implications.


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eases, notably the commonly occurring Fuchs endothelial corneal dystrophy (FECD), influence central corneal thickness (CCT), as do genetic determinants and potentially intraocular pressure (IOP). In healthy corneas, endothelial function is essential in maintaining normal thickness. The endothelium acts as a leaky fluid barrier between the aqueous humor and corneal stroma, enabling necessary nutrients to supply the cornea. The endothelium also acts as an active transporter of ions across this cell layer, creating an osmotic force that removes fluid from the corneal stroma. The balance between these 2 functions is a prime determinant of corneal thickness. Factors that impair the ability of the endothelium to perform these functions disrupt this balance with resultant corneal edema and an increase in thickness.

Fuchs endothelial corneal dystrophy is characterized by endothelial cell dysfunction that results in corneal edema. Thickening is believed to occur mainly in the later stages of FECD, manifesting as clinically apparent stromal and/or epithelial edema. The relationship between earlier stages of FECD and CCT is less clear. Prior studies have been limited by small sample sizes, a lack of consistent definitions of FECD severity, and heterogeneous FECD study populations. To further elucidate understanding of the pathogenesis of corneal thickening in FECD, we examined the relationship between FECD severity and CCT in subjects from the FECD Genetics Multi-Center Study.

**METHODS**

**STUDY POPULATION**

Subjects were selected from the FECD Genetics Multi-Center Study cohort, a study population recruited to identify genetic risk factors for FECD that has been previously de-
In brief, families enriched for FECD were ascertained through severely affected probands, with an emphasis on identifying severely affected sibling pairs, although other family members, affected and unaffected, were also recruited. In addition, unrelated FECD cases and control subjects matched to be 5 years older than index cases were also collected. The controls have also been previously described and included those with pseudophakic eyes at least 1 year from their surgery. Written informed consent was obtained from all subjects after institutional review board approval of the study. Demographic information and ocular and systemic medical histories were obtained via a standardized questionnaire administered to the patient via interview, and each eye was evaluated separately for inclusion in the present study. Eyes were excluded from this study if they had undergone penetrating or endothelial keratoplasty; had cataract surgery within 1 year of the study examination; had a history of blunt, penetrating, or perforating trauma; or had evidence of other corneal endothelial dystrophy. These exclusion criteria were chosen for their possible effect on corneal thickness and thus their potential to confound any relationship between FECD grade and CCT. Subject age, the time of examination, sex, self-reported diabetes mellitus, contact lens wear of any type, use of ocular and systemic medications, and self-reported history of ocular hypertension or glaucoma (open-angle or narrow-angle) were recorded. A slitlamp biomicroscopic examination by a cornea fellowship–trained ophthalmologist was performed to determine the extent of corneal guttae and the presence of any stromal or epithelial edema, along with a manifest refraction and measurement of IOP by means of applanation tonometry. Each ophthalmologist was trained on a standardized protocol for assessing the FECD grading scale, provided with photographic examples of each grade, and tested by grading live patient examples at the outset of the study to ensure consistency in grading across enrollment sites. The spherical equivalent was calculated from the manifest refraction for each eye.

FECD GRADE AND CCT DETERMINATION

The FECD grade was determined on a semiquantitative scale from 0 to 6, modified from a previous severity scale. We used the following grade scale: 0 indicates no guttae; 1, 1 to 12 central/paracentral nonconfluent guttae; 2, more than 12 central/paracentral nonconfluent guttae; 3, 1 to 2 mm of confluent central/paracentral guttae; 4, more than 2 to 5 mm of confluent central/paracentral guttae; 5, more than 5 mm of confluent central/paracentral guttae; and 6, more than 5 mm of confluent central/paracentral guttae with stromal and/or epithelial edema. Cases in which stromal or epithelial edema was observed overlying regions of focally dense guttae were graded according to the diameter of the area of guttae with edema independently recorded. Central corneal thickness was measured by a techniciamasked to the FECD grade of the subject; the technician was instructed to obtain measurements at the center of the cornea and centered over the pupil. Pachymeters were used from several manufacturers (Accutome, Bausch & Lomb Surgical, DGH Technology, KMI Surgical, Eye Technology, Inc, Haag-Streit, Sonogage, Sonomed, and Tomey). Each instrument internally calibrates and takes repeated measurements to determine the thickness ultrasonographically. Given the difficulty in defining the exact center of the cornea, 3 separate readings were obtained immediately after each other, and the mean of these measurements was used as the CCT. Eyes with any CCT measurement of less than 100 µm were excluded from further analysis (n = 4).

