Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

ANNEE 2016

N°

PREVALENCE ET FACTEURS ASSOCIES DE LA SECHERESSE OCULAIRE DANS UNE POPULATION FRANCAISE AGEE

THESE

présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 23 septembre 2016

pour obtenir le grade de Docteur en Médecine

par

Arthur FERRERO

Né le 24 février 1986

A Montauban (Tarn et Garonne)

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

ANNEE 2016

N°

PREVALENCE ET FACTEURS ASSOCIES DE LA SECHERESSE OCULAIRE DANS UNE POPULATION FRANCAISE AGEE

THESE

présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 23 septembre 2016

pour obtenir le grade de Docteur en Médecine

par

Arthur FERRERO

Né le 24 février 1986

A Montauban (Tarn et Garonne)

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

Année Universitaire 2016-2017
au **1er Septembre 2016**

Doyen :	**M. Frédéric HUET**
1er Assesseur :	M. Yves ARTUR
Assesseurs :	Mme Laurence DUVILLARD
	M. Pablo ORTEGA-DEBALLON
	M. Marc MAYNADIE

PROFESSEURS DES UNIVERSITES - PRATICIENS HOSPITALIERS

			Discipline
M.	Marc	**BARDOU**	Pharmacologie clinique
M.	Jean-Noël	**BASTIE**	Hématologie - transfusion
M.	Emmanuel	**BAULOT**	Chirurgie orthopédique et traumatologie
M.	Laurent	**BEDENNE**	Gastroentérologie et hépatologie
M.	Yannick	**BEJOT**	Neurologie
M.	Alain	**BERNARD**	Chirurgie thoracique et cardiovasculaire
M.	Jean-François	**BESANCENOT**	Médecine interne
Mme	Christine	**BINQUET**	Epidémiologie, économie de la santé et prévention
M.	Bernard	**BONIN**	Psychiatrie d'adultes
M.	Philippe	**BONNIAUD**	Pneumologie
M.	Alain	**BONNIN**	Parasitologie et mycologie
M.	Bernard	**BONNOTTE**	Immunologie
M.	Olivier	**BOUCHOT**	Chirurgie cardiovasculaire et thoracique
M.	Belaid	**BOUHEMAD**	Anesthésiologie - réanimation chirurgicale
M.	Alexis	**BOZORG-GRAYELI**	ORL
M.	Alain	**BRON**	Ophtalmologie
M.	Laurent	**BRONDEL**	Physiologie
M.	François	**BRUNOTTE**	Biophysique et Médecine Nucléaire
M.	Patrick	**CALLIER**	Génétique
M.	Jean-Marie	**CASILLAS-GIL**	Médecine physique et réadaptation
Mme	Catherine	**CHAMARD-NEUWIRTH**	Bactériologie - virologie; hygiène hospitalière
M.	Pierre-Emmanuel	**CHARLES**	Réanimation
M.	Pascal	**CHAVANET**	Maladies infectieuses
M.	Nicolas	**CHEYNEL**	Anatomie
M.	Alexandre	**COCHET**	Biophysique et médecine nucléaire
M.	Luc	**CORMIER**	Urologie
M.	Yves	**COTTIN**	Cardiologie
M.	Charles	**COUTANT**	Gynécologie-obstétrique
M.	Gilles	**CREHANGE**	Oncologie-radiothérapie
Mme	Catherine	**CREUZOT-GARCHER**	Ophtalmologie
M.	Frédéric	**DALLE**	Parasitologie et mycologie
M.	Serge	**DOUVIER**	Gynécologie-obstétrique
Mme	Laurence	**DUVILLARD**	Biochimie et biologie moléculaire
Mme	Laurence	**FAIVRE-OLIVIER**	Génétique médicale
Mme	Patricia	**FAUQUE**	Biologie et Médecine du Développement
Mme	Irène	**FRANCOIS-PURSSELL**	Médecine légale et droit de la santé
M.	Pierre	**FUMOLEAU**	Cancérologie
M.	François	**GHIRINGHELLI**	Cancérologie
M.	Claude	**GIRARD**	Anesthésiologie – réanimation chirurgicale
M.	Vincent	**GREMEAUX**	Médecine physique et réadaptation
M.	Frédéric	**HUET**	Pédiatrie
M.	Pierre	**JOUANNY**	Gériatrie

M.	Denis	**KRAUSÉ**	Radiologie et imagerie médicale
M.	Sylvain	**LADOIRE**	Histologie
M.	Gabriel	**LAURENT**	Cardiologie
M.	Côme	**LEPAGE**	Hépato-gastroentérologie
M.	Romaric	**LOFFROY**	Radiologie et imagerie médicale
M.	Luc	**LORGIS**	Cardiologie
M.	Jean-Francis	**MAILLEFERT**	Rhumatologie
M.	Cyriaque Patrick	**MANCKOUNDIA**	Gériatrie
M.	Sylvain	**MANFREDI**	Hépato-gastroentérologie
M.	Laurent	**MARTIN**	Anatomie et cytologie pathologiques
M.	David	**MASSON**	Biochimie et biologie moléculaire
M.	Marc	**MAYNADIE**	Hématologie - transfusion
M.	Thibault	**MOREAU**	Neurologie
M.	Klaus Luc	**MOURIER**	Neurochirurgie
Mme	Christiane	**MOUSSON**	Néphrologie
M.	Paul	**ORNETTI**	Rhumatologie
M.	Pablo	**ORTEGA-DEBALLON**	Chirurgie Générale
M.	Jean-Michel	**PETIT**	Endocrinologie, diabète et maladies métaboliques
M.	Lionel	**PIROTH**	Maladies infectieuses
Mme	Catherine	**QUANTIN**	Biostatistiques, informatique médicale
M.	Jean-Pierre	**QUENOT**	Réanimation
M.	Patrick	**RAT**	Chirurgie générale
M.	Jean-Michel	**REBIBOU**	Néphrologie
M.	Frédéric	**RICOLFI**	Radiologie et imagerie médicale
M.	Paul	**SAGOT**	Gynécologie-obstétrique
M.	Emmanuel	**SAPIN**	Chirurgie Infantile
M.	Henri-Jacques	**SMOLIK**	Médecine et santé au travail
M.	Éric	**STEINMETZ**	Chirurgie vasculaire
Mme	Christel	**THAUVIN**	Génétique
M.	Pierre	**VABRES**	Dermato-vénéréologie
M.	Bruno	**VERGÈS**	Endocrinologie, diabète et maladies métaboliques
M.	Narcisse	**ZWETYENGA**	Chirurgie maxillo-faciale et stomatologie

PROFESSEURS ASSOCIES DES DISCIPLINES MEDICALES

M.	Bruno	**MANGOLA**	Urgences (du 01/05/2016 au 14/11/2016)

PROFESSEURS EN SURNOMBRE

M.	Roger	**BRENOT**	(surnombre jusqu'au 31/08/2018)
M.	Philippe	**CAMUS**	(surnombre jusqu'au 31/08/2019)
Mme	Monique	**DUMAS-MARION**	(surnombre jusqu'au 31/08/2018)
M.	Maurice	**GIROUD**	(surnombre jusqu'au 21/08/2018)
M.	Frédéric	**MICHEL**	(surnombre du 20/10/2015 au 31/12/2016)
M.	Pierre	**TROUILLOUD**	(surnombre du 05/02/2014 au 31/08/2017)

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

MAITRES DE CONFERENCES DES UNIVERSITES
PRATICIENS HOSPITALIERS DES DISCIPLINES MEDICALES

			Discipline Universitaire
M.	Sylvain	**AUDIA**	Médecine interne
Mme	Shaliha	**BECHOUA**	Biologie et médecine du développement
Mme	Marie-Claude	**BRINDISI**	Nutrition
M.	Jean-Christophe	**CHAUVET-GELINIER**	Psychiatrie, psychologie médicale
		(Mobilité Novembre 2016 à 2017)	
M.	Alexis	**DE ROUGEMONT**	Bactériologie-virologie ; hygiène hospitalière
M.	Hervé	**DEVILLIERS**	Médecine interne
M.	Olivier	**FACY**	Chirurgie générale
Mme	Ségolène	**GAMBERT-NICOT**	Biochimie et biologie moléculaire
Mme	Françoise	**GOIRAND**	Pharmacologie fondamentale
Mme	Agnès	**JACQUIN**	Physiologie
M.	Alain	**LALANDE**	Biophysique et médecine nucléaire
M.	Louis	**LEGRAND**	Biostatistiques, informatique médicale
Mme	Stéphanie	**LEMAIRE-EWING**	Biochimie et biologie moléculaire
M	Maxime	**SAMSON**	Médecine interne
		(Mobilité Novembre 2016 à 2017)	
M.	Benoit	**TROJAK**	Psychiatrie d'adultes ; addictologie
M.	Paul-Mickaël	**WALKER**	Biophysique et médecine nucléaire

