Aus der Augenklinik und Poliklinik
der Universitätsmedizin der Johannes Gutenberg-Universität Mainz

Geschlechtsaspekte in der Ophthalmologie und ophthalmologischen Versorgung

Inauguraldissertation
zur Erlangung des Doktorgrades Dr. rer. physiol.
der Universitätsmedizin
der Johannes Gutenberg-Universität Mainz

Vorgelegt von

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Mainz, 2025

Wissenschaftlicher Vorstand: Univ.-Prof. Dr. med. Philipp Drees

Tag der Promotion: 20. Februar 2026

Erklärung

Teile der Dissertation wurden in wissenschaftlichen Journals veröffentlicht und auf internationalen Konferenzen präsentiert. Die Dissertation wurde an der Augenklinik der Universitätsmedizin Mainz, unter der Betreuung von [redacted], verfasst. Diese folgt dem Design einer kumulativen Arbeit.

Publikationen

Hartmann A, Grabitz SD, Wagner FM, Wild PS, Müller-Nurasyid M, Lackner KJ, Beutel ME, Münzel T, Tüscher O, Schattenberg JM, Pfeiffer N & Schuster AK**.** Bi-Gaussian analysis reveals distinct education-related alterations in spherical equivalent and axial length—results from the Gutenberg Health Study. *Graefes Arch Clin Exp Ophthalmol* (2024): https://doi.org/10.1007/s00417-024-06395-z

Hartmann A, Scholz I, Hoffmann EM, Strzalkowska A, Lackner KJ, Münzel T, Wicke F, Schmidtmann I, Tüscher O, Schattenberg JM, Konstantinides S, Wild PS, Pfeiffer N, Schuster AK. Change of intraocular pressure over 5 years and its relationship to cardiovascular parameters – results from the Gutenberg Health Study. *Investigative Ophthalmology & Visual Science (2024):* https://doi.org/10.1167/iovs.65.1.12

Laspas P*, **Hartmann A*,** Scholz I, Hoffmann EM, Khawaja AP, Lackner KJ, Münzel T, Beutel ME, Schmidtmann I, Tüscher O, Schattenberg J, Pfeiffer N, Wild PS, Schuster AK. Change in systemic medication and its influence on intraocular pressure – results from the Gutenberg Health Study. *Investigative Ophthalmology & Visual Science (2024):* https://doi.org/10.1167/iovs.65.14.4

Hartmann A, Stephanie D. Grabitz, Esther M. Hoffmann, Philipp S. Wild, Irene Schmidtmann, Karl J. Lackner, Manfred E. Beutel, Thomas Münzel, Oliver Tüscher, Jörn M. Schattenberg, Norbert Pfeiffer, and Alexander K. Schuster. Intraocular Pressure and Its Relation to Climate Parameters — Results From the Gutenberg Health Study. *Investigative Ophthalmology & Visual Science (2023)*: https://doi.org/10.1167/iovs.64.7.15

Hartmann A, Grabitz SD, Wild PS, Lackner KJ, Münzel T, Ghaemi Kerahrodi J, Singer S, Geschke K, Schattenberg JM, Konstantinides S, Pfeiffer N, Schuster AK. Gender-specific changes in vision-related quality of life over time – results from the Gutenberg Health Study. *Graefes Arch Clin Exp Ophthalmol* (2025). https://doi.org/10.1007/s00417-025-06741-9

Fieß A*, **Hartmann A***, Mildenberger E, Urschitz MS, Laspas P, Schultheis A, Stoffelns B, Pfeiffer N, Gißler S#, Schuster AK#. Sex specific differences in ocular geometry in relation to prematurity. *Investigative Ophthalmology & Visual Science (2024)*: https://doi.org/10.1167/iovs.65.6.23

Hartmann A, Bertram B, Siebelmann S, Böhm M, Faber H, Zhour A, Schuster AK. Berufliche Zukunftsperspektive von Augenärzten unter 49 Jahren**.** Eine Umfrage in Deutschland aus dem Jahr 2022. *Die Ophthalmologie (2023)*: https://doi.org/10.1007/s00347-022-01806-0

* Shared first authorship
# Shared last authorship

Beteiligung an Konferenzen

ARVO 2023

Intraocular pressure and its relation to climate parameters – results from the Gutenberg Health Study ***Alica Hartmann****; Stephanie Grabitz; Esther Hoffmann; Philipp Wild; Irene Schmidtmann; Karl Lackner; Manfred Beutel; Thomas Münzel; Oliver Tüscher; Jörn Schattenberg; Norbert Pfeiffer; Alexander Karl-Georg Schuster*

The impact of education on myopia is mainly due to alteration in axial length – results from the Gutenberg Health Study
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DOG 2022 & 2023

Häufigkeit von COVID19-Symptomen in der Allgemeinbevölkerung: eine Analyse der Gutenberg COVID-19 Studie.
Hartmann A*, Schuster AK, Grabitz SD, Engel AL, Schulz A, Schmidtmann I, Beutel ME, Münzel T, Lackner KJ, Pfeiffer N, and Wild PS*

Veränderungen des Augeninnendrucks über 5 Jahre und dessen Zusammenhang mit kardiovaskulären Parametern – Ergebnisse der Gutenberg Gesundheitsstudie
Hartmann A*., Scholz I., Hoffmann E.M., Strzalkowska A., Lackner K.J., Münzel T., Wicke F.S., Urschitz M.S., Tüscher O., Schattenberg J., Pfeiffer N., Wild P.S , Schuster A.K.*

Der Einfluss von Bildung auf die Geometrie des Auges – Ergebnisse der Gutenberg Gesundheitsstudie
Schuster A.K., ***Hartmann A****., Grabitz S., Wagner F.M., Wild P.S., Müller-Nurasyid M., Lackner K.J., Beutel M.E., Münzel T., Tüscher O., Schattenberg J., Pfeiffer N.*

American Academy of Ophthalmology / AAO 2023

The Prevalence of Glaucoma in Europe: The European Eye Epidemiology (E3) Consortium
Kelsey V. Stuart, Wishal Ramdas, Cedric Schweitzer, Alexander Schuster, Nomdo Jansonius, Victor de Vries, Robert Luben, Shabina Hayat, Kay-Tee Kaw, Cécile Delcourt, Fotis Topouzis, Vassilis Kilintzis, ***Alica Hartmann****, Rufino Silva, Rita Coimbra, Iris Heid, Caroline Brandl, Martina Zimmermann, Louis Arnould, Catherine Creuzot-Garcher, David Wright, Ruth Hogg, Jost B Jonas, Mukharram M Bikbov, Yu Yu, Frank CT van der Heide, Tos TJM Berendschot, Paul J. Foster, Anthony P. Khawaja*

Abkürzungsverzeichnis

AMD	Altersabhängige Makuladegeneration
ATC	The anatomical-therapeutic-chemical classification system
BMI	Body-mass-index
COVID-19	Coronavirus disease 2019
EU	Europäische Union
GEDA	German Health Update 2009
GHS	Gutenberg Health Study
GPES	Gutenberg Prematurity Eye Study
IOD	Intraokularer Druck
IOP	Intraocular pressure
MR	Mendelian Randomization
mmHg	Millimeter-Quecksilbersäule
SES	Socio-emotional scale
VI	Visual impairement
VFS	Vision functioning scale
VRQoL	Vision-related quality of life
WHO	Weltgesundheitsorganisation

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Zusammenfassung

Die Gendermedizin beschäftigt sich mit geschlechtsspezifischen Unterschieden, die sich in verschiedenen Krankheitsverläufen und Symptomen äußern. Das Ziel der Gendermedizin ist somit die Umsetzung einer geschlechtersensiblen Medizin, um eine patientenindividuelle Diagnostik, Therapie und Versorgung zu gewährleisten. Der Fokus der Dissertation liegt auf der Analyse von Geschlechterunterschieden in der Ophthalmologie. Die Untersuchung umfasst die Anatomie und Physiologie des menschlichen Auges sowie die Entwicklung der Anatomie bezogen auf die Frühgeburtlichkeit, geschlechterspezifische Veränderungen der visuellen Lebensqualität und die beruflichen Zukunftsperspektiven von Augenärzten*.

Im Rahmen der Studie fanden wir physiologische Unterschiede zwischen den Geschlechtern, mit längeren beziehungsweise größeren Augenparametern bei Männern. Dies betrifft die Achsenlänge des Auges, die Hornhautverkrümmung, die Linsendicke und den White-to-White Abstand. Die Analyse der Augenbiometrie bei Frühgeborenen zeigte einen geschlechtsspezifischen Zusammenhang zwischen niedrigerem Gestationsalter und einer dickeren zentralen Foveadicke. Diese Auswirkung zeigte sich bei Männern stärker ausgeprägt.

Bei der Veränderung des Augeninnendrucks über 5 Jahre zeigte sich eine stärkere Zunahme bei Männern (0,77 ± 2,11 mmHg) im Vergleich zu Frauen (0,69 ± 1,96 mmHg; $p < 0,05$). Auch im Querschnitt wiesen Männer in der Kohorte der Gutenberg-Gesundheitsstudie einen höheren Augeninnendruck auf. Zudem zeigte die Untersuchung des Augeninnendrucks, dass dieser saisonal unterschiedlich ist, mit niedrigeren Werten im Sommer und höheren Augeninnendruckwerten im Winter. Dies ist bei beiden Geschlechtern gleichermaßen der Fall. Des Weiteren zeigte sich bei Frauen ein Zusammenhang mit der Einnahme von einer Untergruppe der Antidepressiva (ATC-Subtyp N06AX) mit einer Augeninnendruckveränderung über 5 Jahre. Dieser Zusammenhang war bei Männern nicht nachweisbar.

In Bezug auf die Entwicklung der visuellen Lebensqualität über einen Zeitraum von 5 Jahren zeigte sich bei beiden Geschlechtern eine Abnahme, die mit einer Verschlechterung der Sehschärfe assoziiert war. Die Verschlechterung der visuellen Lebensqualität war bei Frauen stärker ausgeprägt. Schließlich zeigten sich auch psychosoziale Unterschiede bei Augenärzten in Deutschland: Frauen zeigten häufiger den Wunsch nach einer beruflichen Veränderung als Männer (49% vs. 40%) und wünschten eine kürzere Arbeitsdauer (21-30 h/Woche vs. 31-39 h/Woche) bei der Analyse von Augenärzten unter 49 Jahren. Des Weiteren wiesen Männer im Vergleich zu den Frauen in der Studienkohorte einen höheren sozioökonomischen Status und eine längere Bildungsdauer auf.

*Aus Gründen der besseren Lesbarkeit wird in dieser Dissertation überwiegend das generische Maskulinum verwendet. Dies impliziert immer alle Formen, schließt also die weibliche und diverse Form mit ein.

Die Dissertation gibt erste Hinweise darauf, dass Geschlechterunterschiede in der Ophthalmologie existieren. In der Zukunft ist es wichtig, weitere Bereiche der Augenheilkunde geschlechterspezifisch zu untersuchen, um eine patientenindividuelle Diagnostik und Therapie sicherzustellen.

1 Einleitung

Die Gendermedizin wird als junge Disziplin definiert, welche sich in den 1990er Jahren entwickelt hat [1, 2]. In der Medizin werden geschlechtsspezifische Unterschiede häufig vernachlässigt, obwohl diese von hoher Relevanz sind, da die Organe bei Frauen und Männern anatomische Unterschiede aufweisen und unterschiedliche Krankheitsverläufe die Folge sein können [2, 3]. Die Gendermedizin nimmt genau diese geschlechtsspezifischen Unterschiede in den Fokus der Betrachtung.

In vielen medizinischen Fachbereichen wurden bereits relevante Unterschiede aufgedeckt, welche zu einer optimierten Therapie und Diagnostik führen sollen oder bereits geführt haben, wie beispielsweise im Bereich der Kardiologie. Kardiovaskuläre Erkrankungen zählen zu einer der Hauptursachen für Mortalität in Europa (etwa 49% von den gesamten Sterbefällen bei Frauen sowie etwa 40% der männlichen Sterbefälle) [4, 5]. Bei der koronaren Herzkrankheit und der Herzinsuffizienz wurden Unterschiede aufgedeckt, insbesondere in der Diagnostik und Behandlung. Gezeigt wurde beispielsweise, dass bei einer Herzinsuffizienz trotz für die Geschlechter gleicher leitlinienbasierter Diagnostik die Echokardiographie seltener bei Frauen eingesetzt wird [6, 7]. Im Hinblick auf koronare Herzkrankheiten konnten unterschiedliche Behandlungsweisen erkannt werden, da Frauen seltener interventionelle Therapien erhielten und insgesamt weniger stark invasiv behandelt wurden [8, 9]. Besonders wichtig ist zudem die Anpassung der Medikamente auf das Körpergewicht sowie die Überprüfung der Nierenfunktion bei kleineren und älteren Frauen [7]. Auch bei der Symptomäußerung von kardiovaskulären Erkrankungen wurden wichtige Unterschiede erkannt, wie der unterschiedliche Verlauf eines Herzinfarktes bei Frauen und Männern. Unterschiede zeigten sich in der Pathophysiologie, den Risikofaktoren und anderen Symptomen, wodurch der Herzinfarkt bei Frauen schwieriger erkennbar ist [10-12].