STATISTICAL ANALYSES

The eyes from subjects were divided into the following 4 categories for analysis: (1) proband and unrelated cases (herein referred to as index cases), (2) affected family members (FECD grade of >0), (3) unaffected family members (FECD grade of 0), and (4) unrelated controls with normal corneas. Enrollment under the genetic study design emphasized severely affected probands and affected siblings with FECD grades of greater than 4 in at least 1 eye, resulting in small sample sizes in groups with FECD grades of 1 to 3. As such, these eyes were combined into a single group for the index cases and affected family member categories. Using a generalized estimating equations approach that accounted for correlation between eyes with an exchangeable working correlation structure, 2 multivariable models were fitted to estimate the effect of FECD grade on CCT. The first model adjusted for eye (right vs left), age, race (white vs nonwhite), presence of glaucoma/ocular hypertension, diabetes, contact lens wear (ever vs never), and IOP. The FECD grade and relationship to the index case were also included as categorical variables with an interaction between them. The second model adjusted for covariates from the first model and spherical equivalent for each eye, the time of the evaluation (morning vs afternoon), and whether the subject reported symptoms of blurred vision in the morning for the eye. The second model was used to estimate the effects of these 3 variables on CCT because they had limited data compared with the other variables included in the first model.

Because clinically evident edema was observed in several subjects at FECD grades for which edema was not a defining grading criterion, an interaction between FECD grade and the presence or the absence of clinically apparent stromal or epithelial edema was also included to investigate whether the effect of FECD grade on CCT differed between those subjects with and without edema. Unless otherwise indicated, data are expressed as mean (SD).

RESULTS

In total, 3118 eyes from 1559 subjects were considered for this study, with 1610 eyes from 969 subjects meeting inclusion criteria. Of the excluded eyes, 945 had undergone prior keratoplasty, 273 had undergone cataract surgery within 1 year of study enrollment, 77 had a history of trauma, and 11 had findings consistent with an additional corneal dystrophy. Eyes were also excluded if data for CCT, FECD grade, or variables included in the analysis models were missing. We included 18.1% of eyes from index cases, 40.1% from affected family members, 34.2% from controls, and 7.5% from unaffected family members. The cohort was predominantly white (97.6% of subjects) and female (65.3% of subjects), similar to our larger cohort. Index cases were slightly older than affected family members (mean age, 68.9 [11.4] vs 63.2 [12.8] years) (Table 1). Given the matching practice of the primary study of selecting controls 5 years older than corresponding cases, controls were older than the index cases (mean age, 71.2 [7.6] years). Unaffected family members were the youngest group, with a mean age of 52.2 (13.6) years. The proportion of female subjects was greatest in the affected family member group (72.6%) compared with the index case, control, and unaffected family member groups (61.5%, 59.7%, and 65.6%, respectively). A greater proportion of eyes from index cases...
had epithelial or stromal edema than did eyes from affected family members (45.9% vs 21.4%) (Table 2). Eyes from index cases had a higher prevalence of a history of glaucoma or ocular hypertension than did eyes from affected family members or controls (10.6%, 6.6%, and 6.0%, respectively). No unaffected family member reported a history of glaucoma or ocular hypertension. Mean IOP was greatest in the controls (15.8 ± 3.2 mm Hg) and lowest in the index cases (14.9 ± 3.1 mm Hg) (Table 2). Among patients who contributed both eyes to our sample, no unaffected family member had epithelial or stromal edema compared with eyes from affected family members or controls (45.9% vs 21.4%) (Table 2). Eyes from index cases had a higher prevalence of a history of glaucoma or ocular hypertension than did eyes from affected family members or controls (10.6%, 6.6%, and 6.0%, respectively). No unaffected family member reported a history of glaucoma or ocular hypertension. Mean IOP was greatest in the controls (15.8 ± 3.2 mm Hg) and lowest in the index cases (14.9 ± 3.1 mm Hg) (Table 2). Among patients who contributed both eyes to our sample, no unaffected family member had epithelial or stromal edema compared with eyes from affected family members or controls (45.9% vs 21.4%) (Table 2).
fected family members was not significantly different (\(P = .97\)).