PROFESSEURS EMERITES

M.	Jean	**CUISENIER**	(01/09/2014 au 31/08/2017)
M.	Jean	**FAIVRE**	(01/09/2012 au 31/08/2018)
M	Philippe	**GAMBERT**	(01/09/2014 au 31/08/2017)
M.	Patrick	**HILLON**	(01/09/2016 au 31/08/2019)
M.	François	**MARTIN**	(01/09/2015 au 31/08/2018)
M.	Pierre	**POTHIER**	(01/09/2015 au 31/08/2018)

PROFESSEURS DES UNIVERSITES DE MEDECINE GENERALE

M.	Jean-Noël	**BEIS**	Médecine Générale

PROFESSEURS ASSOCIES DE MEDECINE GENERALE

M.	Didier	**CANNET**	Médecine Générale
M.	Gilles	**MOREL**	Médecine Générale
M.	François	**MORLON**	Médecine Générale

MAITRES DE CONFERENCES ASSOCIES DE MEDECINE GENERALE

M.	Clément	**CHARRA**	Médecine Générale
M.	Rémi	**DURAND**	Médecine Générale
M.	Arnaud	**GOUGET**	Médecine Générale
Mme	Anne	**WALDNER-COMBERNOUX**	Médecine Générale

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

MAITRES DE CONFERENCES DES UNIVERSITES

M.	Didier	**CARNET**	Anglais
M.	Jean-Pierre	**CHARPY**	Anglais
Mme	Catherine	**LEJEUNE**	Pôle Epidémiologie
M.	Gaëtan	**JEGO**	Biologie Cellulaire

PROFESSEURS DES UNIVERSITES

Mme	Marianne	**ZELLER**	Physiologie

PROFESSEURS AGREGES de L'ENSEIGNEMENT SECONDAIRE

Mme	Marceline	**EVRARD**	Anglais
Mme	Lucie	**MAILLARD**	Anglais

PROFESSEURS CERTIFIES

Mme	Anaïs	**CARNET**	Anglais
M.	Philippe	**DE LA GRANGE**	Anglais
Mme	Virginie	**ROUXEL**	Anglais (Pharmacie)

PROFESSEURS DES UNIVERSITES - PRATICIENS HOSPITALIERS DES DISCIPLINES PHARMACEUTIQUES

Mme	Evelyne	**KOHLI**	Immunologie
M.	François	**GIRODON**	Sciences biologiques, fondamentales et cliniques

MAITRES DE CONFERENCES DES UNIVERSITES PRATICIENS HOSPITALIERS DES DISCIPLINES PHARMACEUTIQUES

M.	Mathieu	**BOULIN**	Pharmacie clinique
M.	Philippe	**FAGNONI**	Pharmacie clinique
M.	Frédéric	**LIRUSSI**	Toxicologie
M.	Marc	**SAUTOUR**	Botanique et cryptogamie
M.	Antonin	**SCHMITT**	Pharmacologie

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

L'UFR des Sciences de Santé de Dijon, Circonscription Médecine, déclare que les opinions émises dans les thèses qui lui sont présentées doivent être considérées comme propres à leurs auteurs, et qu'elle n'entend ne leur donner ni approbation, ni improbation.

COMPOSITION DU JURY

Présidente :	Madame le Professeur Catherine CREUZOT-GARCHER
Membres :	Monsieur le Professeur Alain BRON
	Monsieur le Docteur Hervé DEVILLIERS
	Madame le Docteur Aurore MUSELIER-MATHIEU

A notre Présidente de thèse,

Madame le Professeur Catherine Creuzot-Garcher,

Nous vous remercions de l'honneur que vous nous avez fait en acceptant de présider notre jury.

Votre patience, votre ouverture d'esprit et vos compétences nous ont permis de nous bâtir professionnellement avec des bases solides.

Votre disponibilité et votre sens de l'écoute avec nous, comme avec les patients, sont exemplaires.

Nous vous remercions pour votre considération chaleureuse ressentie tout au long de notre cursus ainsi que pour la confiance que vous nous avez accordé durant ces 5 ans.

Nous mesurons la chance que nous avons de faire partie de votre service.

Soyez assurée de notre plus grande reconnaissance et de notre plus profond respect.

A notre Juge,

Monsieur le Professeur Alain Bron,

Nous vous remercions de l'honneur que vous nous avait fait d'accepter de juger ce travail.

Votre sens du travail, de la rigueur et du geste juste nous ont permis de fonder au fil des années les bases d'un exercice médical des plus efficaces toujours pour le bien du patient.

Votre savoir immense et votre amour de la profession sont pour nous un exemple.

Nous sommes fier d'avoir été votre élève.

Soyez assuré de notre plus grande reconnaissance et de notre plus profond respect.

A notre Juge,

Monsieur le Docteur Hervé Devilliers,

Soyez vivement remercié d'avoir accepté de juger ce travail.

Vous nous faites l'honneur de continuer à enrichir la vive collaboration entre les différents services du CHU de Dijon.

Veuillez accepter l'expression de mes remerciements les plus chaleureux et de mon plus profond respect.

A notre Juge,

Madame le Docteur Aurore Muselier-Mathieu,

Soyez remerciée de l'honneur que vous nous avez fait d'encadrer et de juger ce travail. Votre sens du travail, votre capacité d'analyse et votre attention à nous enseigner votre savoir nous enrichissent un peu plus chaque jour.

Nous partageons avec les patients la chance de bénéficier de votre gentillesse, votre disponibilité et votre grande connaissance médicale et chirurgicale, et ce toujours avec une humilité sources d'inspiration.

Soyez assurée de notre plus profond respect et de notre plus sincère amitié.

A **Papa**, quelle force et quel courage ! je suis tellement content que tu sois là ! Merci

A **Maman**, merci pour ton soutien sans faille et tes petits colis.

Merci à tout le **service** pour ces 5 années passées à vos côtés. Je mesure la chance que j'ai eu de faire partie de cette incroyable équipe.

A tous mes co-internes et chefs du plus jeune au plus vieux, j'ai toujours fait de mon mieux pour être à la hauteur. C'est grâce à vous si j'ai pu apprendre et progresser. Merci. Vous allez me manquer.

Cyril mon chef du bloc, gracias por tu confiancia y por ton assurance chirurgicale ! **Denis**, **Yann**, pour vos conseils avisés et vos parcours exemplaires, sources d'inspirations. Aux anciens : **Rodica**, **Caroline**, **Till, Arnaud, Philippe, Anna, Morgane, Jean-Christophe, Benjamin** : merci de m'avoir appris à allumer une lampe à fente et à éteindre les OCT. Merci pour le coaching strict initial (Anna et JC !) et le soutien continu (tous). **Charlotte, Clémence** et **Jacques** : meilleure promo, à nos week-end love autour du monde #londres, #nice, #seattle ! merci pour votre accueil dès mon arrivée, et bonne chance pour la suite. **Aurélie** #teamcornée #teamcontacto ☺ Encore quelques épisodes du journal de la Santé avant la fin de la saison. **Louis** (PUPHipster), **Pierre-Henry** (& Synthia), **Youssef** (mon préféré), **Ghisou** (du bled). **Elsa** (#paysbasque #teamcornée), **Julie** (#chefcafé #200firastouteseule), **Florian** (#teamcornée, au top), **Edouard** (dans la team mais jamais co-interne en fait :p), **Martin** (bienvenue !), **Lucie** (très bon choix), **Sophia** (jamais co-interne non plus ;)), **Solenne**, **Inès**… quelqu'un peut me dire dans quelle promo vous êtes ? Merci pour tout et continuez comme ça !

Aux infirmières et aides-soignantes, merci pour tous ce que vous faites en plus du boulot, je ne trouverai jamais mieux, je reviendrai donc vers vous au moment de m'installer ;) **Fabienne, Pascalou, Anne-Claude, Sarah, Fabienne, Christelle** : quelle équipe, vous nous montrez l'exemple du travail dans la bonne humeur et entre copines en plus ! A nos discussions entre 2 OCT… A l'UCA, même si on monte plus vous voir ☺ Jeanne, Katy, Véro, Pascale, Babeth, Cyndy…

Aux orthoptistes et à leurs élèves, **Aurélie, Céline, Amel, Audrey, Clémence, Magalie, Constance, Benoit**, et tous les autres !