Ziel ist es, durch die Individualisierung der Medizin die Gesundheit aller Personen gleichermaßen zu sichern und spezifisch auf die Krankheitscharakteristiken eingehen zu können. In der Ophthalmologie sind Geschlechterunterschiede bisher weitgehend unerforscht. Unterschiede in der Epidemiologie der häufigsten Augenerkrankungen, wie beispielsweise der altersabhängigen Makuladegeneration (AMD) [13, 14] und des Glaukoms [15, 16] sind ansatzweise erfasst worden, doch die Ausprägung der Erkrankung durch die biologischen Unterschiede sowie unterschiedliche Reaktionen auf Therapiemaßnahmen wurden bisher kaum untersucht. Therapien werden in der Ophthalmologie bisher für alle Patienten gleichermaßen durchgeführt, unabhängig von geschlechtsspezifischen Unterschieden [17]. In der Ophthalmologie sind Geschlechterunterschiede in der Anatomie der Augen des physiologischen Alterungsprozesses ohne Funktionseinschränkung („Healthy Ageing“) und in der Behandlung von Augenerkrankungen bisher nur geringfügig untersucht wurden, wobei dieser Erkenntnisgewinn einen positiven Einfluss auf die Gewährleistung der Gesundheit beider Geschlechter haben könnte. Auch zeigt sich in der augenärztlichen Versorgung eine Veränderung des Tätigkeitsspektrums: weibliche Augenärzte nahmen über die letzten Jahrzehnte zu, zudem wird eine Teilzeittätigkeit häufiger gewünscht [18, 19]. Auch dies ist entsprechend zu berücksichtigen.

Der Fokus dieser Arbeit liegt auf der Untersuchung der Geschlechterunterschiede in der Ophthalmologie. Folgende Schwerpunkte werden in der Arbeit bezogen auf Geschlechterunterschiede untersucht: die Anatomie der Augen und die Physiologie des Augeninnendrucks, Unterschiede bei der Symptomwahrnehmung sowie Veränderungen der visuellen Lebensqualität im Rahmen des „Healthy Ageing“. Das „Healthy Ageing“ wird von der Weltgesundheitsorganisation (WHO) definiert als *„A process of maintaining functional ability to enable well-being in older age”* [20]. Durch die Forschung im Bereich des „Healthy Ageing“ soll untersucht werden, inwiefern der Verlust der biologischen Funktion des Auges die Geschlechter unterschiedlich beeinflusst. Beispielsweise wird untersucht, wie sich der Verlust der Sehschärfe im Alter auf die Lebensqualität beider Geschlechter auswirkt. Nachdem die Untersuchung der einzelnen Schwerpunkte nur einige wenige geschlechtsspezifische Unterschiede aufgezeigt hat, wurde entschieden, einen erweiterten Blick auf die beruflichen Zukunftsaussichten von Augenärzten beider Geschlechter zu werfen.

Durch die vorliegende Dissertation soll ein Betrag zur Verbesserung der geschlechtersensiblen Forschung geschaffen werden:

„It is also important to note that the study of sex/gender differences benefits men as much as it benefits women. Therefore, when we fail to routinely consider the impact of sex/gender in research, we are leaving everyone’s health to chance.” [21, 22]

2 Theoretischer Rahmen

Im folgenden Kapitel wird die relevante Terminologie beschrieben, die Entwicklung der Gendermedizin erläutert und zuletzt die aktuellen Barrieren einer geschlechtersensiblen medizinischen Forschung betrachtet.

2.1 Das Konzept von „Sex“ und „Gender“

„Sex“ beschreibt ein biologisches Konzept, das bei Säugetieren zwei primäre Geschlechter (männlich und weiblich) umfasst [23]. Menschen lassen sich biologisch differenzieren in Frauen mit weiblichen Geschlechtsorganen und Männer mit den männlichen Geschlechtsorganen. Personen mit weiblichen und männlichen Geschlechtsmerkmalen treten selten auf [24]. Die biologische Zuordnung ist somit meist eine dichotome Variable in der Forschung [25].

Neben dem biologischen Geschlecht ist den Menschen auch das psychosoziales Geschlecht „Gender“ zuordenbar. Dieses Konzept ist ein soziales und kulturell geprägtes Konzept, welches psychosoziale Faktoren beschreibt [26]. Es sind Merkmale gemeint, welche als typisch weiblich oder männlich von der Gesellschaft anerkannt werden (die erworbene Geschlechterrolle) [27]. Durch die Unterscheidung beider Begrifflichkeiten soll verdeutlicht werden, dass die Erwartungen der Gesellschaft an Männer und Frauen nicht biologisch vorherbestimmt sind, sondern durch ein gesellschaftliches Konstrukt entstanden und nicht festgesetzt sind [28, 29].

2.2 Geschichte der Gendermedizin

Erste Ansätze der Gendermedizin entwickelte sich während der 1960er und 1970er Jahre im Rahmen der Frauenbewegung. Aktivisten forderten eine verbesserte Gesundheitsversorgung, welche frei von Sexismus ist. Zu diesem Zeitpunkt wurde der „Gender“ Begriff definiert, welcher die Differenzierung zwischen dem biologischen und psychosozialen Geschlecht ermöglichen soll. „Gender“ wurde als Begriff für das psychosoziale Geschlecht genutzt und „Sex“ diente der Beschreibung des biologischen Geschlechtes [30].

Im Jahr 1982 zeigte eine Publikation die Unterrepräsentation von Frauen in der Wissenschaft auf. Dies führte später zu verschiedenen Initiativen und Gesetzesvorstößen zur Förderung der Geschlechtergerechtigkeit im Gesundheitswesen, darunter der „Women’s Health Equity Act“ in den USA [31]. Dieses Gesetz verfolgt das Ziel die Gesundheit von Frauen durch die Wissenschaft, medizinische Behandlung und Prävention zu verbessern. Mithilfe des Gesetzes sollten mehr Frauen in Studien inkludiert werden, um eine geschlechtersensible Diagnostik und Behandlung zu ermöglichen [32]. Im Jahr 1998 hat die WHO die Relevanz des biologischen und psychosozialen Geschlechtes mithilfe des „Equity Act“ verdeutlicht und die Gendermedizin in dem Gesetz verankert [33].

Des Weiteren folgte im Jahr 2001 ein Bericht des „US Institutes of Medicine“ mit dem Titel „Exploring the biological contributions to human health: does sex matter?“ [31]. Dieser legte die Grundlagen für die geschlechtersensible Forschung. Der Bericht erläuterte verschiedene Empfehlungen zur Verankerung der Gendermedizin in der Forschung. So wurde Forschenden unter anderem empfohlen die entsprechende Terminologie („Sex“ und „Gender“) als Begrifflichkeiten zu verwenden, die Ergebnisse nach Geschlechtern zu stratifizieren und zu analysieren. Auch bei der Zellforschung sollten Geschlechterunterschiede betrachtet werden [34].

Zusätzlich entwickelte die EU im Jahr 2002 das 6. Forschungsrahmenprogramm, welches sich erstmals mit dem psychosozialen Geschlecht als Variable in der Forschung befasste und auch die Geschlechterverteilung des Forschungsteam in den Blick nahm [31]. In den nächsten Jahren folgten weitere Gesetze und Publikationen zur Verankerung der Gendermedizin. Die Gendermedizin entwickelte sich durch einen gesamtgesellschaftlichen Prozess.

2.3 Barrieren einer geschlechtersensiblen medizinischen Forschung

Die Gendermedizin erlangte in den letzten Jahren eine größere Aufmerksamkeit im medialen Bereich. Dennoch besteht weiterhin Handlungsbedarf, auch in der klinischen Forschung. Der Anteil an Frauen in medizinischen Studien hat sich in den letzten Jahren erhöht, dennoch sind Frauen in einigen Bereichen weiterhin unterrepräsentiert [35-37]. Für die höhere Anzahl an Männern in medizinischen Studien gibt es verschiedene Gründe. Hormonelle Unterschiede sowie der damit einhergehende weibliche Zyklus spielen eine Rolle. Es besteht Sorge vor einer verringerten Fruchtbarkeit sowie Beeinträchtigung einer bestehenden Schwangerschaft [38]. Teils sind diese Einschränkungen durchaus gerechtfertigt, doch im Vordergrund sollte bei jeder Studie eine sorgfältige Abwägung der Risiken erfolgen. Diese Abwägung findet häufig nicht statt und der Ausschluss erfolgt ohne diese kritische Auseinandersetzung. Dadurch entstehen Forschungslücken und Frauen wird eventuell unrechtmäßig der Zugang zu Studien und der damit einhergehende Nutzen verwehrt [39].

Eine Umfrage zur Verwendung von Verhütungsmitteln bei Forschungsstudien zeigte eine weitere Barriere auf beim Zugang zu Studien für Frauen, welche hormonelle Verhütungsmittel verwenden. Die befragten Frauen mussten vor Beginn der Studie bis zu drei Unterschriften im Voraus einholen, welche die angegebene Einnahme des Verhütungsmittels bestätigten [40]. Dies erhöht den zeitlichen Aufwand für Frauen.

Ein weiterer Punkt ist, dass nun zwischen dem biologischen Geschlecht und dem psychosozialen Geschlecht differenziert wird, die Begrifflichkeiten „Sex“ und „Gender“ allerdings häufig verwechselt werden und die Terminologie bei Forschenden zu Verwirrung führen. Dadurch wird eine mögliche geschlechtersensible Analyse negativ beeinflusst [41, 42]. Grund hierfür könnte sein, dass sich das Konstrukt des psychosozialen Geschlechtes in der zweiten Hälfte des 20. Jahrhunderts äußerst schnell entwickelt hat. Durch die schnelle Entwicklung der Geschlechterforschung könnte es für Forschende problematisch sein über die neusten Entwicklungen ausreichend informiert zu sein. Die korrekte Nutzung der Terminologie und Beschreibung dieser ist wichtig, da sonst Forschungsergebnisse vom Leser falsch interpretiert werden könnten [27].

Zudem werden das biologische sowie psychosoziale Geschlecht zwar häufiger als früher erfasst, dies führt jedoch nicht zwangsläufig zu deren Berücksichtigung bei der Datenaufbereitung und -auswertung [35]. Als eine mögliche Begründung wird von den Forschenden genannt, dass die Berücksichtigung von dem biologischen und psychosozialen Geschlecht höchst zeitaufwendig und kostenintensiv ist [43, 44]. An einem Beispiel in den USA zeigt sich, dass die nicht vorhandene Berücksichtigung der Geschlechter langfristig zu vergleichbar höheren Kosten führen könnte. Eine Analyse zeigte, dass 10 verschreibungspflichtige Medikamente zwischen den Jahren 1997 bis 2001 vom Markt genommen wurden. Von diesen wiesen 8 von 10 Medikamenten ein höheres Gesundheitsrisiko für Frauen als für Männer auf [45]. Durch eine frühere geschlechtersensible Analyse hätte die Gesundheit von Frauen geschützt werden können und somit auch präventiv Kosten für das Gesundheitssystem eingespart werden können.

3 Ziele der Arbeit

Im vorherigen Kapitel wurde aufgezeigt, dass es immer noch einige Barrieren hin zu einer geschlechtersensiblen Forschung gibt und das biologische sowie psychosoziale Geschlecht bei der Analyse häufig nicht hinreichend berücksichtigt wird. Auch in der Augenheilkunde wurden Geschlechterunterschiede häufig nicht differenziert betrachtet. Dies wird verdeutlicht anhand des Faktes, dass es keine geschlechterspezifischen Unterschiede bei der Therapie und Diagnostik gibt. Mithilfe dieser Dissertation sollen Geschlechterunterschiede in der Augenheilkunde in drei Bereichen untersucht werden:

1. Biologische Unterschiede der Augenanatomie, in der Entwicklung der Augenanatomie im Zusammenhang mit der Frühgeburtlichkeit, und der Physiologie des Augeninnendrucks
2. Geschlechtsunterschiede in der visuellen Lebensqualität über einen Zeitraum von 5 Jahren
3. Psychosoziale Unterschiede in der Zukunftsperspektive der augenärztlichen Versorgung

Durch die Betrachtung von biologischen und psychosozialen Aspekten soll es ermöglicht werden mögliche Geschlechterunterschiede aufzuzeigen und zu erläutern wie diese von Relevanz für das Feld der Ophthalmologie sind.

4 Publikationen

4.1 Publikation I

Hartmann A, Grabitz SD, Wagner FM, Wild PS, Müller-Nurasyid M, Lackner KJ, Beutel ME, Münzel T, Tüscher O, Schattenberg JM, Pfeiffer N & Schuster AK**.** Bi-Gaussian analysis reveals distinct education-related alterations in spherical equivalent and axial length—results from the Gutenberg Health Study. Graefes Arch Clin Exp Ophthalmol (2024): https://doi.org/10.1007/s00417-024-06395-z

Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-024-06395-z

BASIC SCIENCE

Bi-Gaussian analysis reveals distinct education-related alterations in spherical equivalent and axial length—results from the Gutenberg Health Study

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Received: 25 September 2023 / Revised: 26 December 2023 / Accepted: 31 January 2024

Abstract

Purpose The aim of this study is to investigate the distribution of spherical equivalent and axial length in the general population and to analyze the influence of education on spherical equivalent with a focus on ocular biometric parameters.