As anticipated, corneas with slitlamp-observed edema were thicker than corneas without edema (Table 5). Mean CCT in index cases without edema was thicker than in controls for FECD grades 4 and 5 (\(P < .001\)), whereas mean CCT in affected family members without edema was thicker than mean CCT in unaffected family members in the FECD grade 5 group (\(P < .001\)). By definition, cases with FECD grade 6 had edema on examination and could not be included in these results. Comparisons between index cases and affected family members without edema demonstrated significantly thicker corneas in the index group for subjects with FECD grades of 4 and 5 (\(P = .02\)). Alternatively, in the subjects with edema, the mean CCT in index cases was thicker than the mean CCT in affected family members only for grade 6 (\(P = .01\)). Subjects with a grade 5 guttae diameter and also observed to have edema were, by definition, classified as having FECD grade 6 and were not included in these results. After adjustment for an interaction between edema and FECD grade, there was evidence of an association among IOP, age, and contact lens wear on CCT (\(P = .045\), results not shown).

**COMMENT**

General understanding based on compensatory mechanisms in the deteriorating endothelium in FECD is that CCT remains normal until the late stages of the disease, when there are extensive confluent guttae.\(^1\) Another possibility, however, is that a gradual increase in CCT arises as FECD progresses. Studies have been limited in their ability to distinguish between these mechanisms because of a lack of standardization of grading criteria, small sample sizes, and a lack of prospective studies. The present study suggests that there is a gradual increase in CCT as FECD progresses clinically. Significant differences in CCT were even detectable at early grades of FECD compared with normal controls. Our results indicate that subjects with as few as 1 to 2 mm of confluent guttae may begin to develop central corneal thickening, pointing to a gradual process of endothelial dysfunction rather than an acute “tipping point” of endothelial decompensation as a likely mechanism of corneal edema in FECD. Our findings were not limited to 1 subset of our cohort but rather were observed in the affected family members and index cases, indicating this is not an isolated phenomenon.

Corneal hydration is mainly regulated by endothelial barrier function and ionic gradients set up by the Na/K-ATPases (sodium-potassium–adenosine triphosphatase...
pump). The physiological basis for corneal edema in FECD has been attributed to alterations in Na/K ATPase pump site density and/or breakdown in barrier function. There is a possible increase in the pump site density in early FECD stages, with a gradual decline as the disease progresses.\(^8,9\) Conversely, one of the earliest defects in FECD is a breakdown in barrier function that results in the increased permeability of corneal endothelium to solutes and increased corneal thickening.\(^1\) Although our study did not specifically study the mechanisms of corneal edema, it corroborates these studies by showing that corneal hydration could be affected in early stages of the disease process. Unfortunately, ultrasonographic pachymetry only measures total corneal thickness and cannot distinguish changes in thickness by individual corneal layers as can be accomplished by other methods, such as confocal microscopy;\(^2,3\) however, it seems feasible that subclinical thickening of the stroma may occur at lower FECD grades as endothelial function and compensatory mechanisms become impaired.