Aux ARCs**, Laurène, Emmanuella, Sophie**…

Aux secrétaires, pardon si j'ai parfois râlé, faites bien attention à vous. Je n'avais jamais reçu autant de petits mots dans mon casier avant vous : **Françoise, Annick, Emilie, Anna, Amandine, Aude, Marion** …

Au filles du bloc, merci pour votre patience et vos encouragements, **Nathalie**, **Marie, Séverine, Sophie, Delphine, Cécile, Marie-Claude, Sandrine, Danielle.** #collierdimmunité

Au **Dr Seydou Alassane**, merci pour ton aide précieuse, et ta participation active dans ce travail. Bonne chance pour la suite.

Au **Dr. Damien Gatinel**, votre façon d'appréhender l'ophtalmologie est une source d'inspiration, merci pour ce semestre passé à vos côtés au top de la réfractive et dans la bonne humeur. (#staffchampagne)

Au **Dr. Alain Saad**, votre dextérité chirurgicale est un exemple, merci pour la DMEK de mes 30ans, je n'oublierai jamais !

Au service du Dr. Gatinel, **Dr. Romain Courtin** (FFI/interne) et **Dr. Christophe Panthier**, merci pour l'accueil, les enseignements, la chirurgie… j'ai tellement progressé à vos côtés. Les co-internes de Paris : un dijonnais qui a l'accent de Montauban ça n'a pas dû être facile, et pourtant quel semestre on a passé ! (#godsquad, #passioncornée)

Merci à mes amis,

A **Alex** et **Caro**, ma famille à Dijon, quelle chance de vous avoir rencontré, vous me manquez déjà,

A mes amis que j'ai laissés pour Dijon, après 5 ans, chacun de notre côté, nous sommes toujours aussi proches ! Je suis rassuré, maintenant on a fait le plus dur : c'est pour la vie ! **Joseph, Anne-Sophie, Oliver, Alix, Maxime, Jessica, Raph** (muchas gwacias especial for the support and tips) **Laura, Mathieu, Fanny, Alice, Bertrand, La Mique, Anne-Lolo, Quentin, Gwénola, Sophie, Benjamin P, Cathy, Marion, Pierre, Paul, Viiiinou, Zave, Camcam, Chico…**

(Je m'adresse bien sur uniquement à ceux qui ont fait le déplacement pour ma thèse ☺)

A **Manue** et **Simon** qui méritaient leur dédicace à part, vous me manquez trop ! (et **Dorian**, et **Maud**)

A **Marina**, **Henri** et **Lazare**, on ne devrait jamais quitter Montauban…

A **Constance** et **Stefano,** pour que l'on se voit plus souvent et … congrats !

A toute ma famille qui m'a toujours soutenu !

A mes frères et sœurs, et à leurs enfants, **Juju, Didi, Piépié, Nicole, Thibaut, Sarah, Elise, Victor, Joseph, Henri, Diane, Clément, Auguste**

A la famille **Drouillard-Sala-Barrière** ☺ ☺ ☺

A la SNCF, même si vous avez supprimé le train du matin…

A **Arnaud, Coco, Sylvain, Patricia, Adrien, Peggy, Sandra**…. Et tous les autres ! Merci pour votre accompagnement à nos formations depuis le premier jour !

Aux patients,

Et enfin, à **Mylène**, tu mériterais un diplôme aussi ce soir, d'une part pour tes connaissances en ophtalmo (à force d'écoute et de relectures) et d'autre part pour m'avoir toujours soutenu (supporté ?). Quel bonheur de t'avoir à mes côtés ! Je t'aime.

SERMENT D'HIPPOCRATE

"Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque."

Prévalence et facteurs associés de la sècheresse oculaire dans une population française âgée

Tableaux et figures

Liste des abréviations

3C: Three city

BCVA: Best Corrected Visual Acuity

CI: Confidence Interval

DED: Dry eye disease

DEWS: Dry Eye WorkShop

ETDRS: Early Treatment Diabetic Retinopathy Study

HOA: High Order Aberration

IQR: Interquartile Range

LASIK: Laser-Assisted In Situ Keratomileusis

Montrachet: Maculopathy, Optic Nerve, nutrition, neurovAsCular and HEarT diseases

OR: Odd Ratio

OSDI: Ocular Surface Disease Index

SD: Standard Deviation

TF-BUT: Tear Film Break-Up Time

INTRODUCTION

La sécheresse oculaire est une pathologie fréquente, souvent sous-estimée et sous-diagnostiquée. Elle représente environ 25 % des motifs de consultation en ophtalmologie. La fréquence relativement élevée de la sécheresse oculaire, son coût financier et son retentissement significatif sur la qualité de vie et même de la vision en font un véritable problème de santé publique.

La sécheresse oculaire est décrite par les patients comme pouvant entraîner des troubles de la vision : œil sec, rouge, sensation de grains de sable, brûlure, larmoiement, démangeaison… Cliniquement, on retrouve une diminution de la sécrétion lacrymale, une coloration à la fluorescéine anormale (kératite, ulcères, filaments…) et une instabilité du film lacrymal.

De nouvelles définitions de la sécheresse oculaire permettent d'appréhender plus facilement les mécanismes complexe de cette maladie, en introduisant les notions d'atteintes tissulaire et visuelle, d'inflammation et d'hyperosmolarité. L'œil sec fonctionne comme un véritable cercle vicieux biologique auto-entretenu dans lequel les malades glissent progressivement ou parfois brutalement sous l'effet d'une maladie autonome ou d'une accumulation de facteurs de risque. Une fois le cycle enclenché, la sécheresse peut s'autonomiser par rapport à sa cause, et il devient alors très difficile de bloquer les mécanismes qui entretiennent la kératite et l'inflammation chronique de la surface oculaire.

Du fait de cette complexe définition il est souvent difficile de classer nos patients atteints de sécheresse oculaire. Les grandes études épidémiologiques retrouvent des prévalences allant de 3,1 % à plus de 90 % en fonction des critères utilisés pour définir la sècheresse oculaire et des populations étudiées. Du fait de cette variation les facteurs associés ne sont pas encore clairement définis, hormis l'âge avancé et le sexe féminin.

L'objectif de notre étude était d'évaluer la prévalence de la sécheresse oculaire dans une population française de sujets âgés de plus de 75 ans et d'analyser les facteurs associés.

ARTICLE

Dry eye disease in the elderly in a French population-based study (The Montrachet study: Maculopathy, Optic Nerve, nutrition, neurovAsCular and HEarT diseases): Prevalence and associated factors.

Arthur Ferrero[1], Seydou Alassane, MD[2], Christine Binquet, MD, PhD[2], Lionel Bretillon, PhD[4], Niyazi Acar, PhD[2], Louis Arnould [1], Aurore Muselier-Mathieu, MD[1], Cécile Delcourt, MD, PhD[3], Alain M Bron, MD[1, 4], Catherine Creuzot-Garcher, MD, PhD[1, 4]

[1] Department of Ophthalmology, Dijon University Hospital, Dijon, France

[2] Department of Epidemiology, Dijon University Hospital, Dijon, France

[3] INSERM, Centre INSERM U897-Epidemiologie- Biostatistique, F-33000, Bordeaux, France

[4] Eye and Nutrition Research Group, CSGA, UMR 1324 INRA, 6265 CNRS, Burgundy University, Dijon, France

Financial Support: Funding was provided by an Inter-regional grant (PHRC) and the Regional Council of Burgundy. This study was also funded by INRA, CNRS, Université de Bourgogne, Regional Council of Burgundy France (PARI Agrale 1), FEDER (European Funding for Regional Economic Development) and French Government grant managed by the French National Research Agency (ANR) under the 'Investissements d'Avenir" program with reference ANR-11-LABX-0021-01-LipSTIC Labex.

Corresponding author: Catherine Creuzot-Garcher, MD, PhD, Department of Ophthalmology, Dijon University Hospital,14 rue Paul Gaffarel, 21079 Dijon, France;

Phone Number: +33 3 80 29 51 73

Fax Number: +33 3 80 29 35 89

Email: Catherine.creuzot-garcher@chu-dijon.fr

Running head: Prevalence of dry eye disease in the elderly

Abstract

Purpose: To estimate the prevalence of DED in the Montrachet population aged of 75 years and over, and to describe associations of DED with risk factors.

Design: Population-based study.

Subjects: Participants from the Montrachet study recruited from the ongoing population-based 3C study in Dijon, Burgundy, France.