Methods The Gutenberg Health Study is a population-based cohort study in Mainz, Germany. Participants underwent comprehensive ophthalmologic examinations as part of the 5-year follow-up examination in 2012–2017 including genotyping. The spherical equivalent and axial length distributions were modeled with gaussian mixture models. Regression analysis (on person-individual level) was performed to analyze associations between biometric parameters and educational factors. Mendelian randomization analysis explored the causal effect between spherical equivalent, axial length, and education. Additionally, effect mediation analysis examined the link between spherical equivalent and education.

Results A total of 8532 study participants were included (median age: 57 years, 49% female). The distribution of spherical equivalent and axial length follows a bi-Gaussian function, partially explained by the length of education (i.e., < 11 years education vs. 11–20 years). Mendelian randomization indicated an effect of education on refractive error using a genetic risk score of education as an instrument variable (− 0.35 diopters per SD increase in the instrument, 95% CI, − 0.64–0.05, $p = 0.02$) and an effect of education on axial length (0.63 mm per SD increase in the instrument, 95% CI, 0.22–1.04, $p = 0.003$). Spherical equivalent, axial length and anterior chamber depth were associated with length of education in regression analyses. Mediation analysis revealed that the association between spherical equivalent and education is mainly driven (70%) by alteration in axial length.

Conclusions The distribution of axial length and spherical equivalent is represented by subgroups of the population (bi-Gaussian). This distribution can be partially explained by length of education. The impact of education on spherical equivalent is mainly driven by alteration in axial length.

Keywords Refraction · Myopia · Biometry · Mendelian randomization · Gaussian mixture model

Extended author information available on the last page of the article

Published online: 06 March 2024

Key messages

What is known:

- Limited studies have provided indications of a bi-gaussian distribution of axial length and spherical equivalent, suggesting the presence of two distinct subgroups within the population
- Associations between genetic factors, education, and biometric parameters have been previously identified

What is new:

- This study revealed an accurate representation of axial length and spherical equivalent through a bi-gaussian distribution in a large cohort, partially explained by education
- Participants with a shorter education length demonstrated better representation through a gaussian distribution of axial length, and education influenced the spherical equivalent by 70% through alteration in axial length

Introduction

Most biological parameters under physiological circumstances follow a Gaussian distribution, as it was assumed for biometric eye parameters [1–3]. While there has been a consideration that refractive error follows a Gaussian distribution [4], it is essential to acknowledge early indications of a leptokurtic distribution dating back to 1864 [5]. In 2014, a European clinical study showed that the distribution of spherical equivalent resembles a bi-Gaussian distribution indicating a population with two separate subgroups. The same characteristic was seen for axial length, while anterior chamber depth (ACD) and lens power were better described as one Gaussian curve [1]. Understanding ocular biometry and its variation is essential to determine the power of intraocular lenses for achieving target refraction in cataract surgery [6], and to identify subjects at risk for ocular diseases.

Education and genetic factors have been shown to influence refractive error and axial length. Higher or longer education is correlated with longer axial length and myopia [7–11].

Mountjoy et al. [9] used Mendelian randomization technique to examine a possible causal relationship and reported a myopic increase of the refractive error of – 0.27 diopters per every additional year of education.

Genetic risk alleles for myopia were identified, which could lead to a higher risk of developing myopia [12–14]. In the past, the relationship between the genetic risk score and myopia showed a small effect in multivariable analysis [10]. An earlier study showed an impact of education on spherical equivalent independently of genetic risk. Still, it did not investigate the potential bi-Gaussian distribution and the underlying biometric parameters causing this association [10].

Thus, we aim to analyze the distribution of spherical equivalent and axial length in the general population in Germany. We model the impact of genetic parameters and education on axial length and spherical equivalent and also elaborate on the underlying ocular biometric parameters leading to the well-known association between higher education and myopia.

Methods

Procedure and study sample

The Gutenberg Health Study (GHS) is a population-based, prospective, observational single-center cohort study in the Rhine-Main-Region in Germany. The sample was equally stratified for sex, residence (urban or rural), and age-decade. A total of 12,423 individuals were re-examined at the 5-year follow-up (2012–2017) [15, 16].

Ophthalmic parameters

The ocular biometry of the study participants was recorded using optical low-coherence reflectometry technology (LenStar900, Haag Streit, Switzerland) [15]. Patients were instructed to fixate on the center of the internal fixation target of the ocular biometer during the examination. The device performs three single measurements per examination and the parameters are averaged out of these measures. Ocular biometric measurements were excluded when they were likely to be invalid compared with other imaging modalities including Scheimpflug imaging (Pentacam HR, Oculus, Wetzlar, Germany). Objective refraction was measured with Humphrey Automated Refractor/Keratometer (HARK) 5991 [17].

General parameters

Characteristics of the study population including age, sex, body height and body weight were surveyed. Other covariates included were socioeconomic status (SES) and education.

The degree of education was captured by three different variables:

Participants were asked to report their total duration of education in years (sum of years in school, vocational school and university; range: 0–20 years). Furthermore, the level of the completed educational training was queried by two additional questions:

1. What is your highest school-leaving qualification?
    a. Secondary school (lowest level), total of 9 years of schooling ("Hauptschule")
    b. Secondary school (intermediate level), total of 10 years of schooling ("Realschule")
    c. High-school diploma/technical college certificate ("Abitur")

2. What is your highest professional degree?
    a. Vocational school (apprenticeship)
    b. Vocational school, technician-, master school
    c. University degree

Genetic scores

An IlluminaOmniEURHD chip was used for genotyping. Imputation of the missing genotypes was performed using the imputation software Beagle using the 1000GP3 reference panel. The results were filtered and summarized as "allele dosage", with imputation quality calculated using a ratio of observed and expected variance.

Three genetic risk scores were calculated: one for myopia, axial length and one for education. Single nucleotide polymorphisms (SNPs) known to be associated with refractive error were integrated, and 57 variants had been identified through the scientific literature [10, 14, 18], of which 4 were not in the panel of the phenotyping of the GHS (Appendix #1). For the axial length score, 46 SNPs were identified in the literature [18–20]. Of these, 21 were in the GHS panel (Appendix #2).

A previous study from the UK Biobank reported the calculation of a genetic risk score associated with education attainment/duration of education [9, 21]. Of the reported 74 genetic variants associated with education, 70 could be included in this analysis (Appendix #3).

Inclusion and exclusion criteria

For the selection of study participants, only those with phakic lens status were included and participants who had cataract surgery were excluded.

Statistical analysis

Descriptive analysis was conducted for primary and secondary variables. For categorical parameters, absolute and relative frequencies were computed. For continuous variables, mean and standard deviation was calculated for approximately normal-distributed data, otherwise median and interquartile range. The mean value from both eyes was used for the ophthalmic parameters, if available. Only phakic eyes were included [22].

Gaussian mixture models with the implementation of the expectation–maximization (EM) algorithm were used to analyze the distribution of spherical equivalent and axial length in the general population. Multivariate gaussian functions allow us to investigate whether the respective parameter follows a gaussian distribution or is better represented by subgroups in the population (bi- or multi-model-Gaussian distribution) [1]. The analysis considered the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) values of the Gaussian mixture models. The AIC value indicates the likelihood of a model to estimate future values, with a good model characterized by a minimal AIC [23]. On the other hand, the BIC criterion captures the balance between the fit of the model and its complexity. A lower BIC value indicates a better fit of the model, striking a balance between accuracy and simplicity [24].

The genetic risk score for myopia was calculated by multiplying the frequency (0, 1, or 2) of the risk alleles with the effect estimate of the respective risk allele [25]. The same principle was applied to calculate the genetic score for education. However, in this case there were genes with negative coefficients. Here, three sum scores were calculated:

- Sum of SNPs with negative coefficients
- Sum of SNPs with positive coefficients
- Sum of SNPs

Linear regression analyses with generalized estimating equations were conducted to analyze the association between biometric parameters and education adjusted for age, sex and genetic risk score for myopia. The GEEMediate package in R was used to examine the natural direct effect on the mediation proportion on person-level using the mean value of both eyes.

As additionally analyses, possible sex differences were analyzed with linear regression models (with generalized estimating equations) stratified by sex. In addition, we conducted two sensitivity analyses. Firstly, we excluded all individuals over 70 years old to eliminate those with potential lens opacities, as this could impact the biometric parameters. The choice of the age threshold at 70 is based on a study by Stingl et al. [26]. In their investigation, a scatterplot reveals a quadratic relationship between a 5-year change in spherical equivalent (SE) and age. Specifically, there is a hyperopic shift observed between the ages of 44 and 70 years, and a myopic shift is evident at older ages. As a second sensitivity analysis, we excluded individuals with hyperopic refractive error that may be influenced by residual accommodation.

Bidirectional Mendelian randomization was performed to examine possible causal correlations between the duration of education and spherical equivalent, using the genetic risk score for education and the effect of spherical equivalent on duration of education, using the genetic risk score for myopia. The same principle was applied for axial length, involving a genetic score composed of SNPs associated with variations in axial length. Mendelian randomization (MR) is an analysis method which uses instrumental variables (IV). This analysis method allowed us to explore possible correlations by considering a genetically calculated risk. In MR analysis, alleles are randomly assigned; therefore, the analysis resembles a natural randomized control trial. This makes it less susceptible to bias than other analysis methods [27]. We conducted multiple MR methods: the inverse-variance weighted MR approach is most commonly used to examine the correlation between exposure and outcome in genome-wide association studies (GWAS). The approach is subject to the assumption that all SNPs are valid IVs. Further, the weighted MR method assumes that not all SNPs are valid IVs [28]. The MR-Egger approach is a sensitivity analysis to tests for directional pleiotropy; a low p-value demonstrates directional pleiotropy [29].

Data was processed with the statistical program R (version: 4.0.3 (2020–10-10)) with the packages clusterR, flexmix, GEEmediate, MendelianRandomization.

Results

Overall, 8532 study participants were included. The median age of the study population was 57 years (age range: 40–80 years) and 49% were female. Table 1 shows the participant's characteristics at the time point of the ophthalmologic examination (2012–2017). The biometric eye parameters of men were slightly larger/longer than women's. Socioeconomic status and duration of education were also higher among men.

Gaussian mixture models

The Gaussian mixture models showed that a bi-Gaussian function could better represent the distribution of some biometric parameters in the population. Two subgroups better represent the distribution of axial length and the spherical equivalent, while one Gaussian curve best describes the distribution of anterior chamber depth and corneal curvature (Fig. 1). The AIC and BIC values of the bi-Gaussian models were lower than those with one curve, indicating a better population representation of the population by two subgroups.

When stratifying the study sample for persons with 0–10 years and 11 + years, there was a Gaussian distribution in subjects for persons with a shorter duration of education for axial length (Fig. 2). However, with a longer duration of education the axial length showed a bi-Gaussian distribution. Additionally, the spherical equivalent still showed a flattened second curve with shorter duration of education but the histogram is less left skewed (Fig. 3).

Associations between refractive error and education

Linear regression analysis using generalized estimating equations (GEE) showed an association between axial length and duration of education. The association mentioned above were also found for anterior chamber depth and spherical equivalent. Results highlight the spherical equivalent decreases with each additional year of education. Axial length becomes longer with each additional year of education. This is also the case for anterior chamber depth, while lens thickness, corneal curvature and white-to-white distance did not reveal an association with education (Table 2). In the conducted sensitivity analyses, where individuals over 70 were excluded in one instance and those with a hyperopic refractive error were excluded in the second, comparable results were observed.

We additionally stratified the regression models by sex and found one sex-related difference (Supplemental Table 1). Corneal curvature and duration of education is associated only in female participants. Apart from this result, the results fit the regression analysis for all participants.

To investigate whether the association between duration of education and spherical equivalent is mediated by alteration of axial length, a further model was applied. The marginal model (model without the mediator) showed a significant relationship between the spherical equivalent and duration of education (beta $= -0.18$, $p < 0.001$). The conditional model (with the mediator axial length) demonstrated that the effect estimate decreases by 70%, the remaining effect was still significant (beta $= -0.05$, $p < 0.001$).

Mendelian randomization

The inverse-variance weighted (IVW) MR indicated that there might be a causal effect of education years on refractive error using the genetic score for education (−0.35 diopters per SD increase in the instrument, 95% CI, −0.64–0.05, $p = 0.02$; Table 3, Fig. 4a). Furthermore, there was no evidence of a causal effect of refractive error on education, based on the risk score for myopia (Table 3, Fig. 4b). The MR-Egger intercept test showed no average directional pleiotropy in either models ($p = 0.09$ and $p = 0.25$).