The average CCT in our 2 groups of unaffected subjects was consistent with the current understanding of normal corneal thickness measured by ultrasonographic pachymetry.\(^21\) The lack of a significant difference in mean CCT between explicitly recruited controls with normal corneas on slitlamp biomicroscopy findings and unaffected family members collected during familial recruitment is reassuring. Affected family members had on average thinner corneas at a given FECD grade than those of the index cases despite identical grading criteria for both groups. We hypothesized that index cases, as the subjects who brought the family to the attention of the study, were more likely to be symptomatic and thus more likely to have greater corneal thickening, regardless of the extent of guttae. Our results show that index cases did indeed have a higher rate of blurred vision in the morning than did affected family members (50.3% vs 36.4%), but adjusting for this symptom in the model had no effect on the observed difference between the 2 groups. This symptom as measured in our study might not be a sensitive enough symptomatic marker.

### Table 4. Model 1 Estimates and Comparisons of Mean CCT

<table>
<thead>
<tr>
<th>FECD Grade (^a)</th>
<th>Mean CCT (95% CI), µm</th>
<th>(P) Value (^b)</th>
<th>Mean CCT (95% CI), µm</th>
<th>(P) Value (^c)</th>
<th>Mean CCT (95% CI), µm</th>
<th>(P) Value (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>558 (554 to 562)</td>
<td>.003</td>
<td>578 (564 to 577)</td>
<td>.04</td>
<td>598 (584 to 598)</td>
<td>.07</td>
</tr>
<tr>
<td>Index Cases</td>
<td>586 (567 to 605)</td>
<td>.003</td>
<td>606 (592 to 620)</td>
<td>.001</td>
<td>626 (612 to 640)</td>
<td>.001</td>
</tr>
<tr>
<td>Affected Family Members</td>
<td>598 (584 to 607)</td>
<td>.001</td>
<td>618 (604 to 620)</td>
<td>.001</td>
<td>638 (624 to 652)</td>
<td>.001</td>
</tr>
<tr>
<td>Difference</td>
<td>0 (-12 to 12)</td>
<td>.97</td>
<td>0 (-12 to 12)</td>
<td>.97</td>
<td>0 (-12 to 12)</td>
<td>.97</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; FECD, Fuchs endothelial corneal dystrophy.

\(^a\) Grades and study analysis groups are explained in the Figure and the "FECD Grade and CCT Determination" subsection of the "Methods" section.

\(^b\) Calculated as the comparison of the mean CCT between each index case FECD grade group and controls.

\(^c\) Calculated as the comparison of the mean CCT between each affected family member FECD grade group and unaffected family members.

\(^d\) Calculated as the comparison of the mean CCT between affected family members and index cases or unaffected family members and controls.

### Table 5. Estimates and Comparisons of CCT for Subjects Without and With Edema\(^a\)

<table>
<thead>
<tr>
<th>FECD Grade</th>
<th>No.</th>
<th>Mean CCT (95% CI), µm</th>
<th>(P) Value (^b)</th>
<th>No.</th>
<th>Mean CCT (95% CI), µm</th>
<th>(P) Value (^c)</th>
<th>Difference</th>
<th>Mean CCT (95% CI), µm</th>
<th>(P) Value (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0</td>
<td>558 (554 to 562)</td>
<td>.003</td>
<td>121</td>
<td>558 (548 to 569)</td>
<td>.06</td>
<td>0 (-11 to 12)</td>
<td>566 (554 to 578)</td>
<td>.36</td>
</tr>
<tr>
<td>Index Cases</td>
<td>0</td>
<td>558 (554 to 562)</td>
<td>.003</td>
<td>121</td>
<td>558 (548 to 569)</td>
<td>.06</td>
<td>0 (-11 to 12)</td>
<td>566 (554 to 578)</td>
<td>.36</td>
</tr>
<tr>
<td>Affected Family Members</td>
<td>0</td>
<td>558 (554 to 562)</td>
<td>.003</td>
<td>121</td>
<td>558 (548 to 569)</td>
<td>.06</td>
<td>0 (-11 to 12)</td>
<td>566 (554 to 578)</td>
<td>.36</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; FECD, Fuchs endothelial corneal dystrophy.