Methods: Nine thousand three hundred and ninety-four individuals older than 65 were included in the 3C cohort study since 1999 from 3 French cities (Bordeaux, Dijon and Montpellier). In Dijon, an additional ophthalmic examination was performed ten years later to assess the relation between systemic age-related degenerative and eye diseases in the Montrachet Study (Maculopathy. Optic Nerve. nuTRition. neurovAsCular and HEarT diseases). Dry eye symptoms were collected with self-reported history of dry eye symptoms, use of artificial tears and evaluated by the Ocular Surface Disease Index (OSDI) questionnaire. Every patient underwent an ophthalmic evaluation which included Schirmer I test without anesthesia, tear film break up time measurement and fluorescein corneal staining evaluation. Prevalence of dry eye disease was evaluated according to the Dry Eye Workshop definition of 2007.

Main outcome measure: Prevalence of dry eye disease.

Results: One thousand and forty-five subjects were included in the study. Mean age was 82.2 ± 3.8 years old. Prevalence of dry eye disease according to subjective symptoms and objective signs were 34.5% and 34.3%, respectively. Patients with both signs and symptoms represented 13.0% of the cases. Associated factor reported were gender, age, short secondary school, history of no sun protection, dark iris color, BCVA < 20/60, systemic hypertension, use of antihypertensive drugs, use of preserved and unpreserved eye drops and history of cataract extraction.

Conclusions: DED is a major ophthalmologic condition with a high prevalence among the elderly. We reported well-known associated factor and new associations deserving further investigations.

Introduction

Dry eye disease (DED) is a chronic and progressive condition. Symptoms of DED are hugely prevalent, and in case of severe disease, can be difficult to treat. [1] Patients describe their symptoms as feeling of dryness, grittiness or soreness worsening throughout the day, burning and red eyes, temporarily blurred vision and visual discomfort. Signs of DED are unspecific. Most common clinical signs of severe DED or *keratoconjunctivitis sicca* are: redness, corneal and/or conjunctival staining with dye, inhomogeneity of the tear film and poor tear secretion assessed with Schirmer test. [2] Complications of DED can be vision threatening and include corneal neovascularization, bacterial keratitis and perforation.

Dry eye disease is divided in two main categories: excessive tear evaporation and insufficient tear production. [3] The International Dry Eye Workshop (DEWS) defined DED as « a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface (…)». [4] Increased osmolarity of the tear film and inflammation of the ocular surface were also included in this definition. Hence, DED may be difficult to evaluate because it is a multifactorial disorder involving multiple interacting mechanisms.

All epidemiological studies covered a wide range of age for included subjects.[5] Elderly population-based studies help us to better identify the characteristics of aging subjects. Several studies have already assessed DED prevalence in various populations. Dry eye disease prevalence was found in 4.3% of the Physicians' health study population, [5] 7.8% in the Women's health study, [6] 14.4% in the Beaver Dam eye study [7] and 14.6% in the Salisbury eye study. [8] Recently, the Alienor study reported a prevalence of 21.9% in a population whose mean (SD) age was 80.0 (4.0) years old. [9] Other studies published prevalence varying from 3.1% [10] to 93.2%, [11] depending on the population studied and the criteria used for the definition. This variation illustrates the difficulty to assess the prevalence of DED and

89 to establish comparison between population and countries. For these reasons, risk
90 factors, except for gender, age, hormonal changes and history of refractive surgery
91 remains putative. [12]

92 The aim of this study was first to estimate the prevalence of DED in the
93 Montrachet population aged of 75 years and over, and then to describe associations
94 of DED with risk factors.

Material and Methods

Montrachet population

The Montrachet study (Maculopathy Optic Nerve and nuTRition neurovAsCular and HEarT disease) is an ancillary study of the population-based study, the Three-City (3C) study, which examined the vascular risk factors for dementia. [13] The 3C study, included 9294 persons aged 65 years and over, selected from the electoral rolls of three French urban cities (Bordeaux, Dijon and Montpellier). In Dijon, 4931 participants participated in the first run of the 3C Study in 1999. At the fifth run, ten years later, a subgroup of participants was invited to participate in the Montrachet study investigating the relationship between age-related eye disease, neurologic and heart disease in the elderly. From 22 October 2009, until 31 March 2013, 1153 volunteers were recruited in the Montrachet study.

The methodology of the Montrachet study and baseline characteristics of volunteers have already been described. [14] In short, participants underwent a complete eye examination in the Department of Ophthalmology of the Dijon University Hospital, France. Fasting blood samples were drawn to measure plasma carotenoids and fatty acids. All participants were asked to complete a questionnaire about lifestyle (alcohol consumption and smoking status), environment (sun exposure) and nutrition (food frequency questionnaire). The study was approved by the regional ethics committee and was registered as 2009-A00448-49. All participants gave their informed consent and the followed procedures were in accordance with the Helsinki Declaration of 1975.

Ocular surface evaluation

Symptoms were evaluated by the Ocular Surface Disease Index (OSDI) questionnaire. [15, 16] The 12 items of the OSDI questionnaire resumed the main symptoms related to DED and were graded on a scale from 0 to 4. The total OSDI score was calculated from subject's response with the following formula: OSDI = [sum of the scores for all questions answered ×100]/total number of questions

123 answered] ×4. Then, the grade of DED severity was evaluated with the OSDI chart.
124 To be consistent with latest studies, a score < 22 was considered as normal,
125 between 22 and 35 as moderate and > 36 as a severe subjective DED. [9, 15] Patients
126 mentioned the use of topical treatment either to treat their ocular dryness or other
127 ocular conditions (ie. glaucoma, allergy…). We took in consideration the fact that
128 these medications were preserved or not. Self-reported DED was recorded by asking
129 'Do you know if you have dry eye disease?'. If details were needed, DED was
130 described as a feeling of dryness or grittiness and burning eyes.
131 Ocular surface was studied with the following tests performed successively in
132 both eyes. Fluorescein tear film breakup time (TF-BUT) was evaluated at the slit-
133 lamp using a blue cobalt illumination. A sterile tip was used to instill a drop of about 2
134 µL of fluorescein (Fluoresceine Faure 0.5% single dose, Novartis, Rueil-Malmaison,
135 France) in each conjunctival sac. After a few blinks (at least three) the timing of
136 breakup of the pre-corneal tear film was recorded in seconds. The average of three
137 consecutive measurements was used for analysis then corneal staining was
138 assessed and impregnation of 10 isolated points or less was considered as normal.
139 [17] Corneas with more than 10 positive points were classified as corneal staining
140 positive. TF-BUT and corneal staining were recorded in sequence, first on one eye
141 and then on the fellow eye, recording the TF-BUT first. A five-minute Schirmer I test
142 was performed without anesthesia a minimum of 30 minutes after fluorescein
143 assessment. A dedicated paper strip (Liposic-Schirmer-Test-Streifen; Dr Mann
144 Pharma, Berlin, Germany) was introduced laterally in the lower conjunctival fornix
145 without any contact with the cornea and removed after 5 minutes. The amount of
146 wetting in millimeters was recorded from the pre-calibrated strip. [3, 17] The most
147 severe eye for each subject was retained for analysis. If equal, we arbitrary selected
148 the right eye.
149 Tear osmolarity measurements were performed in the first 149 consecutive
150 participants. We used a single-use lab-on-a-chip system which simultaneously collect

and analyze the electrical impedance of a 50 nanoliter of tear sample from the inferior lateral meniscus (TearLab™ Osmolarity System, TearLab Corp., San Diego, CA, USA). [18-20]

Dry eye disease definition

DEWS classification was used to classify every participant (Table 2). [4] First, we considered separately subjective symptoms and objective signs. Subjective data were analyzed to sort out participants. OSDI score > 22, use of artificial tears or self-reported DED was considered as "subjective DED". Objective thresholds were positive corneal staining and/or TF-BUT < 5 seconds and/or Schirmer I test < 5 mm. To be considered as suffering from "objective DED", subjects should present at least 2 out of the 3 preceding conditions. Participants were also classified using the DEWS stages of DED (Table 2). Stage 0 (no DED) and 1 (early DED) included every patient with negative corneal staining and/or TF-BUT > 10 seconds and/or Schirmer I test > 10 mm. Stage 2 (mild DED) included every patient with negative corneal staining and/or TF-BUT < 10 seconds and/or Schirmer I test < 10 mm.

Stage 3 (moderate DED) included patients with positive corneal staining and/or TF-BUT< 5 seconds and/or Schirmer I test < 5 mm.

To be included in stage 0 to 3, 2 criteria out of the 3 should be present. To be included in the stage 4 (severe DED), all the criteria should be present: positive corneal staining and TF-BUT < 2 seconds and Schirmer I test < 2 mm. For statistical analysis we considered stage 0, 1 and 2 as normal since corneal staining remains negative. Subjects classified as DED in both subjective and objective classification were considered having a "definite DED".