Figure 4 shows the findings of the IVW approach. 5 of 70 variants associated with duration of education were significantly associated with higher levels of myopia in our study population (more negative SE, Fig. 4a). A total of 21 of 53

Table 1 Participants' characteristics (N = 8532, data from the examination of the population-based Gutenberg Health Study 2012–2017). Values are presented as mean ± standard deviation unless stated otherwise

	Overall	Men	Women
Anthropometric data	8,532	4359	4173
Age (years), median (IQR), (min–max)	57 [49, 66] (40–80 years)	58 [50, 66] (40–80 years)	57 [49, 66] (40–80 years)
Weight (kg)	80.2 ± 16.87	87.85 ± 14.65	72.19 ± 15.24
Height (cm)	171 ± 10	177 ± 7	164 ± 7
BMI (kg/m^2)	27.40 ± 5.00	27.92 ± 4.31	26.86 ± 5.59
Ophthalmic parameters			
Spherical equivalent, OD (diopter)	− 0.41 ± 2.51	–0.44 ± 2.44	–0.38 ± 2.58
Spherical equivalent, OS (diopter)	–0.42 ± 2.54	–0.45 ± 2.49	–0.39 ± 2.61
Axial Length, OD (mm)	23.74 ± 1.22	24.02 ± 1.19	23.44 ± 1.17
Axial Length, OS (mm)	23.71 ± 1.22	24.00 ± 1.22	23.41 ± 1.17
Anterior chamber depth, OD (mm)	3.25 ± 0.35	3.30 ± 0.36	3.20 ± 0.34
Anterior chamber depth, OS (mm)	3.24 ± 0.35	3.28 ± 0.35	3.19 ± 0.34
Corneal curvature, OD (mm)	7.84 ± 0.28	7.90 ± 0.28	7.78 ± 0.26
Corneal curvature, OS (mm)	7.83 ± 0.28	7.89 ± 0.28	7.77 ± 0.26
Lens thickness, OD (mm)	4.35 ± 0.37	4.37 ± 0.38	4.34 ± 0.35
Lens thickness, OS (mm)	4.42 ± 0.36	4.44 ± 0.37	4.39 ± 0.35
White-to-white, OD (mm)	12.21 ± 0.43	12.29 ± 0.44	12.12 ± 0.41
White-to-white, OS (mm)	12.21 ± 0.44	12.29 ± 0.45	12.13 ± 0.41
Socio-economic data			
Socio-economic status (SES)	13.30 ± 4.38	13.91 ± 4.41	12.66 ± 4.27
Duration of education (years)	13.05 ± 2.09	13.26 ± 2.15	12.84 ± 2
Completion of training			
Secondary school (lowest level), total of 9 years of schooling), Hauptschule, *n* (%)	2727 (32.1)	1422 (32.8)	1305 (31.4)
Secondary school (intermediate level), total of 10 years of schooling, Realschule, *n* (%)	2174 (25.6)	871 (20.1)	1303 (31.3)
Technical college certificate, *n* (%)	901 (10.6)	591 (13.6)	310 (7.5)
High-school diploma (Abitur), *n* (%)	2652 (31.2)	1426 (32.9)	1226 (29.5)
Other degree/no degree	40 (0.5)	26 (0.6)	14 (0.3)
Training degree			
Vocational school (apprenticeship), *n* (%)	3836 (45.1)	1622 (37.4)	2214 (53.2)
Vocational school, technician-, master school, *n* (%)	1300 (15.3)	815 (18.8)	485 (11.7)
College of applied science, *n* (%)	1098 (13.0)	733 (16.9)	365 (8.8)
University degree, *n* (%)	1725 (20.3)	987 (22.8)	738 (17.7)
Other degree/no degree (%)	535 (6.3)	179 (4.2)	356 (8.6)

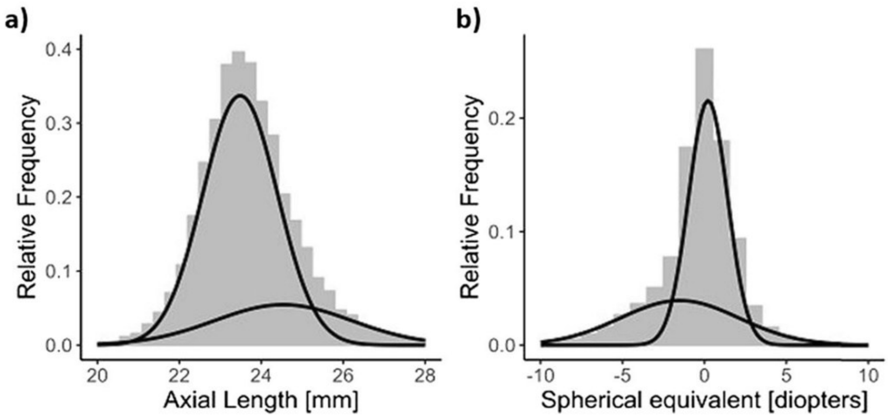

Fig. 1 Bi-Gaussian model: **a** axial length, **b** spherical equivalent. Results from the population-based Gutenberg Health Study (n = 8532; 2012–2017)

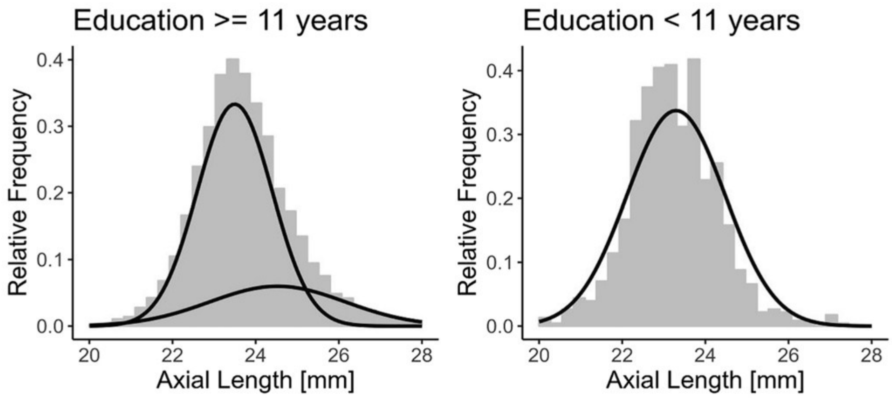

Fig. 2 Gaussian and bi-Gaussian model. Axial length stratified on educational length. Results from the population-based Gutenberg Health Study (n = 8532; 2012–2017)

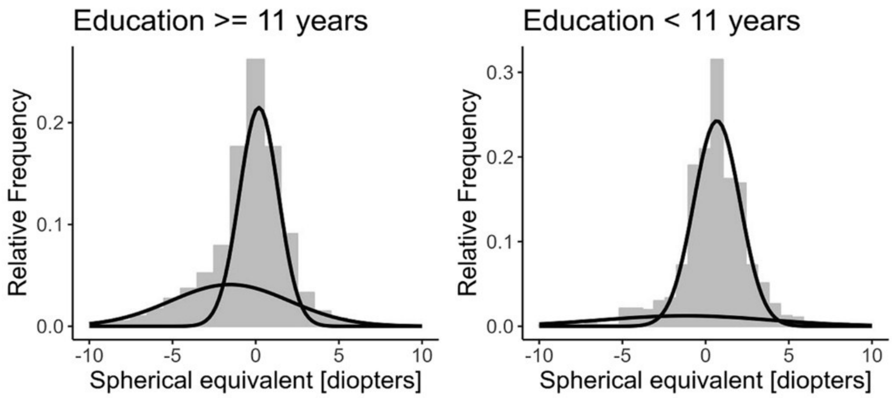

Fig. 3 Gaussian and bi-Gaussian model. Spherical equivalent stratified on educational length. Results from the population-based Gutenberg Health Study (n = 8532; 2012–2017)

Table 2 Association analysis between ocular biometric parameters and duration of education, data from the German population-based Gutenberg Health Study (2012–2017). Linear regression analyses were performed using GEE estimations, adjusted for age, sex, and genetic risk score for myopia

	Year of education		
	Estimate	95%-CI	p
Spherical equivalent	−0.10	[−0.13–−0.08]	< 0.001
Axial length	0.06	[0.05–0.07]	< 0.001
Corneal curvature	0.002	[0.00–0.01]	0.12
Anterior chamber depth	0.01	[0.00–0.01]	< 0.001
Lens thickness	−0.002	[−0.01–0.00]	0.08

variants associated with myopia were not associated with longer duration of education (Fig. 4b).

An effect of duration of education on axial length was also demonstrated using the genetic score for education (0.63 mm per SD increase in the instrument, 95% CI, 0.22–1.04, $p = 0.003$). There was no significant effect of axial length on education when using the genetic score for axial length. No directional pleiotropy was demonstrated in both models ($p = 0.07$ and $p = 0.88$).

Discussion

This study investigated the distribution of spherical equivalent and axial length in the general population. The impact of education on the spherical equivalent and axial length as biometric parameters was analyzed. Our results highlight that the spherical equivalent and axial length distribution follow a bi-Gaussian distribution. The distribution can be partially explained by the length of education (i.e., < 11 years of education vs. 11–20 years). Mendelian randomization showed that spherical equivalent and axial length is influenced by duration of education.

In 2013, Rozema et al. investigated the distribution of spherical equivalent in more detail and further analyzed the distribution of axial length. This study supports the finding of a bi-Gaussian distribution for the axial length and spherical equivalent [1]; nevertheless, the reason for this bi-Gaussian distribution remained in the most studies unexplained. Flitcroft's review [30] suggests that human myopia may result from a failure of homeostasis, particularly emmetropization—a natural process where the eye tends to grow towards an optimal state in early life [31, 32]. Homeostatic failures can lead to refractive errors, increasing variability.

Table 3 Results of bidirectional Mendelian randomization (MR) for refractive error and axial length. Data from the German population-based Gutenberg Health Study (2012–2017)

MR Analysis for education years on refractive error				MR Analysis for education years on axial length		
	Estimate	95% CI	*p*-value	Estimate	95% CI	*p*-value
Simple median	−0.36	[−0.80–0.08]	0.11	0.80	[0.18–1.42]	0.01
Weighted median	−0.18	[−0.62–0.27]	0.44	0.92	[0.28–1.56]	0.01
IVW	−0.35	[−0.64–−0.05]	0.02	0.63	[0.22–1.04]	0.003
MR-Egger	−0.42	[−0.89–0.06]	0.09	0.61	[−0.05–1.23]	0.07
Intercept	0.004	[−0.02–0.02]	0.71	0.001	[−0.01–0.01]	0.93
MR Analysis for refractive error on years of education				MR analysis for axial length on years of education		
Simple median	0.01	[−0.21–0.23]	0.94	0.10	[−0.54–0.73]	0.77
Weighted median	−0.003	[−0.19–0.19]	0.97	0.26	[−0.29–0.81]	0.35
IVW	0.03	[−0.09–0.15]	0.65	0.19	[−0.29–0.67]	0.45
MR-Egger	0.12	[−0.09–0.33]	0.25	0.06	[−0.68–0.80]	0.88
Intercept	−0.01	[−0.03–0.01]	0.27	0.01	[−0.02–0.04]	0.65

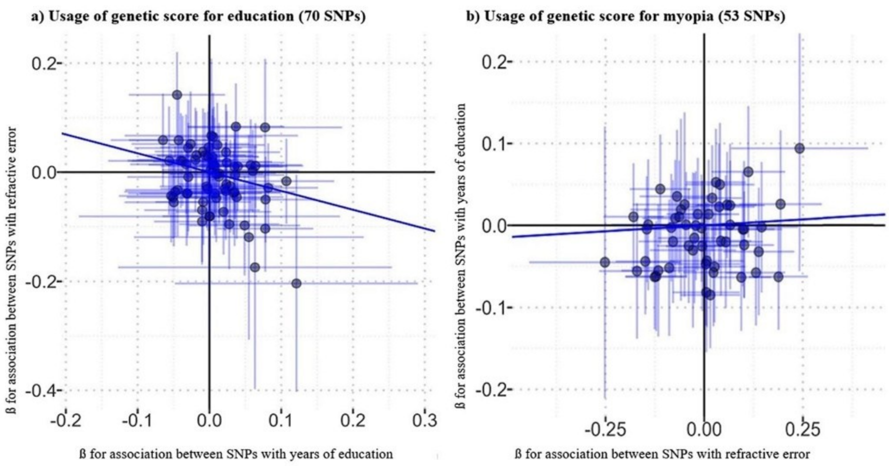

Fig. 4 Results of bidirectional Mendelian Randomization, standard inverse-variance weighted method. Data from the German population-based Gutenberg Health Study (2012–2017). Regression line and standard errors (shaded area) fitted using robust linear regression. Whiskers represent 95% confidence intervals

Acknowledging myopia as a homeostatic failure implies diverse causes, allowing identification of subgroups responsive to specific influences, genes [33], or treatments [30].

Our study showed an association between spherical equivalent and duration of education in linear regression analysis and through Mendelian randomization technique. This is in line with a recent study [9] investigating the direction of causality in the relationship of myopia and education using Mendelian randomization technique. While the authors concluded that myopia did not influence educational level, a myopic shift of −0.27 diopters was observed for each additional year of education [9]. This finding is higher than our result of -0.10 diopters for each additional year of education in the regression analysis.

Furthermore, the stratification of the regression models by sex showed one relevant difference. The association between corneal curvature and duration of education was only visible in female participants. It is important to note that, overall, no consistent relationship between education duration and corneal curvature has been observed, and other studies have also failed to demonstrate a significant association between education and corneal curvature [34]. This sex difference could therefore result from different sample characteristics, or chance finding.

In 2016, Mirshahi et al. analyzed the relationship between myopia and cognitive performance. Cognitive performance was assessed using the Tower of London Test. The findings of the linear mixed model indicated that the length of education influences on myopia (beta = −0.14, $p < 0.001$). In contrast, there was no relationship between cognitive performance and myopia (beta = −0.0017, $p = 0.21$) [35].