\(^a\) Grades and study analysis groups are explained in the Figure and the "FECD Grade and CCT Determination" subsection of the "Methods" section.

\(^b\) Calculated as the comparison of the mean CCT between explicitly recruited controls with normal corneas on slitlamp biomicroscopy findings and unaffected family members collected during familial recruitment.

\(^c\) Calculated as the comparison of the mean CCT between each index case FECD grade group and controls for subjects without clinically apparent edema.

\(^d\) Calculated as the comparison of the mean CCT between each affected family member FECD grade group and unaffected family members for subjects without clinically apparent edema.

\(^e\) Calculated as the comparison of the mean CCT between affected family members and index cases or between unaffected family members and controls for subjects without clinically apparent edema.

\(^f\) Calculated as the comparison of the mean CCT between affected family members and index cases for subjects with clinically apparent edema.

\(^g\) Subjects with edema at FECD grades 1 through 4 represent individuals with focally dense guttae observed to also have clinically evident edema on slitlamp examination findings. Subjects with FECD grade 5 and also noted to have clinically observed edema had findings equivalent to an FECD grade 6 and were classified accordingly.
to adequately account for the effect, or other hypotheses for the phenomenon should be considered. Recent work has examined the progressive loss of endothelial cell density in corneas with guttae without clinical edema and found that these eyes could be classified as likely asymptomatic guttae, borderline guttae that may progress to development of corneal edema, and guttae likely to be a preliminary form of FECD (as defined by the development of stromal or epithelial edema or other late-stage complications) based on changes in cell density.22 Our observed difference in CCT between index cases and affected family members may represent a greater proportion of index case eyes falling into the latter 2 categories with resultant endothelial dysfunction. Because the other eye of each index case must have been severely affected for the subject to have initially qualified for the study, it would not be surprising that the companion eye would likely progress to late-stage FECD.

Also of interest was the identification of a small subgroup of subjects with locally dense guttae that resulted in clinically evident edema, with a greater proportion of index cases than affected family members encompassed in this subgroup. These subjects do not entirely account for the differences in CCT between the index cases and affected family members because analyses excluding subjects with edema still identify differences in CCT. These subjects may partially contribute to the findings of increased CCT at lower FECD grades because we observed the loss of a significant difference in CCT between index cases and controls for FECD grades 1 through 3 and affected and unaffected family members for FECD grades 1 through 3 and grade 4 when these subjects were excluded, although a trend toward an effect remained. The same factors that underlie the difference in CCT between index cases and their affected familial counterparts may also underlie the development of edema in the presence of only focally dense guttae.

Several factors, including IOP and contact lens wear, have been previously implicated in affecting corneal thickness and were examined as potential confounders in the current study. There is a known association between increased IOP and greater CCT.24,25 Multiple studies have also shown that subjects with ocular hypertension have increased CCT,7,23 and some evidence suggests that chronic elevation of IOP contributes to this increase.24 Within our cohort, increases in IOP were significantly associated with increased CCT, although the causal relationship remains unclear. Whether this represents the known association between IOP and CCT or whether FECD itself may have a relationship with IOP requires further study.

Prior research has demonstrated an association between corneal thinning and long-term extended wear of contact lenses.23,26 Although there appears to be significant individual variability in the corneal response to use of extended-wear contact lenses,27 our models show some evidence of lower CCT among those who have worn contact lenses (P = .09 in our main model and P = .045 in the model that includes a group × edema interaction). Because our study is limited by the lack of complete data on the type, duration, and time interval of contact lens wear, it is feasible that the contact lens effect in our study would be diluted compared with what has been previously shown in the literature and could explain why the association is inconclusive despite the large sample size.