Statistics

Descriptive statistics are given as mean (SD) or median [IQR] for continuous variables according to their distribution and number (percentage) for categorical variables. For comparisons, we used the Fischer exact test or χ^2 for dichotomous data and Student's t-tests, Mann-Whitney, ANOVA, or Kruskal-Wallis tests for

179 continuous variables according to their distribution. Correlations between variables
180 were tested using Pearson or Spearman correlation coefficients. Multivariate
181 analyses were performed using multiple regression logistic models. Models were
182 systematically adjusted for age and sex. In the first step, we investigated
183 associations between DED as a dependent variable and factors associated with $P <$
184 0.20 in bivariate analysis with the individual eye as unit analysis. Deviation from
185 linearity of the relationship between the continuous covariates retained and DED was
186 systematically tested using chi-squared tests for linear trend after having categorized
187 the covariates according to the quintiles of their distribution. Then a final model was
188 performed when the factors associated in age and sex model above were significant
189 with $P < 0.05$. For all analysis, the tests were two sided and significant results were
190 considered when $P < 0.05$. Data analyses were performed using SAS software
191 (version 9.3; SAS institute Inc; Cary, NC, USA).

Results

A total of 1045 subjects had both objective and subjective data about DED (Figure 1). The characteristics of the study population are displayed in Table 1. The mean (SD) age was 82.2 (3.8) years. More than one third of subjects were former or current smokers. The present mean time spent watching a screen was 3.3 (1.8) hours per day.

For DED evaluation, subject selection is displayed in Figure 1. An OSDI score > 22 was found in 224 (21.4%) subjects. A history of DED was reported by 188 (18.0%) subjects and the use of artificial tears by 112 (10.7%). The prevalence of symptoms of DED was 34.5% (364).

A TF-BUT < 5 s, a corneal staining positive and a Schirmer I test < 5 mm were observed in 403 (38.6%), 404 (38.6%) and 267 (25.6%) subjects, respectively. Objective DED was found in 392 (34.3%) subjects. Almost one percent of subjects had severe DED (Table 2). Definite DED in the Montrachet population was found in 136 (13%) subjects.

We found a strong association between self-reported dry eye symptoms and use of artificial tears (r = 0,64; $P < 0.0001$). There was no correlation between TF-BUT < 5 seconds and an OSDI score > 22 nor between Schirmer I test < 5mm and an OSDI score > 22. Concordance between signs and symptoms of DED was poor with a Kappa coefficient as low as 0.05 (95% CI; -0.009-0.1). The sensitivity of the OSDI score in detecting definite DED taking clinical signs tests as the reference was 37.8%, while the specificity was 67.4%. The positive predictive value and the negative predictive value were 37.9% and 67.3%, respectively. Indeed, the accuracy of using a combination of the subjective symptoms perceived for DED identification was 52.2%.

In bivariate analysis (Table 3), we found a significant difference between DED groups according to age ($P = 0.04$), sex ($P = 0.02$), current or former smokers ($P = 0.002$), education level ($P = 0.05$), sun protection ($P = 0.02$), Best-Corrected Visual

Acuity in ETDRS letters (BCVA ETDRS) < 20/60 (P = 0.01), systemic hypertension (P = 0.01), antihypertensive drug use (P = 0.005), preserved and unpreserved eye drops use (P < 0.001) and history of cataract extraction (P = 0.003).

After adjustment for age and sex (Table 4), definite DED was more frequent in subjects with short secondary school level (OR = 1.9; 95% CI, 1.1-3.3; P = 0.02), with BCVA ETDRS < 20/60 (OR = 2.5; 95% CI, 1.1-6.0; P = 0.03), with dark iris color (OR = 1.7; 95% CI, 1.1-2.6; P = 0.02), systemic hypertension (OR = 1.6; 95% CI, 1.1-2.4; P = 0.01), use of antihypertensive drugs (OR = 1.8; 95% CI, 1.1-2.7; P = 0.01), treatment with preserved eye drops (OR = 3.2; 95% CI, 1.9-5.4; P < 0.001), treatment with unpreserved eye drops (OR = 7.3; 95% CI, 4.5-11.7; P < 0.001) and history of cataract extraction (OR = 1.6; 95% CI 1.1-2.3; P = 0.02). DED was less frequent in subjects protecting themselves from sunlight (OR = 0.3, 95% CI, 0.2-0.8; P = 0.02).

In our final multivariate model, use of antihypertensive drugs and topical treatment was not included due to missing data (13%). Previous associated factors did not change except for history of cataract surgery, which became not significantly associated with DED (Data not showed).

Osmolarity measurement was available for 149 subjects. In order to extrapolate these data to our entire population, we compared participants with osmolarity data with the Montrachet population (data not showed). These 2 populations were similar for every studied parameter except for iris color (P = 0.04), use of preserved drops (P = 0.02) and AMD status (P < 0.001). Analysis in this group revealed that the mean tear film osmolarity was significantly higher in patients with DED (n = 19 (12.8%); mean (SD): 322 (25) mOsms) compared with the non-DED patients (n = 130 (87.2%); mean (SD): 310 (16) mOsms; P = 0.002). This difference was also found in objective DED versus non-DED: n = 49 (32.9%); 316 (21) mOsms and n = 100 (67.1%); 309 (15) mOsms, respectively (P = 0.03). Conversely, no difference of the tear film osmolarity was found using the subjective DED

248 classification: 105 (70.5%) participants presented subjective symptoms of DED with a
249 mean (SD) of 311 (23) mOsms and 44 (29.5%) had no symptoms with a mean (SD)
250 of 312 (15) mOsms (P = 0.80). Analysis in this group did not reveal any correlation
251 between OSDI score > 22 and an elevated tear film osmolarity, neither between
252 osmolarity value and DED group. However, a Schirmer test < 5 mm was correlated
253 with an elevated tear film osmolarity (r = 0.41; P < 0.0001).

Discussion

The objective of this study was to assess the prevalence of DED in the elderly according to the DEWS classification. In our population, we defined DED as objective based on three clinical parameters: TF-BUT, corneal staining and Schirmer I test; and as subjective based on OSDI score, use of symptomatic treatment for DED and self-declaration of DED. We found that the prevalence of DED was 34.3% and 34.5% for objective and subjective signs, respectively. Thirteen percent of our population presented definite DED. The sensitivity of the OSDI score in detecting definite DED when compared with clinical signs tests was 37.8%, while the specificity was 67.4%. Associated factors were gender, age, short secondary school, history of no sun protection, dark iris color, BCVA < 20/60, systemic hypertension, use of antihypertensive drugs, use of preserved and unpreserved eye drops and history of cataract extraction.

Differences in DED definition make comparison between studies difficult. [21] In the Salisbury eye study, DED prevalence was 4.5% on participants over 80 years-old with more than one symptom and at least one clinical sign (Schirmer I test or corneal staining positive). [8] Our population presents a higher prevalence of DED in the symptomatic subjects with clinical signs (13%). The Salisbury eye study did not include the instability of the tear film in their clinical signs. As meibomian gland dysfunction increases with age, we included the TF-BUT, leading to a higher prevalence of DED. [22] Our results on the TF-BUT < 5 seconds are consistent with the Alienor study which reported a TF-BUT < 5 seconds in 44.9% of their subjects (38.6% in the Montrachet population). [9]

In most population-based studies, classification of DED was done with self-reported symptoms. The Beaver Dam eye study, the Blue mountains eye study and the Beijing eye study reported prevalence of symptomatic DED of 14.0%, 15.3% and 16.6%, respectively. [7, 23, 24] Our result of self-reported DED is in agreement with these studies with a reported a prevalence of 18%. When considering not only symptoms but also clinical signs, we found a lower DED prevalence (13%). Lower subjective results, based on a questionnaire evaluating symptoms were reported by the Women's health study (9.8%) and the Physician's health study (7.7%). [5, 6] However, in these two large studies 28% of women and 18% of men reported having