Previous studies have demonstrated a correlation between axial length and myopia with a higher level of education [7–11, 36]. This study provides evidence that the correlation between myopia and education may be attributed, in part, to a bi-Gaussian distribution of axial length.

In addition, our analysis showed that axial length increased with each year of education.

Education contributes to increased hours of near work through reading and writing. Studies showed that a longer duration of near work and a small distance between the eyes and the objects viewed are associated with an increased risk of myopia [37–39]. Data from the "British Twins Early Development Study (TEDS)" [40], examined twins aged 5 to 12 years in 1996. This study indicated that near work and screen time were associated with a higher risk of myopia in childhood. Near work requires the eye to adjust to the varying distances of the objects constantly. One possible reason for this could be when individuals engage in prolonged near activities, such as reading, this may lead to a blurred retinal image in the mid-periphery known as peripheral hyperopic defocus. Studies in animals have indicated that peripheral hyperopic defocus stimulate the growth of the eye [39, 41, 42].

Previous studies have demonstrated an association between myopia and environmental and genetic factors. Studies of identical twins and families showed a strong hereditary component to myopia [40, 43]. Several genes have been identified that influence axial length and spherical equivalent [18, 20]. Possible environmental risk factors for myopia, such as using electronic devices, television, or computer [44, 45], are addressed. Outdoor time and light exposure are myopia protective factors [46]. Sherwin et al. reported 2% reduced odds of myopia per additional hour per week spent outside [47].

The change in refractive error is directly linked to the previously identified risk factors: The risk factors lead to a change in biometric parameters for instance axial length [45]. In the retina, dopamine is an important neurotransmitter responsible for various functions: it is relevant for the creation of visual signals as well as refractive development [48]. Brighter light leads to a release of dopamine attenuating axial length growth. Some of the risk factors may arise due to competing activities: increased media use is associated with less time outdoors, thus resulting in less exposure of the eye to bright light [46].

Strengths and limitations

This study analyzed data from a large population-based representative sample and contributed to a better understanding of the distribution of spherical equivalent and axial length in the general population. Education as an underlying factor for the occurred distributions could be demonstrated. Compared to other studies on this topic, the large study population offers the possibility of obtaining representative findings. However, some limitations in our study need to be considered. First, the included GHS subjects mainly consist of Caucasian origin. Therefore, the results cannot be generalized to other ethnicities. A second limitation is that no data on the previous outdoor activity of the study population and no parameters on light exposure, especially during childhood, adolescence and early adulthood were collected. The influence of outdoor activity separate light exposure on myopia has been proven [49–51]. Thus, adjusting for outdoor activity in the regression analysis was impossible. After age 35, a further myopic shift is less likely as a recent publication has shown [26], and there is no association between type of occupation and refractive error.

Conclusion

In conclusion, this study demonstrated that the distribution of axial length and spherical equivalent is better represented by two subgroups (bi-Gaussian) in a population-based study. Stratification of the study population by duration of education (education 0–10 years vs. education 11–20 years) showed that for a short duration of education, the distribution of axial length follows the physiological Gaussian distribution. The distribution of spherical equivalent follows nearly a Gaussian distribution. Myopic spherical equivalent, longer axial length and deeper anterior chamber depth were associated with duration of education, while corneal curvature and lens thickness were not. Mediation analysis showed that about 70% of the effect of education on spherical equivalent is due to elongation in axial length.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00417-024-06395-z.

Funding Open Access funding enabled and organized by Projekt DEAL. All authors: The Gutenberg Health Study is funded through the Government of Rhineland-Palatinate („Stiftung Rheinland-Pfalz für Innovation," contract AZ 961–386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study.

Declarations

Ethics approval All procedures performed in studies involving were in accordance with the ethical standards of the ethics committee of the Medical Chamber of Rhineland-Palatinate, Mainz, Germany and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all study participants prior to their study entry and the GHS complies with Good Clinical Practice (GCP), Good Epidemiological Practice (GEP). The study protocol and study documents were approved by the ethics committee of the Medical Chamber of Rhineland-Palatinate, Mainz, Germany (reference no. 837.020.07).

Conflict of interest Schuster AK holds the professorship for ophthalmic healthcare research endowed by "Stiftung Auge" and financed by "Deutsche Ophthalmologische Gesellschaft" and "Berufsverband der Augenärzte Deutschlands e.V." Schuster AK acted as consultant for Apellis and Abbvie, and received financial and research support by Abbvie, Bayer Vital, Heidelberg Engineering, Novartis, Santen.
Wild PS is funded by the Federal Ministry of Education and Research (BMBF 01EO1503) and he and Münzel T are PI of the German Center for Cardiovascular Research (DZHK). Pfeiffer N receives financial support by Novartis, Ivantis, Santen, Thea, Boehringer Ingelheim Deutschland GmbH & Co. KG, Alcon, Sanoculis.

Schattenberg JM acts as consultant to Apollo Endosurgery, Bayer, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers. Research Funding: Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH.

References

1. Rozema JJ, Tassignon MJ (2014) The bigaussian nature of ocular biometry. Optom Vis Sci 91:713–722. https://doi.org/10.1097/opx.0000000000000296
2. Ojaimi E, Rose KA, Morgan IG et al (2005) Distribution of ocular biometric parameters and refraction in a population-based study of Australian children. Invest Ophthalmol Vis Sci 46:2748–2754. https://doi.org/10.1167/iovs.04-1324
3. Tron E (1934) Über die optischen Grundlagen der Ametropie. Albrecht v. Graefes Arch. Ophthal 132:182–223
4. Steiger A (1913) Die Entstehung der sphärischen Refraktionen des menschlichen, 1st edn. Auges. Verl. Karger
5. Donders FC, Moore WD, Society NS (1864) On the anomalies of accommodation and refraction of the eye: with a preliminary essay on physiological dioptrics. Br Foreign Med Chir Rev 34(68):443–445
6. Kassa MS, Gessesse GW (2021) Ocular biometry and intra ocular lens power among cataract patients in rural Eastern Ethiopia. Ethiop J Health Sci 31:823–830. https://doi.org/10.4314/ejhs.v31i4.17
7. Wong TY, Foster PJ, Johnson GJ et al (2002) Education, socioeconomic status, and ocular dimensions in Chinese adults: the Tanjong Pagar Survey. Br J Ophthalmol 86:963–968. https://doi.org/10.1136/bjo.86.9.963
8. Bikbov MM, Kazakbaeva GM, Rakhimova EM et al (2021) Axial length and its associations in the Ural Very Old Study. Sci Rep 11:18459. https://doi.org/10.1038/s41598-021-98039-z
9. Mountjoy E, Davies NM, Plotnikov D et al (2018) Education and myopia: assessing the direction of causality by mendelian randomisation. BMJ 361:k2022. https://doi.org/10.1136/bmj.k2022
10. Mirshahi A, Ponto KA, Hoehn R et al (2014) Myopia and level of education: results from the Gutenberg Health Study. Ophthalmology 121:2047–2052. https://doi.org/10.1016/j.ophtha.2014.04.017
11. Foster PJ, Broadway DC, Hayat S et al (2010) Refractive error, axial length and anterior chamber depth of the eye in British adults: the EPIC-Norfolk Eye Study. Br J Ophthalmol 94:827–830. https://doi.org/10.1136/bjo.2009.163899
12. Kiefer AK, Tung JY, Do CB et al (2013) Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. PLoS Genet 9:e1003299. https://doi.org/10.1371/journal.pgen.1003299
13. Verhoeven VJ, Hysi PG, Saw SM et al (2012) Large scale international replication and meta-analysis study confirms association of the 15q14 locus with myopia. The CREAM consortium Hum Genet 131:1467–1480. https://doi.org/10.1007/s00439-012-1176-0
14. Verhoeven VJ, Hysi PG, Wojciechowski R et al (2013) Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. Nat Genet 45:314–318. https://doi.org/10.1038/ng.2554
15. Höhn R, Kottler U, Peto T et al (2015) The ophthalmic branch of the Gutenberg Health Study: study design, cohort profile and self-reported diseases. PLoS ONE 10:e0120476. https://doi.org/10.1371/journal.pone.0120476
16. Mirshahi A, Ponto KA, Höhn R et al (2013) Ophthalmologische Aspekte der Gutenberg Gesundheitsstudie. Ophthalmologe 110:210–217. https://doi.org/10.1007/s00347-012-2666-0
17. Hoffmann EM, Aghayeva F, Wagner FM et al (2022) Intraocular pressure and its relation to ocular geometry: results from the Gutenberg Health Study. Invest Ophthalmol Vis Sci 63:40–40. https://doi.org/10.1167/iovs.63.1.40
18. Fan Q, Pozarickij A, Tan NYQ et al (2020) Genome-wide association meta-analysis of corneal curvature identifies novel loci and shared genetic influences across axial length and refractive error. Communications Biology 3:133. https://doi.org/10.1038/s42003-020-0802-y
19. Fuse N, Sakurai M, Motoike IN et al (2022) Genome-wide Association study of axial length in population-based cohorts in Japan: the Tohoku Medical Megabank Organization Eye Study. Ophthalmology Science 2:100113. https://doi.org/10.1016/j.xops.2022.100113
20. Cheng CY, Schache M, Ikram MK et al (2013) Nine loci for ocular axial length identified through genome-wide association studies, including shared loci with refractive error. Am J Hum Genet 93:264–277. https://doi.org/10.1016/j.ajhg.2013.06.016
21. Okbay A, Beauchamp JP, Fontana MA et al (2016) Genome-wide association study identifies 74 loci associated with educational attainment. Nature 533:539–542. https://doi.org/10.1038/nature17671
22. Schuster AK, Nickels S, Pfeiffer N et al (2020) Frequency of cataract surgery and its impact on visual function-results from the German Gutenberg Health Study. Graefes Arch Clin Exp Ophthalmol 258:2223–2231. https://doi.org/10.1007/s00417-020-04770-0
23. Akaike H (1998) A new look at the statistical model identification. In: Parzen E, Tanabe K, Kitagawa G (eds) Selected Papers of Hirotugu Akaike. Springer, New York, New York, NY, pp 215–222
24. Stone M (1979) Comments on Model Selection Criteria of Akaike and Schwarz. J Roy Stat Soc: Ser B (Methodol) 41:276–278. https://doi.org/10.1111/j.2517-6161.1979.tb01084.x
25. Choi SW, Mak TS-H, O'Reilly PF (2020) Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc 15:2759–2772. https://doi.org/10.1038/s41596-020-0353-1
26. Stingl JV, Ban SA, Nagler M, Schmidtmann I, Wild PS, Lackner KJ, Münzel T, Beutel ME, Pfeiffer N, Schuster AK (2022) Five-year change in refractive error and its risk factors: results from the Gutenberg Health Study. British Journal of Ophthalmology: bjophthalmol-2021–318828 https://doi.org/10.1136/bjophthalmol-2021-318828
27. Stuart KV, Luben RN, Warwick AN et al (2022) The association of alcohol consumption with glaucoma and related traits: findings from the UK Biobank. Ophthalmology Glaucoma. https://doi.org/10.1016/j.ogla.2022.11.008
28. Burgess S, Foley CN, Allara E et al (2020) A robust and efficient method for Mendelian randomization with hundreds of genetic variants. Nat Commun 11:376. https://doi.org/10.1038/s41467-019-14156-4
29. Burgess S, Thompson SG (2017) Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 32:377–389. https://doi.org/10.1007/s10654-017-0255-x
30. Flitcroft DI (2013) Is myopia a failure of homeostasis? Exp Eye Res 114:16–24. https://doi.org/10.1016/j.exer.2013.02.008
31. Straub M (1909) Über die Atiologie der Brechungsanomalien des Auges und den Ursprung der Emmetropie. Albrecht von Graefes Archiv für Ophthalmologie 70:130–199. https://doi.org/10.1007/BF02002778
32. Brown NP, Koretz JF, Bron AJ (1999) The development and maintenance of emmetropia. Eye (Lond) 13(Pt 1):83–92. https://doi.org/10.1038/eye.1999.16