Numerous previous studies have examined the correlation between age and CCT without any obvious trends emerging.21,28 Our models show some evidence of lower CCT being associated with increased age (P = .06 in our main model and P = .02 in the model that includes an interaction between group and edema), consistent with the ambiguity in the literature. Also, because our population was predominantly older (average age, 66 years), it is difficult to draw conclusions about age and CCT that could be generalized to a broader population.

The cross-sectional nature, the method chosen for assessing CCT, and the measurement of thickness only in the central cornea are limitations to this study. Within the general population, there is a normal variation of corneal thickness,27 and it is on this variability that the effects of FECD are superimposed. Our study did not follow up subjects longitudinally because the primary objective of the study was to assess the genetic factors associated with advanced late-onset FECD; thus, the change in CCT over time with advancing FECD and genetic factors associated with this phenotype by individual, as studied in several families with late-onset FECD,29,30 was not examined. Some subjects may have corneas thinner than 500 µm before development of advanced FECD31; therefore, they may never develop CCT values of greater than 700 µm, usually considered abnormally thick, even with advanced disease. The spread in normal CCT before disease onset was most likely reflected in the CCT spread of our own index and affected family members; cases with FECD grade 6, in which some subjects had a CCT of less than the average CCT for controls and unaffected family members (Figure). As such, an individual’s overall change in CCT will likely be most useful in clinical management rather than a comparison with the CCT from other individuals with FECD. This observation particularly affects decision making regarding cataract surgery in the setting of FECD. The decision to perform cataract surgery alone, cataract surgery with keratoplasty, or keratoplasty alone should be based on a number of factors, including the type and degree of cataract and the density and location of the guttae, which may cause light scattering and a decrease in visual acuity directly.12,23 As well as, based on our findings, the change in CCT between visits and the clinical presence of stromal and/or epithelial edema rather than the absolute CCT value.34 With the advent of earlier surgical intervention in FECD with endothelial keratoplasty, the application of these proposed principles and their role in the management of earlier stages of FECD becomes even more important.

Ultrasonographic pachymetry, our method for assessing CCT, was chosen because it is commonly used clinically and was thus available across the many sites enrolling subjects for the genetic study. In using ultrasonographic pachymetry, we were unable to examine the individual layers of the cornea for changes contributing to increased thickness. In addition, thickness was solely measured in the center of the cornea for consistency; thus, our conclusions can only apply to this measurement. The measurement of CCT may be an underestimate of the thickest area of the cornea when more severe disease is located in the paracentral region. However, paracentral measurement is confounded by the increasing thickness of the cornea from the center to the periphery and by variability from subject to subject for a defined paracen-
nal location. Despite these limitations, our study provides evidence from a large cohort of subjects that changes in CCT occur in patients with FECD before clinically apparent edema.

Our findings provide evidence supporting the use of CCT as a quantitative factor in following FECD progression in addition to more subjective modalities, such as slitlamp examination. A clear connection between CCT values and FECD severity grade points to the potential use of CCT to guide treatment decisions and prognosticate for surgical intervention. The cross-sectional design of our study limits our ability to examine this question in the current cohort; however, future prospective, longitudinal studies could do so. Our findings also highlight the benefit of collecting additional clinical data in a cohort initially assembled to investigate genetic risk factors for FECD. Our insights into the pathologic features of earlier stages of FECD enhance the current clinical paradigm and add to the disease model through which the results of any future studies—genetic analyses or otherwise—will be interpreted.

Submitted for Publication: June 11, 2011; final revision received September 30, 2011; accepted October 10, 2011.

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Author Contributions: Drs Iyengar and Lass contributed equally to this study. Drs Kopplin, Iyengar, and Lass had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants RO1EY16482, R21 EYO15145, and P30 EY11373 from Research to Prevent Blindness and the Ohio Lions Eye Research Foundation.

Additional Contributions: David Musch, PhD, provided advice on the study design.

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