282 “sometimes” symptoms of dryness. Our study has gone a step further using a DED definition
283 including objective signs and subjective symptoms.
284 None of the previous reported measurements presented high specificity or sensitivity to
285 be considered as a gold standard to diagnose DED. As reported by Nichols *et al.*, no consistent
286 relationship was found between objective signs and subjective symptoms of DED in our study.
287 [25] Indeed, all objective signs do not induce symptoms of DED as it can be associated with a
288 decreased corneal sensitivity. [26] These findings strengthen the need to evaluate the corneal
289 sensitivity of our patient and to combine signs and symptoms to define DED. [27, 28]
290 Prior studies have already examined risk factors for DED. Most consistent are age,
291 gender (female), postmenopausal estrogen therapy, history of LASIK or refractive excimer laser
292 surgery, radiation therapy, hematopoietic stem cell transplantation, vitamin A deficiency,
293 Hepatitis C infection and androgen deficiency. [12] Questionable associated factors are systemic
294 medications such as tricyclic antidepressants, isotretinoin, diuretics and beta-blockers; general
295 condition, such as diabetes mellitus and history of ophthalmic surgical procedure with large
296 incision. Tear film changes associated with hormonal modifications and meibomius gland
297 dysfunction in the elderly may explain that in our study, age was found associated with DED. [22,
298 29] Denoyer *et al.* reported that corneal higher-order aberrations (HOAs) were increased in DED
299 patients due to the tear film irregularity, decreasing the quality of vision and objective visual
300 acuity. [30] This mechanism is in favor to our findings suggesting that a BVCA ETDRS < 20/60
301 was associated with DED (OR = 2.5; 95% CI, 1.1-6.0; *P* = 0.03). Our results are consistent with
302 previous work as history of cataract extraction is associated with DED (OR = 1.6; 1.1-2.3; *P* =
303 0.02) in our first multivariate model. [31] Most accepted hypothesis is that DED may be related to
304 post-operative local treatment more than the surgery by itself. [32] Moreover, as DED, the rate of
305 cataract surgery increases with age and there may be a collinearity between these two
306 parameters. In our population, as in Alienor study, low educational level was correlated with
307 DED. [9] Conversely, the Korean national health study found that high educational level was
308 associated with DED, and rural way of life with no-DED. [9, 33] In this case, the way of life
309 (rural/urban) may be more related to DED than education (and Montrachet study mostly

included urban population). Diabetes mellitus was not associated with DED in our population with the definite DED definition. However, diabetes mellitus was associated with objective DED (OR: 1.9; IC 95%, 1.2-2.9; *P* = 0.004) in a multivariate analysis (data not showed). The common corneal hypoesthesia reported in diabetics may explain this discrepancy. [34] Glaucoma was not reported as associated with DED in our population regardless of the DED definition used. Nevertheless, the use of preserved drops as unpreserved ones was associated with definite DED. As the recruitment for our study began in 2009, ophthalmologists were already informed of the deleterious consequences of preservative on the ocular surface and may have already switched their treatment for DED patients. [35] As pointed out by the 2007 International Dry Eye Workshop, beta blockers and diuretics are risk factor of DED with a suggestive level of evidence. [12] These two drugs are the recommended treatment of systemic hypertension. [36] Our treated subjects with systemic antihypertensive drugs confirmed the DEWS findings (OR = 1.8; 1.1-2.7; *P* = 0.01). Of note hypertensive subjects (treated or not) were more likely to suffer from DED (OR = 1.6; 1.1-2.4; *P* = 0.01). Finally, tear hyperosmolarity is known to be responsible for a cell suffering, and to promote keratitis. [19] Lemp *et al.* reported similar osmolarity values as ours for non to moderate dry eye subjects at 308 mOsms. [18] According to their study, DED subjects tended to have a more elevated tear film osmolarity around 315 mOsms (322 mOsms in the reported population).

We acknowledge several limitations to this study. First, corneal staining was only recorded as present or absent. We were not able to apply the entire Oxford classification, limiting the accuracy of our clinical classification. Second, we considered subjects with mild DED as normal. Despite the DEWS classification depicted mild subjects suffering from DED, this choice was made in agreement with other studies considering than TF-BUT > 5 second, corneal staining negative or a Schirmer test > 5 millimeters as normal. [8] Indeed, DEWS classification is difficult to apply strictly in epidemiological study. [21] Third, corneal aesthesia was not recorded. With this criterion, we may have sorted subjects with severe objective DED with no symptoms in definite DED. Therefore, we may have excluded potential subjects from the definite DED classification, and virtually lowering our prevalence. Fourth, osmolarity

measurements concerned only a part of our population and were only done once per participants. However, in order to extrapolate these data to our entire population, we compared participants with osmolarity data with the entire Montrachet population. Difference were found in only 3 of the studied parameters, allowing us to consider the osmolarity subgroup comparable. As there was only one measurement, we were not able to evaluate intereye variation in tear osmolarity. Indeed, Lemp *et al.* reported that not only the highest value of osmolarity was a good diagnostic criterion of DED but also the difference between two measurements. [18] Fifth, this study only deals with a white and urban population; therefore, the results cannot be extrapolated to other groups.

The strength of this study include its large sample of population, the strict criteria used for DED definition and potential associated risk factors analysed. We may add the fact that all of our subjects underwent a clinical examination of the ocular surface with four different clinical diagnostic test performed.

This study provided epidemiological data on dry eye among the elderly. DED is a major ophthalmologic condition with a high prevalence among the elderly. We reported well-known associated factor such as female gender, age, poor visual acuity, history of cataract surgery, use of hypotensive drugs, use of preserved or unpreserved drops and an O-level of education. The new associations such as history of no sun protection, dark iris and systemic hypertension deserve further investigation.

Author Contributions

Conception and design: Creuzot-Garcher, Bron

Data collection: Nicot, Gascard, Ferrero, Alassane, Creuzot-Garcher, Bron

Analysis and interpretation: Ferrero, Alassane, Creuzot-Garcher, Bron

Obtained funding: Funding was provided by an Inter-regional grant (PHRC) and the Regional Council of Burgundy. This study was also funded by INRA, CNRS, Université de Bourgogne, Regional Council of Burgundy France (PARI Agrale 1), FEDER (European Funding for Regional Economic Development) and French Government grant managed by the French National Research Agency (ANR) under the ‘Investissements d’Avenir” program with reference ANR-11-LABX-0021-01-LipSTIC Labex.

Overall responsibility: Creuzot-Garcher, Bron

TABLES AND FIGURES

Table 1: Characteristics of the Montrachet population evaluated for dry eye disease

	n (%)
Age	
<80	397 (34.8)
80-85	481 (42.1)
>85	264 (23.1)
Female sex	717 (62.8)
Former or current smokers	387 (34.5)
BMI ≥25 kg/m²	550 (48.2)
Alcohol consumption	64 (6.4)
Education level	
No education or primary school	323 (28.3)
Short secondary school	159 (13.9)
Long secondary school	206 (18.1)
High school ou university	453 (39.7)
Iris Color	
Blue/Gray	462 (40.5)
Green/Brown	355 (31.1)
Dark brown	325 (28.5)
Sun protection	
Never	112 (9.9)
Occasionally	257 (22.6)
Often	768 (67.6)
Best Corrected Visual Acuity, ETDRS	
≥20/60	1048 (97.8)
<20/60	94 (8.2)
Central corneal thickness µm, mean (SD)	554.6 (35.2)
Medical history	
Systemic blood pressure >160/95	669 (58.6)
Diabetes (yes)	93 (9.2)
Ocular history	
Cataract extraction (yes)	562 (49.2)
Diabetic Retinopathy (yes)	9 (0.8)
Age-Related Macular Degeneration (yes)	39 (3.7)
Glaucoma (yes)	135 (11.8)
Ocular hypertension (yes)	38 (3.3)
Medical use	
Antihypertension drug use (yes)	612 (60.7)
Lipids lowering drug use (yes)	423 (42.0)
Eye drop use (yes)	233 (24.8)
Preserved eye drop	120 (12.8)
Unpreserved eye drop	113 (12.0)
Time spent outdoors (h/day), mean (SD)	0.9 (1.2)
Time spent on television screen (h/day), mean (SD)	3.3 (1.8)
Time spent on computer screen (h/day), mean (SD)	0.5 (1.0)

Missing data for smokers (n=19), BMI (n=100), Alcohol consumption (n=134), education level (n=1), sun protection (n=5), central corneal thickness (n=4), systemic blood pressure (n= 100), diabetes (n=135), AMD (n=78), glaucoma (n=1), antihypertension drug use (n=134), lipids lowering drugs (n=134), eye drop use (n=105), time spent outdoors (n=4), time spent on TV (n=20) and time spent on computer (n=29).