33. Dirani M, Shekar SN, Baird PN (2008) Evidence of shared genes in refraction and axial length: the Genes in Myopia (GEM) twin study. Invest Ophthalmol Vis Sci 49:4336–4339. https://doi.org/10.1167/iovs.07-1516
34. Nickels S, Hopf S, Pfeiffer N et al (2019) Myopia is associated with education: results from NHANES 1999–2008. PLoS ONE 14:e0211196. https://doi.org/10.1371/journal.pone.0211196
35. Mirshahi A, Ponto KA, Laubert-Reh D et al (2016) Myopia and cognitive performance: results from the Gutenberg Health Study. Invest Ophthalmol Vis Sci 57:5230–5236. https://doi.org/10.1167/iovs.16-19507
36. Reis RD, Lira RPC, Mélega MV et al (2022) Association between axial length and level of education in elderly patients with cataracts unexposed to electronic devices in the first two decades of life. Arq Bras Oftalmol. https://doi.org/10.5935/0004-2749.2021-0294
37. Huang H-M, Chang DS-T, Wu P-C (2015) The Association between near work activities and myopia in children—a systematic review and meta-analysis. PLoS ONE 10:e0140419. https://doi.org/10.1371/journal.pone.0140419
38. Dutheil F, Oueslati T, Delamarre L et al (2023) Myopia and near work: a systematic review and meta-analysis. Int J Environ Res Public Health 20. https://doi.org/10.3390/ijerph20010875
39. Ip JM, Saw S-M, Rose KA et al (2008) Role of near work in myopia: findings in a sample of Australian school children. Invest Ophthalmol Vis Sci 49:2903–2910. https://doi.org/10.1167/iovs.07-0804
40. Williams KM, Kraphol E, Yonova-Doing E et al (2019) Early life factors for myopia in the British Twins Early Development Study. Br J Ophthalmol 103:1078–1084. https://doi.org/10.1136/bjophthalmol-2018-312439
41. Schaeffel F, Glasser A, Howland HC (1988) Accommodation, refractive error and eye growth in chickens. Vision Res 28:639–657. https://doi.org/10.1016/0042-6989(88)90113-7
42. Irving EL, Callender MG, Sivak JG (1991) Inducing myopia, hyperopia, and astigmatism in chicks. Optom Vis Sci 68:364–368. https://doi.org/10.1097/00006324-199105000-00007
43. Pärssinen O, Kauppinen M, Viljanen A (2014) The progression of myopia from its onset at age 8–12 to adulthood and the influence of heredity and external factors on myopic progression. A 23-year follow-up study. Acta Ophthalmol 92(8):730–739. https://doi.org/10.1111/aos.12387
44. Foreman J, Salim AT, Praveen A et al (2021) Association between digital smart device use and myopia: a systematic review and meta-analysis. Lancet Digit Health 3:e806–e818. https://doi.org/10.1016/s2589-7500(21)00135-7
45. Harrington SC, Stack J, O'Dwyer V (2019) Risk factors associated with myopia in schoolchildren in Ireland. Br J Ophthalmol 103(12):1803–1809. https://doi.org/10.1136/bjophthalmol-2018-313325
46. Zhang J, Deng G (2020) Protective effects of increased outdoor time against myopia: a review. J Int Med Res 48:300060519893866. https://doi.org/10.1177/0300060519893866
47. Sherwin JC, Reacher MH, Keogh RH et al (2012) The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. Ophthalmology 119:2141–2151. https://doi.org/10.1016/j.ophtha.2012.04.020
48. Zhou X, Pardue MT, Iuvone PM et al (2017) Dopamine signaling and myopia development: What are the key challenges. Prog Retin Eye Res 61:60–71. https://doi.org/10.1016/j.preteyeres.2017.06.003
49. Gupta S, Joshi A, Saxena H et al (2021) Outdoor activity and myopia progression in children: a follow-up study using mixed-effects model. Indian J Ophthalmol 69:3446–3450. https://doi.org/10.4103/ijo.IJO_3602_20
50. Guo Y, Liu LJ, Tang P et al (2017) Outdoor activity and myopia progression in 4-year follow-up of Chinese primary school children: the Beijing Children Eye Study. PLoS ONE 12:e0175921. https://doi.org/10.1371/journal.pone.0175921
51. Jin J-X, Hua W-J, Jiang X et al (2015) Effect of outdoor activity on myopia onset and progression in school-aged children in northeast china: the sujiatun eye care study. BMC Ophthalmol 15:73. https://doi.org/10.1186/s12886-015-0052-9

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4.2 Publikation II

Fieß A*, **Hartmann A***, Mildenberger E, Urschitz MS, Laspas P, Schultheis A, Stoffelns B, Pfeiffer N, Gißler S#, Schuster AK#. Sex-specific differences in the relation of prematurity on ocular geometry. Investigative Ophthalmology & Visual Science (2024):
https://doi.org/10.1167/iovs.65.6.23

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Clinical and Epidemiologic Research

Sex-Specific Differences in the Relationship Between Prematurity and Ocular Geometry

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Received: December 15, 2023
Accepted: March 19, 2024
Published: June 14, 2024

Citation: Fieß A, Hartmann A, Mildenberger E, et al. Sex-specific differences in the relationship between prematurity and ocular geometry. *Invest Ophthalmol Vis Sci.* 2024;65(6):23.
https://doi.org/10.1167/iovs.65.6.23

Purpose. To explore differences in the relationship between gestational age (GA) and birth weight (BW) percentile and ocular geometry between males and females.

Methods. The Gutenberg Prematurity Eye Study involved a prospective ophthalmic examination of adults, aged 18 to 52 years, who were born preterm or at term, in Germany. The associations between GA and BW percentile on the main outcome measures were evaluated by uni- and multivariable linear regression analyses. The main outcome measures were central corneal thickness, corneal radius, anterior chamber depth, lens thickness, posterior segment length, and central foveal thickness. Potential sex-specific differences and an effect modification by sex were analyzed.

Results. This study involved 438 participants (245 females, 193 males) with an average age of 28.6 ± 8.7 years. In female participants, central foveal thickness was negatively associated with a higher GA ($B = -2.99$; $P < 0.001$). Similarly, male participants also demonstrated a negative association between central foveal thickness and GA ($B = -4.27$; $P < 0.001$). The multivariable model with effect modification revealed that the central foveal thickness was thicker with lower GA. There was an association between the effect modification of GA with sex and central foveal thickness, demonstrating a more pronounced effect of GA on central foveal thickness in male participants ($B = 1.29$; $P = 0.04$).

Conclusions. This study identified a sex-specific correlation between lower GA and thicker central foveal thickness, suggesting differences in the developmental trajectory of this biometric parameter concerning GA. A thicker central foveal thickness might affect the visual acuity of individuals born preterm in adulthood, with a more pronounced impact in males and a potential predisposition to age-related diseases later in life. Sex did not influence the association of GA or BW percentile to other ocular geometric parameters.

Keywords: prematurity, epidemiology, birth weight, anatomy, sex differences

Numerous studies have demonstrated disparities in ocular biometry between infants born preterm with and without retinopathy of prematurity (ROP) compared to individuals born full-term contributing to the increased risk for reduced visual acuity and increased myopic refractive errors of individuals born preterm in infancy and childhood.[1–3] Furthermore, there are biometric differences between men and women in adults.[4,5] However, the expression of these biometric differences between the sexes in children born preterm remains unclear, raising questions about the existence of sex-specific differences regarding ocular biometry. There is evidence that preterm birth affects women and men differently in various aspects, with sex-specific differences becoming evident during fetal development. Female fetuses rely more on intrinsic placental growth, whereas male fetuses depend more on nutrient transfer through the placenta. Consequently, in times of maternal stress and deprivation, male fetuses are at a higher risk of experiencing growth retardation, including reduced growth.[6–8] Moreover, male preterm infants have an elevated risk of mortality, morbidity, and brain injury,[9–11] and certain studies have indicated a higher incidence of severe ROP in male individuals.[12,13] The long-term effects of prematurity also appear to differ between female and male individuals, with several studies indicating that females born preterm have better cognitive outcomes compared to males.[14–16]

Sex differences in ocular biometry in children as well as in adults have been investigated. In a study

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examining 155 eyes, female adults had a thinner central corneal thickness, but the axial length, anterior chamber depth, lens thickness, and white-to-white distance were not significantly different between sexes.[17] Conversely, other studies have demonstrated that males tend to have larger morphometric eye parameters. In one study, sex-specific biometric differences in children were examined by analyzing 64 eyes of 64 adolescents from 32 sets of twins.[18] The authors discovered sex-specific variations in optical biometry measurements. It was observed that girls were more likely to show shorter axial lengths and white-to-white distances.[18] Other studies in adults have shown comparable results related to generally larger morphometric parameters in men.[4,5]

In a prior investigation conducted as part of the Gutenberg Prematurity Eye Study, it was demonstrated that low gestational age (GA) and a low birth weight (BW) percentile were linked to a steeper corneal curvature and a reduced corneal diameter. Meanwhile, ROP was solely associated with reduced corneal diameter, with ROP-treated eyes exhibiting a shallower anterior chamber and a thicker lens. Additionally, lower GA and the presence of pre-eclampsia were linked to a shorter axial length.[19] Other studies have yielded similar findings.[20–22]

This study aims to build upon the previous findings by exploring sex-specific differences in ocular biometry, with a primary focus on individuals born preterm. This study represents the first of its kind, to our knowledge, to investigate disparities in adults born preterm, and it is anticipated that it will uncover sex-specific variations that could impact vision. Understanding these potential sex-specific differences in ocular biometry could provide valuable insights for clinical practice.

Materials and Methods

Study Population

The Gutenberg Prematurity Eye Study (GPES) is a single-center cohort study conducted at the University Medical Center of the Johannes Gutenberg University Mainz (UMCM) in Germany. The study included individuals born preterm or full term between 1969 and 2002 who were between the ages of 18 to 52 years at the time of enrollment. This study has a retrospective cohort design with prospective follow-up data collection.

For the GPES, preterm newborns with a GA at birth of ≤32 weeks and every second randomly chosen preterm newborn with a GA of 33 to 36 weeks were invited to participate. Additionally, for each month from 1969 to 2002, six individuals (three males and three females) born full term with a BW between the 10th and 90th percentiles were invited as controls, as reported earlier.[23,24]

The study examinations were conducted from June 2019 to November 2021. Each participant underwent a comprehensive ophthalmological examination, including ocular biometry, and a medical history interview. Furthermore, the participants' medical records documenting perinatal and postnatal histories were reviewed.

Written informed consent was obtained from all participants before they entered into the study, complying with Good Clinical Practice, Good Epidemiological Practice, and the tenets of the Declaration of Helsinki. The study protocol and documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 2019-14161; original vote: 29.05.2019, latest update: 02.04.2020).

Assessment of Prenatal, Perinatal, and Postnatal Medical History

The medical records of the participants archived at the UMCM were thoroughly reviewed to gather essential information related to their prenatal, perinatal, and postnatal medical history. Data included parameters such as GA (in weeks); BW (in kilograms); the presence and stage of ROP and ROP treatment details; occurrences of placental insufficiency; cases of pre-eclampsia; breastfeeding practices; gestational diabetes; maternal hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; and maternal smoking. Additionally, BW percentiles were calculated following the method developed by Voigt et al.[25]

Categorization

The participants were categorized into the following groups for descriptive analysis:

- Group 1. Full-term participants (born with a GA of ≥37 weeks)
- Group 2. Preterm participants with a GA at birth between 33 and 36 weeks (moderate-to-late preterm) without ROP
- Group 3. Preterm participants with a GA at birth between 29 and 32 weeks without ROP
- Group 4. Preterm participants with a GA at birth of ≤28 weeks without ROP
- Group 5. Preterm participants with a GA at birth of ≤32 weeks with postnatal ROP but no ROP treatment
- Group 6. Preterm participants with a GA at birth of ≤32 weeks with postnatal ROP and ROP treatment

In cases where only one eye of a participant had ROP, the analysis excluded the fellow eye without ROP.

Ophthalmological Examination

Ocular biometry was conducted with the Lenstar 900 instrument from Haag-Streit (Köniz, Switzerland).[23] During each examination, three individual measurements were taken, and the average value was calculated. Several Lenstar parameters were recorded, including corneal radius, anterior chamber depth, lens thickness, and axial length. Each parameter underwent outlier checks to ensure data quality as reported earlier.[19] Furthermore, nonmydriatic fundus photography and imaging of the macula using spectral-domain optical coherence tomography (SD-OCT) were conducted with the SPECTRALIS OCT system (Heidelberg Engineering, Heidelberg, Germany).[19,26] The macula was captured using SD-OCT in a 15° × 15° block scan format in enhanced depth imaging mode and assuming a corneal curvature of 7.7 mm. Heidelberg Eye Explorer software (HEYEX and SPX; Heidelberg Engineering) was employed, utilizing a research software tool for the automatic segmentation of macular retinal thickness and that of each individual retinal layer. The calculation of reti-

Table 1. Characteristics of the GPES Sample ($n = 438$) Stratified by Study Group and Grouped by Female and Male Participants

	Group 1 (GA ≥ 37)	Group 2 (GA 33–36) No ROP	Group 3 (GA 29–32) No ROP	Group 4 (GA ≤ 28) No ROP	Group 5 (GA ≤ 32) ROP Without Treatment	Group 6 (GA ≤ 32) ROP With Treatment
Female participants						
Participants/eyes, *n*	81/162	80/159	47/94	10/18	23/44	4/7
Age (y), mean ± SD	29.40 ± 8.9	29.28 ± 9.7	28.66 ± 8.7	28.50 ± 10.5	23.65 ± 6.5	24.25 ± 5.2
BW (g), mean ± SD	3320 ± 375	2090 ± 487	1520 ± 282	1017 ± 182	933 ± 344	844 ± 228
BW < 1500 g, *n* (%)	0 (0)	7 (8.8)	19 (40.4)	10 (100)	21 (91.3)	4 (100)
BW < 1000 g, *n* (%)	0 (0)	0 (0)	3 (6.4)	4 (40.0)	14 (60.9)	3 (75.0)
GA (wk), mean ± SD	39.44 ± 1.3	34.43 ± 1.0	30.51 ± 1.2	27.00 ± 1.3	27.57 ± 2.0	26.25 ± 2.1
ROP, stages 1/2/3, *n*	0/0/0	0/0/0	0/0/0	0/0/0	17/25/2	0/2/5
Preeclampsia, *n* (%)	9 (11.1)	13 (16.3)	7 /14.9)	1 (10.0)	4 (17.4)	0 (0)
Placental insufficiency, *n* (%)	2 (2.5)	13 (16.3)	2 (4.3)	0 (0)	1 (4.3)	0 (0)
Maternal smoking, *n* (%)	5 (6.2)	6 (7.5)	4 (8.5)	1 (10.0)	3 (13.0)	0 (0)
HELLP syndrome, *n* (%)	0 (0)	2 (2.5)	0 (0)	0 (0)	2 (8.7)	0 (0)
Gestational diabetes, *n* (%)	1 (1.2)	4 (5.0)	0 (0)	0 (0)	0 (0)	0 (0)
Breastfeeding, *n* (%)	43 (53.1)	45 (56.3)	23 (48.9)	3 (30.0)	10 (43.5)	3 (75.0)
Male participants						
Participants/eyes, *n*	59/118	54/108	41/81	10/18	20/36	9/16
Age (y), mean ± SD	30.49 ± 9.6	29.63 ± 8.6	27.80 ± 7.5	20.90 ± 3.1	25.90 ± 4.1	28.44 ± 5.3
BW (g), mean ± SD	3558 ± 376	2023 ± 440	1582 ± 377	835 ± 156	1166 ± 411	803 ± 288
BW < 1500 g, *n* (%)	0 (0)	6 (11.1)	18 (43.9)	10 (100)	16 (80)	9 (100)
BW < 1000 g, *n* (%)	0 (0)	0 (0)	2 (4.9)	8 (80)	7 (35)	7 (77.8)
GA (wk), mean ± SD	39.12 ± 1.3	34.07 ± 0.91	30.80 ± 1.1	26.30 ± 1.6	28.10 ± 2.2	27.33 ± 2.4
ROP, stages 1/2/3, *n*	0/0/0	0/0/0	0/0/0	0/0/0	13/19/4	0/2/14
Preeclampsia, *n* (%)	2 (3.4)	11 (20.4)	3 (7.3)	2 (20)	5 (25)	4 (44.4)
Placental insufficiency, *n* (%)	0 (0)	3 (5.6)	0 (0)	1 (10)	1 (5)	0 (0)
Maternal smoking, *n* (%)	2 (3.4)	1 (1.9)	4 (9.8)	0 (0)	2 (10.0)	2 (22.2)
HELLP syndrome, *n* (%)	0 (0)	4 (7.4)	1 (2.4)	0 (0)	2 (10.0)	0 (0)
Gestational diabetes, *n* (%)	0 (0)	3 (5.6)	1 (2.4)	1 (10)	1 (5.0)	0 (0)
Breastfeeding, *n* (%)	36 (61)	28 (51.9)	21 (51.2)	6 (60)	8 (40)	3 (33.3)

nal layer thickness within the fovea and perifoveal area was executed using an Early Treatment Diabetic Retinopathy Study (ETDRS) grid featuring circles at 1-mm, 2-mm, and 3-mm distances from the foveal center, which was presumed to be the point of deepest foveal depression. Central foveal thickness was determined as the minimal retinal thickness at the fovea. Each scan underwent review by a board-certified ophthalmologist to identify any issues with decentration or layer segmentation errors, with any affected eyes being excluded from the study. Consequently, this study incorporated only those images that were of high quality and perfectly centered, possessed a signal strength of over 15 dB, and showcased precise automated delineation.[27] Moreover, foveal scans from both eyes were assessed by two independent graders (A.K.S., S.G.) for signs of foveal hypoplasia, defined per criteria outlined in a prior publication.[26]

Covariates

Covariates may affect the main outcome measures such as GA (weeks) and BW percentile, so participants with a history of corneal or cataract surgery were excluded, as such medical interventions could potentially impact ocular anatomy ($n = 7$). Also, ocular geometry measurements were not possible in a few participants, particularly in those with low visual acuity ($n = 5$).

Statistical Analysis

The main outcome measures were central corneal thickness, corneal radius, anterior chamber depth, lens thickness, posterior segment length, and central foveal thickness. Descriptive statistics were utilized to analyze these outcome measures stratified by clinical group. For dichotomous parameters, absolute and relative frequencies were calculated, whereas approximately normally distributed variables were assessed using mean and standard deviation (SD) and the median and interquartile range were determined for non-normally distributed variables. Both right and left eyes were included in the analysis. Linear regression models with generalized estimating equations were employed to evaluate associations accounting for correlations between corresponding eyes.

The initial step involved univariable analyses for the main outcome measures considering independent parameters such as GA and BW percentile. The regression analyses were conducted independently for female and male participants to explore potential sex-specific differences. Both GA and BW percentile were incorporated into the multivariable regression analysis concerning various biometric parameters. An additional model was introduced to investigate the potential influence of sex, employing effect modification terms in the regression model. Moreover, a sensitivity analysis was performed by incorporating age into the multivariable model for central foveal thickness.

Further, a separate multivariable analysis was conducted adjusting for the presence of ROP (yes) and ROP treatment (yes) as additional factors. In a separate model, foveal hypoplasia was included as a further adjustment. Because this study is exploratory, no adjustments for multiple testing were applied. The calculations were performed using commercial software (SPSS Statistics 20.0; IBM, Chicago, IL, USA).

RESULTS

A total of 861 eyes of 438 individuals, including 245 females and 193 males, were included in this study with an average age of 28.6 ± 8.7 years. Among the female participants, 81 individuals had a GA of 37 weeks or more (group 1), 80 individuals had a GA between 33 and 36 weeks without ROP (group 2), 47 individuals had a GA between 29 and 32 weeks without ROP (group 3), 10 individuals had a GA of 28 weeks or less without ROP (group 4), 23 individuals had a GA between 24 and 32 weeks with ROP but without treatment (group 5), and four individuals had a GA between 24 and 32 weeks with postnatal treatment for ROP (group 6) (Table 1).

Among the male participants, 59 individuals had a GA of 37 weeks or more (group 1), 54 individuals had a GA between 33 and 36 weeks without ROP (group 2), 41 individuals had a GA between 29 and 32 weeks without ROP (group 3), 10 individuals had a GA of 28 weeks or less without ROP (group 4), 20 individuals had a GA between 24 and 32 weeks with ROP but without treatment (group 5), and nine individuals had a GA between 24 and 32 weeks with postnatal treatment for ROP (group 6) (Table 1). The recruitment efficacy for each group is displayed in Supplementary Figure S1.

Descriptive Ocular Geometric Parameters of Female and Male Participants

A reduced anterior chamber depth and an increased lens thickness were noted in the ROP-treated group for both females and males. However, men showed longer or larger biometric features, including a deeper anterior chamber depth ($P = 0.01$), a bigger posterior segment ($P = 0.02$), a thicker central corneal thickness ($P = 0.009$), and a thicker central foveal thickness ($P = 0.02$) (Table 2).

Univariable and Multivariable Analyses

The univariable analysis showed a positive association between GA and BW percentile with mean corneal radius, whereas GA was negatively associated with central foveal thickness in female participants. The anterior chamber depth and lens thickness were not associated with GA or BW percentile (Table 3). Additionally, GA was positively associated with the posterior segment, whereas BW percentile was associated with central corneal thickness. Similar significant associations were observed in male participants, except that associations between GA and the posterior segment and between BW percentile and central corneal thickness were not evident.

In the multivariable model, both female and male participants had a larger mean corneal radius with higher GA, as well as a higher BW percentile. The posterior segment was

TABLE 2. Ocular Geometric Parameters of the GPES Sample (n = 438) for Each Study Group Presented for Right Eyes and Female and Male Participants Separately

	Female Participants							Male Participants							
	Group							Group							
Parameter	1 (GA ≥ 37)	2 (GA 33–36)	3 (GA 29–32)	4 (GA ≤ 28)	5 (GA < 32) ROP Without Treatment	6 (GA < 32) ROP With Treatment	*P*	1 (GA ≥ 37)	2 GA (33–36)	3 GA (29–32)	4 (GA ≤ 28)	5 (GA < 32) ROP Without Treatment	6 (GA < 32) ROP With Treatment	*P*	Comparison by Sex, *P*
Participants/eyes, *n*	81/162	80/159	47/94	10/18	23/44	4/7		59/118	54/108	41/81	10/18	20/36	9/16		
Central corneal thickness (µm), mean ± SD	545. 69 ± 38.13	538.41 ± 30.45	537.19 ± 39.02	560.11 ± 41.93	550.50 ± 42.67	554.50 ± 25.21	0.29	557.12 ± 33.29	544.24 ± 31.03	549.20 ± 40.47	547.22 ± 46.52	555.00 ± 44.72	567.56 ± 48.60	0.31	0.009
Corneal radius (mm), mean ± SD	7.89 ± 0.33	7.71 ± 0.27	7.69 ± 0.33	7.71 = 0.21	7.55 ± 0.31	7.83 ± 0.15	<0.001	7.89 ± 0.26	7.87 ± 0.27	7.73 ± 0.28	7.76 ± 0.19	7.73 ± 0.31	7.58 ± 0.27	0.003	0.02
Anterior chamber depth (mm), mean ± SD	2.88 ± 0.34	2.96 ± 0.31	3.01 ± 0.32	2.88 = 0.35	2.93 ± 0.53	2.59 ± 0.31	0.21	3.01 ± 0.30	3.08 ± 0.32	3.08 ± 0.27	2.88 ± 0.28	3.08 ± 0.27	2.28 ± 0.78	<0.001	0.01
Lens thickness (mm), mean ± SD	3.78 ± 0.32	3.78 ± 0.34	3.78 ± 0.27	3.85 =0.21	3.58 ± 0.22	4.16 ± 0.44	0.03	3.77 ± 0.35	3.79 ± 0.32	3.72 ± 0.27	3.66 ± 0.25	3.65 ± 0.30	4.61 ± 0.42	<0.001	0.90
Posterior segment length (mm), mean ± SD	16.97 ± 1.16	16.64 ± 1.11	16.65 ± 0.94	16.15 = 0.72	16.23 ± 0.71	16.40 ± 1.10	0.02	17.14 ± 1.08	17.02 ± 0.97	16.48 ± 1.20	16.66 ± 0.88	17.23 ± 1.25	16.42 ± 2.50	0.05	0.02
Foveal retinal thickness (µm), mean ± SD	223.26 ± 16.14	237.16 ± 21.02	247.98 ± 30.16	263.75 = 59.45	251.81 ± 40.07	276.00 ± 27.73	<0.001	223.78 ± 17.79	240.70 ± 19.17	252.64 ± 23.83	274.88 ± 30.04	275.07 ± 29.79	314.00 ± 42.75	<0.001	0.02

Table 3. Linear Associations of Ocular Biometric Parameters With GA and BW Percentile ($n = 438$)

	Female Participants				Male Participants			
	Univariable Model		Multivariable Model		Univariable Model		Multivariable Model	
Parameter	***B*** **(95% CI)**	***P***	***B*** **(95% CI)**	***P***	***B*** **(95% CI)**	***P***	***B*** **(95% CI)**	***P***
Central corneal thickness (µm)								
GA (wk)	−0.021 (−1.1 to 1.05)	0.97	−0.033 (−1.090 to 1.024)	0.95	0.236 (−0.932 to 1.4)	0.69	0.042 (−1.171 to 1.255)	0.95
BW percentile	0.181 (0.006 to 0.356)	0.04	0.181 (0.007 to 0.356)	0.04	0.137 (−0.057 to 0.331)	0.17	0.135 (−0.065 to 0.336)	0.19
Mean corneal radius (mm)								
GA (wk)	0.019 (0.011 to 0.028)	<0.001	0.019 (0.011 to 0.027)	<0.001	0.016 (0.008 to 0.024)	<0.001	0.019 (0.011 to 0.005)	<0.001
BW percentile	0.003 (0.002 to 0.005)	<0.001	0.003 (0.002 to 0.005)	<0.001	0.003 (0.002 to 0.005)	<0.001	0.003 (0.002 to 0.005)	<0.001
Anterior chamber depth (mm)								
GA (wk)	0.005 (−0.01 to 0.011)	0.92	0.001 (−0.010 to 0.011)	0.92	0.004 (−0.008 to 0.015)	0.52	0.003 (−0.009 to 0.014)	0.65
BW percentile	−0.000 (−0.002 to 0.002)	0.74	−0.000 (−0.002 to 0.002)	0.74	0.000 (−0.002 to 0.002)	0.74	0.001 (−0.001 to 0.003)	0.40
Lens thickness (mm)								
GA (wk)	0.003 (−0.005 to 0.012)	0.43	0.003 (−0.005 to 0.012)	0.43	0.001 (−0.010 to 0.013)	0.8	0.002 (−0.009 to 0.013)	0.72
BW percentile	0.000 (−0.002 to 0.002)	0.99	−0.000 (−0.002 to 0.002)	0.98	−0.000 (−0.002 to 0.001)	0.68	−0.000 (−0.002 to 0.001)	0.63
Posterior segment length (mm)								
GA (wk)	0.051 (0.021 to 0.084)	0.001	0.050 (0.021 to 0.080)	0.001	0.026 (−0.013 to 0.066)	0.19	0.020 (−0.018 to 0.058)	0.31
BW percentile	0.003 (−0.002 to 0.008)	0.29	0.002 (−0.003 to 0.007)	0.34	0.006 (0.0 to 0.012)	0.06	0.005 (−0.001 to 0.011)	0.09
Central foveal thickness (µm)								
GA (wk)	−2.986 (−3.86 to −2.11)	<0.001	−2.987 (−3.859 to −2.115)	<0.001	−4.267 (−5.1 to −3.431)	<0.001	−4.271 (−5.166 to −3.383)	<0.001
BW percentile	−0.067 (−0.201 to 0.068)	0.33	−0.067 (−0.183 to −0.049)	0.25	−0.143 (−0.295 to 0.009)	0.065	0.004 (−0.128 to 0.127)	0.95

This is a sex-based analysis from the GPES.