Figure 1: Flow chart of study population selection

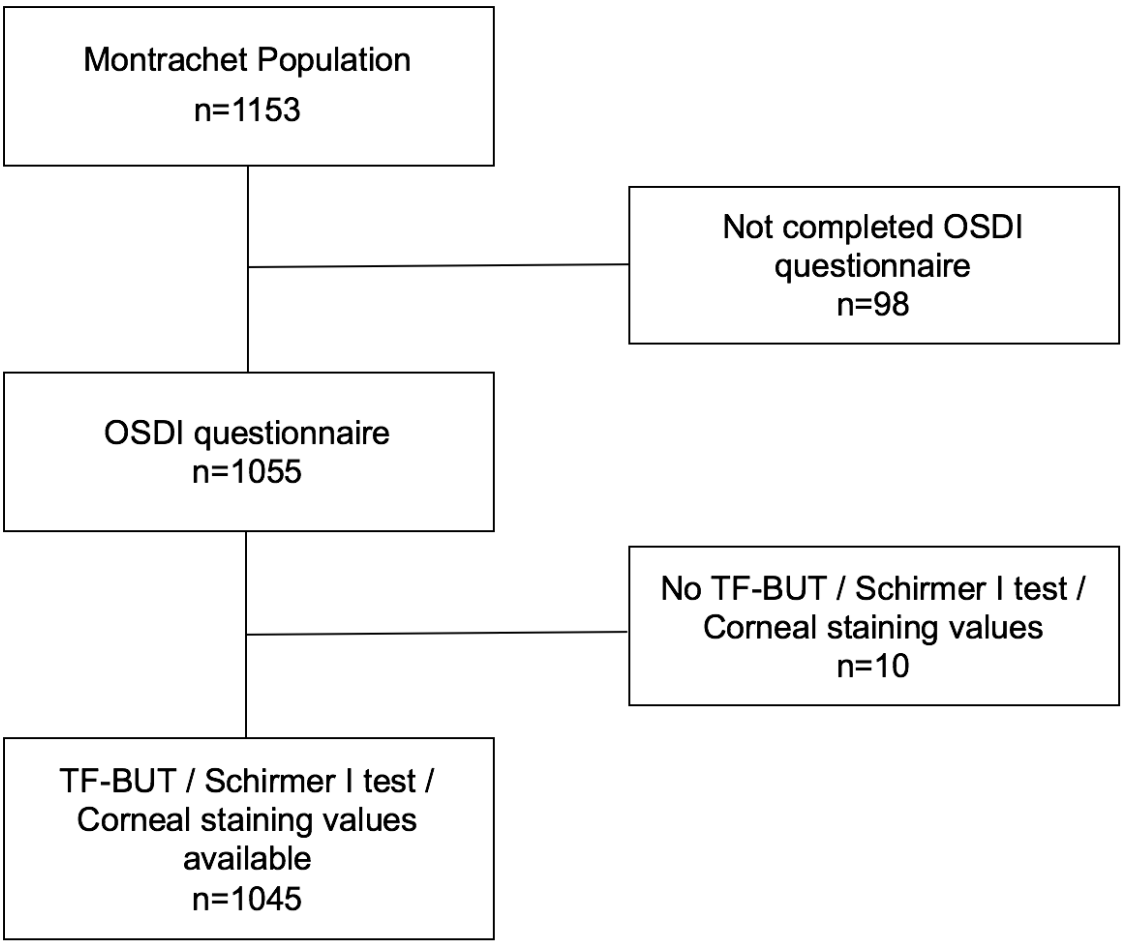

Table 2: Classification of dry eye disease in the Montrachet population according to the DEWS classification

	Clinical signs			
	TF-BUT ≥10 **Schirmer ≥10** **CS-**	**TF-BUT <10** **Schirmer <10** **CS-**	**TF-BUT <5** **Schirmer <5** **CS+**	**TF-BUT ≤2** **Schirmer ≤2** **CS+**
	Normal	**Early**	**Moderate**	**Severe**
n (%)	478 (41.9)	272 (23.8)	379 (33.2)	13 (1.1)

CS-: negative corneal staining; CS+: positive corneal staining

Table 3: Global dry eye disease and population characteristics

	Global DES (n=1045)		
	No (n=909)	**Yes (n=136)**	***P*-value**
Age (years), mean (SD)	82.2 (3.7)	82.9 (4.1)	**0.04**
≤80	314 (34.5)	44 (32.3)	
80-85	395 (43.5)	52 (38.2)	0.16
>85	200 (22.0)	40 (29.4)	
Female sex	549 (60.4)	101 (74.3)	**0.002**
Former or current smokers	323 (36.1)	33 (24.6)	**0.009**
Alcohol consumption (yes)	53 (6.6)	6 (4.9)	0.47
Body Mass Index (kg/m²)			
≤25	472 (51.9)	71 (52.2)	0.95
>25	437 (48.1)	65 (47.8)	
Education level			
No education or primary school	258 (28.4)	37 (27.2)	
Short secondary school	119 (13.1)	26 (19.1)	**0.05**
Long secondary school	161 (17.7)	31 (22.8)	
High school ou university	370 (40.8)	42 (30.9)	
Sun protection			
Never	97 (10.7)	5 (3.7)	
Occasionally	203 (22.4)	28 (20.6)	**0.02**
Often	607 (66.9)	103 (75.7)	
Iris Color			
Blue/Gray	377 (41.5)	47 (34.6)	
Green/Brown	283 (31.1)	39 (28.7)	**0.08**
Dark brown	249 (27.4)	50 (36.8)	
Best Corrected Visual Acuity, ETDRS letters			
≥20/60	840 (92.4)	117 (86.0)	**0.01**
<20/60	69 (7.6)	19 (14.0)	
Central corneal thickness, µm, mean (SD)	554.6 (34.8)	550.3(38.6)	0.19
Medical history			
Diabetes (yes)	75 (9.4)	11 (9.0)	0.89
Systemic blood pressure >160/95	520 (57.2)	93 (68.4)	**0.01**
Age-Related Macular Degeneration (yes)	32(3.8)	7 (5.5)	0.37
Diabetic Retinopathy (yes)	8 (0.9)	1 (0.7)	0.86
Glaucoma (yes)	104 (11.5)	22 (16.2)	0.12
Ocular Hypertension ≥21 mmHg	28 (3.1)	4 (2.9)	0.93
Cataract extraction (yes)	430 (47.3)	83 (61.0)	**0.003**
Lipid lowering drug use	348 (43.6)	44 (36.1)	0.12
Antihypertension drug use	471 (59.0)	88 (72.1)	**0.005**
No Eye drop use	655 (80.0)	52 (43.0)	
Preserved eye drop (yes)	95 (11.6)	25 (20.7)	<0.001
Unpreserved eye drop (yes)	69 (8.4)	44 (36.4)	
Environmental exposition			
Time spent outdoors (h/day), mean (SD)	0.9 (1.2)	0.84 (1.2)	0.38
Time spent on television screen (h/day), mean (SD)	3.2 (1.8)	3.2 (1.6)	0.68
Time spent on computer screen (h/day), mean (SD)	0.5 (1.0)	0.4 (0.8)	0.36
Total cholesterol, g/L, mean (SD)	5.8 (0.9)	5.8 (0.9)	0.90
HDL cholesterol, g/L, mean (SD)	1.7 (0.4)	1.7 (0.4)	0.18
LDL cholesterol, g/L, mean (SD)	3.6 (1.0)	3.6 (0.8)	0.89

Table 4: Age and gender adjusted model of definite dry eye disease with potential associated factors (clinical, lifestyle and demographics)

	Global DED		
	OR	95% CI	*P*-value
Former or current smokers	0.7	0.5-1.2	0.18
Education level vs High school			
No education or primary school	1.2	0.7-1.9	0.56
Short secondary school	1.9	1.1-3.3	**0.02**
Long secondary school	1.5	0.9-2.5	0.10
Sun protection vs Often			
Never	0.3	0.2-0.8	**0.02**
Occasionally	0.8	0.5-1.3	0.40
Iris color vs blue			
Green	1.1	0.7-1.7	0.79
Dark	1.7	1.1-2.6	**0.02**
BCVA <20/60	2.5	1.1-6.0	**0.03**
Central corneal thickness, µm	1.0	0.9-1.0	0.26
Systemic Hypertension	1.6	1.1-2.4	**0.01**
Glaucoma	1.5	0.9-2.5	0.13
Cataract extraction	1.6	1.1-2.3	**0.02**
Antihypertension drug use	1.8	1.1-2.7	**0.01**
Lipid lowering drug use	0.8	0.5-1.1	0.18
Preserved eye drop use	3.2	1.9-5.4	**<0.001**
Unpreserved eye drop use	7.3	4.5-11.7	**<0.001**
HDL cholesterol	1.1	0.7-1.7	0.78

n=1042 for the final model (3 observations were deleted due to missing values).

Statistically significant *P* values are in bold.

CONCLUSIONS

UNIVERSITE DE BOURGOGNE

THESE SOUTENUE PAR M. Arthur FERRERO

CONCLUSIONS

La sécheresse oculaire est une des pathologies les plus rencontrées en ophtalmologie. Nous rapportons les résultats d'une étude de population ayant pour objectif d'évaluer la prévalence de la sècheresse oculaire selon la classification du Dry Eye Workshop de 2007 au sein d'une population âgée et d'en identifier les facteurs associés.

L'étude Montrachet s'est déroulée à Dijon d'octobre 2009 à mars 2013 et avait pour objectif de décrire la prévalence des maladies liées à l'âge ainsi que des associations avec des facteurs nutritionnels. Sur les 1045 participants de cette étude, une sècheresse oculaire dite objective ou clinique est retrouvée chez 34,3% des participants. Une sécheresse oculaire dite subjective ou symptomatique est retrouvée chez 34.5% des participants. La prévalence globale de la sécheresse oculaire, à la fois objective et subjective était de 13%.

Parmi tous les tests diagnostiques utilisés aucun n'était assez sensible ou spécifique pour permettre de poser seul le diagnostic de sècheresse oculaire.

Des facteurs associés à la sécheresse oculaire, déjà connus, ont été retrouvés : l'âge, le sexe, une faible acuité visuelle, les antécédents de chirurgie de la cataracte, un traitement par antihypertenseur, l'utilisation de collyres avec ou sans conservateurs ainsi qu'un faible niveau d'éducation. De nouveaux facteurs de risque comme l'hypertension artérielle ou une couleur d'iris foncé étaient retrouvé associé à la sècheresse oculaire et nécessiteraient des études complémentaires.

Dans cette étude de population nous rapportons une prévalence strictement définie, en accord avec les dernières recommandations internationales, de 13%.

Le Président du jury,

Pr. C. CREUZOT-GARCHER

Vu et permis d'imprimer

Dijon, le 26 Août 2016

Le Doyen

Pr. F. HUET

References

1. Doughty MJ, Fonn D, Richter D, et al. A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada. Optom Vis Sci 1997;74:624-31.

2. Straub M, Bron AM, Muselier-Mathieu A, Creuzot-Garcher C. Long-term outcome after topical ciclosporin in severe dry eye disease with a 10-year follow-up. Br J Ophthalmol 2016;Published Online First: 28/01/2016

3. Lemp MA, Crews LA, Bron AJ, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. Cornea 2012;31:472-8.

4. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007;5:75-92.

5. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol 2009;127:763-8.

6. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136:318-26.

7. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol 2000;118:1264-8.

8. Schein OD, Munoz B, Tielsch JM, et al. Prevalence of dry eye among the elderly. Am J Ophthalmol 1997;124:723-8.

9. Malet F, Le Goff M, Colin J, et al. Dry eye disease in French elderly subjects: the Alienor Study. Acta Ophthalmol 2014;92:e429-36.

10. Schein OD, Hochberg MC, Munoz B, et al. Dry eye and dry mouth in the elderly: a population-based assessment. Arch Intern Med 1999;159:1359-63.

11. Bukhari A, Ajlan R, Alsaggaf H. Prevalence of dry eye in the normal population in Jeddah, Saudi Arabia. Orbit 2009;28:392-7.

12. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007;5:93-107.

13. 3C Study group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003;22:316-25.

14. Creuzot-Garcher C, Binquet C, Daniel S, et al. The Montrachet Study: study design, methodology and analysis of visual acuity and refractive errors in an elderly population. Acta Ophthalmol 2016;94:e90-7.

15. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118:615-21.

16. Walt J RM, Stern K. Evaluating the functional impact of dry eye: the Ocular Surface Disease Index (Abstract). Drug Information Journal 1997:1436.

17. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640-50.

18. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol 2011;151:792-8.e1.

19. Baudouin C, Aragona P, Messmer EM, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf 2013;11:246-58.

20. U.S Food and Drug Administration - Oficial Site http://www.accessdata.fda.gov/cdrh_docs/pdf8/K083184.pdf. 2010. Accessed April 8, 2016.

21. Baudouin C, Aragona P, Van Setten G, et al. Diagnosing the severity of dry eye: a clear and practical algorithm. Br J Ophthalmol 2014;98:1168-76.

22. Alghamdi YA, Mercado C, McClellan AL, et al. Epidemiology of Meibomian Gland Dysfunction in an Elderly Population. Cornea 2016;35:731-5.

23. Chia EM, Mitchell P, Rochtchina E, et al. Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. Clin Experiment Ophthalmol 2003;31:229-32.

24. Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. Eye (Lond) 2009;23:688-93.

25. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. Cornea 2004;23:762-70.

26. Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. Acta Ophthalmol 2014;92:161-6.

27. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea 2006;25:900-7.

28. Sullivan BD, Whitmer D, Nichols KK, et al. An objective approach to dry eye disease severity. Invest Ophthalmol Vis Sci 2010;51:6125-30.

29. Gipson IK. Age-related changes and diseases of the ocular surface and cornea. Invest Ophthalmol Vis Sci 2013;54:48-53.

30. Denoyer A, Rabut G, Baudouin C. Tear film aberration dynamics and vision-related quality of life in patients with dry eye disease. Ophthalmology 2012;119:1811-8.

31. Khanal S, Tomlinson A, Esakowitz L, et al. Changes in corneal sensitivity and tear physiology after phacoemulsification. Ophthalmic Physiol Opt 2008;28:127-34.
32. Li XM, Hu L, Hu J, Wang W. Investigation of dry eye disease and analysis of the pathogenic factors in patients after cataract surgery. Cornea 2007;26:S16-20.
33. Ahn JM, Lee SH, Rim TH, et al. Prevalence of and risk factors associated with dry eye: the Korea National Health and Nutrition Examination Survey 2010-2011. Am J Ophthalmol 2014;158:1205-14.
34. Touzeau O, Levet L, Borderie V, et al. [Anterior segment of the eye and diabetes mellitus]. J Fr Ophtalmol 2004;27:859-70.
35. Vaede D, Baudouin C, Warnet JM, Brignole-Baudouin F. [Preservatives in eye drops: toward awareness of their toxicity]. J Fr Ophtalmol 2010;33:505-24.
36. Royal College of Physicians of London. Hypertension: Management in Adults in Primary Care: Pharmacological Update. 2006.

Université de Bourgogne

UFR des Sciences de Santé

Circonscription Médecine

TITRE DE LA THESE : Prévalence et facteurs associés de la sècheresse oculaire dans une population française âgée

AUTEUR : Arthur Ferrero

RESUME :

Introduction : Evaluer la prévalence de la sécheresse oculaire dans une population française de sujets âgés de plus de 75 ans au sein de l'étude Montrachet et analyser les facteurs associés.

Matériels et Méthodes : L'étude Trois Cités (3C) est une étude de population incluant 9693 sujets de plus de 75 ans dans 3 villes françaises (Bordeaux, Dijon et Montpellier). Après 10 ans de suivi, la cohorte de Dijon a bénéficié d'une étude ophtalmologique dans le cadre de l'étude Montrachet. Les symptômes de sécheresse oculaire (antécédents et traitements lubrifiants) étaient recueillis à l'interrogatoire ainsi qu'à l'aide du questionnaire Ocular Surface Disease Index (OSDI). Tous les sujets ont ensuite bénéficié d'un examen ophtalmologique comprenant un test de Schirmer sans anesthésie cornéenne, une mesure du break up time et une étude de la coloration fluorescéinique. Cent quarante-neuf sujets ont bénéficié d'une mesure de l'osmolarité des larmes. La prévalence du syndrome sec était évaluée sur des critères subjectifs, sur des critères objectifs et de façon globale selon la définition du Dry Eye WorkShop (DEWS) de 2007.

Résultats : Mille quarante-cinq sujets ont été inclus. L'âge moyen était de 82,2 ± 3,8 ans. La prévalence globale était de 13%. La prévalence de la sécheresse oculaire selon les critères subjectifs et objectifs était de 34,5% et 34,3% respectivement. Les facteurs associés retrouvés lors de l'analyse multivariée étaient : l'âge, le sexe, une acuité visuelle inférieure à 20 lettres ETDRS, l'hypertension artérielle, la prise de traitement antihypertenseur systémique, l'utilisation d'un traitement par collyre topique (conservé ou non) et un antécédent de chirurgie de la cataracte. L 'analyse complémentaire sur l'osmolarité retrouvait des valeurs plus élevées chez les participants souffrant de sécheresse oculaire que chez les participants sains (322 mOsms versus 310 mOsms ; *P*=0,002)

Conclusion : Les résultats de l'étude Montrachet confirment la difficulté d'évaluer la prévalence de la sécheresse oculaire et l'importance de sa prise en charge chez le sujet âgé.

Mots clés : Sécheresse oculaire, Epidémiologie, Population âgée, Surface oculaire