Table 4. Linear Associations of Ocular Geometric Parameters With GA and BW Percentile ($n = 438$)

	Multivariable Model	
	***B* (95% CI)**	***P***
Central corneal thickness (µm)		
GA (wk)	0.037 (−1.176 to 1.251)	0.95
GA × sex	−0.069 (−1.679 to 1.540)	0.93
BW percentile	0.136 (−0.065 to 0.336)	0.18
BW percentile × sex	0.046 (−0.220 to 0.311)	0.74
Mean corneal radius (mm)		
GA (wk)	0.012 (0.004 to 0.020)	0.002
GA × sex	0.007 (−0.004 to 0.018)	0.22
BW percentile	0.003 (0.001 to 0.004)	0.001
BW percentile × sex	0.000 (−0.001 to 0.003)	0.56
Anterior chamber depth (mm)		
GA (wk)	0.003 (−0.009 to 0.015)	0.64
GA × sex	−0.002 (−0.018 to 0.013)	0.77
BW percentile	0.001 (−0.001 to 0.003)	0.40
BW percentile × sex	−0.001 (−0.004 to 0.002)	0.41
Lens thickness (mm)		
GA (wk)	0.002 (−0.009 to 0.013)	0.73
GA × sex	0.001 (−0.013 to 0.016)	0.84
BW percentile	−0.000 (−0.002 to 0.001)	0.62
BW percentile × sex	0.004 (−0.002 to 0.003)	0.74
Posterior segment length (mm)		
GA (wk)	0.020 (−0.019 to 0.058)	0.31
GA × sex	0.031 (−0.018 to 0.079)	0.22
BW percentile	0.005 (−0.001 to 0.011)	0.09
BW percentile × sex	−0.003 (−0.010 to 0.005)	0.52
Central foveal thickness (µm)		
GA (wk)	−4.275 (−5.166 to −3.384)	<0.001
GA × sex	1.288 (0.041 to 2.535)	0.04
BW percentile	0.004 (−0.120 to 0.128)	0.95
BW percentile × sex	−0.072 (−0.241 to 0.098)	0.40

This is a sex-based analysis from the GPES with incorporation of effect modification for sex. Adjustments were made for the effect of sex in each analysis (males were used as the reference group).

positively associated with GA only in female participants. Central foveal thickness was negatively associated with GA in female participants and male participants.

Multivariable Analyses With Effect Modification for Sex

The central foveal thickness was thinner with a higher GA in the multivariable model (Table 4). The displayed figure shows the raw data of central foveal thickness by gestational age for males and females (Fig.). Our further effect modification analysis reveals that at lower gestational age, males show a thicker central foveal thickness compared to females ($P = 0.04$). The sensitivity analysis incorporating age in the multivariable model yielded consistent results regarding the association between the effect modification of sex and GA and central foveal thickness ($B = 1.347$; 95% confidence interval [CI], 0.114–2.580; $P = 0.03$). This consistency was also observed in a multivariable model that additionally considered the presence of ROP and ROP treatment ($B = 1.194$; 95% CI, 0.015–2.373; $P = 0.05$). When foveal hypoplasia as an adjustment variable was included in the multivariable model, there was still a significant association of the effect modification between GA × sex and central foveal thickness ($B = 1.026$; 95% CI, 0.006–2.046; $P = 0.05$).

Discussion

The present analysis provides new data on the long-term effects of GA and BW on ocular geometry in adults, with a primary emphasis on existing sex-specific differences. To our knowledge, this is the first study examining sex-specific differences in ocular biometry in individuals born preterm. The findings from our descriptive analysis highlight several notable differences in biometric measurements between male and female participants, with males generally having larger measurements, including a deeper anterior chamber depth, larger posterior segment, and thicker central foveal thickness. A prior investigation of the GPES showed that corneal morphology is influenced by GA and BW percentile.[19] In addition to these findings, we now demonstrate how the associations between male and female participants differ.

The multivariable regression analyses of both female and male participants revealed a larger mean corneal radius with higher GA and BW percentile. The posterior segment was positively associated with GA, but this was only observed in female participants. Furthermore, the

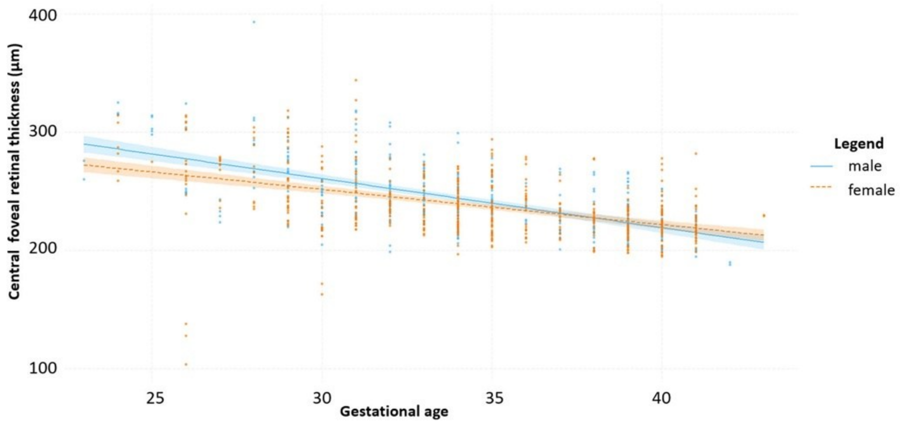

Figure. Relationship between gestational age and central foveal thickness by sex.

central corneal thickness was linked to the BW percentile exclusively in female participants. Central foveal thickness showed a negative association with GA in female and male participants.

The multivariable regression analyses with effect modification for sex on GA revealed a significant association with central foveal thickness ($B = 1.288$; $P = 0.04$) that was further supported by additional sensitivity analyses. Sex-specific differences related to prematurity were identified in other medical specialties, with higher mortality and morbidity among male preterm infants.[28] The reasons for this may include the higher risk of metabolic and neurological complications in males.[29] Furthermore, male preterm infants have a higher risk of developing ROP, intraventricular hemorrhage, and respiratory distress syndrome.[10,12,30] These fundamental sex differences highlight the relevance of exploring additional aspects related to prematurity when sex variations may exist for a comprehensive evaluation of potential long-term consequences.

As there are no studies examining sex-specific differences in the eye biometry of preterm infants, we could not directly compare our results with matching studies; however, studies in adults showed comparable results related to generally larger biometric parameters in men.[4,5] These biometric differences can be partly attributed to the distinct stature of women and men. When adjusting for these parameters (e.g., body height), sex-specific differences were no longer present.[31] In contrast, one study adjusted for body height and the existing biometric sex differences remained, including longer axial length and larger vitreous chamber depth, as well as deeper anterior chamber depth in men.[4]

The association between corneal curvature and GA or BW percentile was present in both sexes. For posterior segment length, however, a relationship was solely observed for GA in female participants. An association between central corneal thickness and BW percentile was only observed in female participants, possibly due to the lower number of male participants.

In our descriptive analysis, we observed that, irrespective of gestational age, men generally show a thicker central foveal thickness compared to women. Wagner-Schuman et al. also showed a thicker central foveal thickness in men compared to women.[32] This sex differences could be due to females possibly possessing a stronger centrifugal force at the macula, which could account for this phenomenon.[33] Another observation was the relationship between GA and central foveal thickness, with a significant effect modification for sex, demonstrating that males have a thicker central foveal thickness at lower GA compared to females. Other studies have also shown a relationship between central foveal thickness and GA, with thinner central foveal thickness with higher GA.[26,34,35] The reason for this could be that there is a disturbed inner retinal layer migration to the periphery after preterm delivery in preterm infants, resulting in a thicker central foveal thickness in preterm infants.[36,37] Our results suggest that the effects of GA on central foveal thickness differ between women and men. A potential association could indicate fundamental differences in the development of central foveal thickness between the sexes in individuals born preterm. Furthermore, male individuals have an increased risk for severe retinopathy of prematurity,[38,39] which is in line with our findings that retinal foveal morphology may be more vulnerable to prematurity in males. However, some studies do not indicate a connection between retinal thickness and an influence on visual acuity,[37,40] in contrast with other studies that do,[26,34] and this sex-specific difference indicates that the risk for lower visual acuity may be higher in males.

Strengths and Limitations

This study is subject to several limitations. First, it is important to note that this was a single-center, hospital-based cohort study. We also encountered challenges in contacting several former newborns, and some participants opted not to take part in the study. Another limitation to consider is the relatively small number of participants with ROP and treated for ROP, which should be taken into account when interpreting our findings. Additionally, a limitation relates to the absence of lateral scaling in the OCT images, which could affect the accuracy of ocular geometry measurements. Despite these limitations, our study is the most extensive examination of adults born preterm at varying GAs. A comprehensive assessment of perinatal medical histories was meticulously conducted through the review of medical records, enabling us to analyze potential perinatal factors that may have influenced ocular geometry development. Furthermore, all measurements adhered to stringent standardized operating procedures to mitigate interrater variability stemming from individual examiners. To maintain objectivity, our investigators remained blinded to the participants' birth-related characteristics throughout the study.

Conclusions

In conclusion, our results demonstrate that biometric parameters differ between the sexes, with larger biometric parameters in male participants. The known associations with GA, however, are not influenced by sex, except for a hint of an association with central foveal thickness, indicating disparities in the developmental trajectory of the macula in relation to GA. A thicker central foveal thickness could affect the visual acuity of individuals born preterm in adulthood, with a more pronounced influence in male individuals.

Acknowledgments

Supported by the Ernst- und Berta-Grimmke Stiftung (Gutenberg Prematurity Eye Study), Stufe 1 support of the University Medical Center Mainz, and the Else Kröner-Fresenius-Stiftung. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure: **A. Fieß**, None; **A. Hartmann**, None; **E. Mildenberger**, None; **M.S. Urschitz**, None; **P. Laspas**, None; **A. Schultheis**, None; **B. Stoffelns**, None; **N. Pfeiffer**, Alcon (F), Boehringer Ingelheim Deutschland (F), Ivantis (F), Novartis (F), Sanoculis (F), Santen (F), Thea (F); **S. Gißler**, None; **A.K. Schuster**, Abbvie (F), Apellis (F), Bayer (F), Heidelberg Engineering (F), Novartis (F), PlusOptix (F)

References

1. Fieß A, Gißler S, Mildenberger E, et al. Optic nerve head morphology in adults born extreme, very and moderate preterm with and without retinopathy of prematurity: results from the Gutenberg Prematurity Eye Study. *Am J Ophthalmol.* 2022;239:212–222.
2. Xie X, Wang Y, Zhao R, et al. Refractive status and optical components in premature infants with and without

retinopathy of prematurity: a 4- to 5-year cohort study. *Front Pediatr.* 2022;10:922303.

3. Mora JS, Waite C, Gilbert CE, Breidenstein B, Sloper JJ. A worldwide survey of retinopathy of prematurity screening. *Br J Ophthalmol.* 2018;102:9–13.
4. Shufelt C, Fraser-Bell S, Ying-Lai M, Torres M, Varma R. Refractive error, ocular biometry, and lens opalescence in an adult population: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci.* 2005;46:4450–4460.
5. Wong TY, Foster PJ, Ng TP, Tielsch JM, Johnson GJ, Seah SK. Variations in ocular biometry in an adult Chinese population in Singapore: the Tanjong Pagar Survey. *Invest Ophthalmol Vis Sci.* 2001;42:73–80.
6. Rosenfeld CS. Sex-specific placental responses in fetal development. *Endocrinology.* 2015;156:3422–3434.
7. Lampl M, Gotsch F, Kusanovic JP, et al. Sex differences in fetal growth responses to maternal height and weight. *Am J Hum Biol.* 2010;22:431–443.
8. Rosenkrantz TS, Hussain Z, Fitch RH. Sex differences in brain injury and repair in newborn infants: clinical evidence and biological mechanisms. *Front Pediatr.* 2019;7:211.
9. Shim S-Y, Cho SJ, Kong KA, Park EA. Gestational age-specific sex difference in mortality and morbidities of preterm infants: a nationwide study. *Sci Rep.* 2017;7:6161.
10. Tioseco JA, Aly H, Essers J, Patel K, El-Mohandes AA. Male sex and intraventricular hemorrhage. *Pediatr Crit Care Med.* 2006;7:40–44.
11. Kent AL, Wright IM, Abdel-Latif ME. Mortality and adverse neurologic outcomes are greater in preterm male infants. *Pediatrics.* 2012;129:124–131.
12. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics.* 2005;115:990–996.
13. Nødgaard H, Andreasen H, Hansen H, Sørensen HT. Risk factors associated with retinopathy of prematurity (ROP) in northern Jutland, Denmark 1990–1993. *Acta Ophthalmol Scand.* 1996;74:306–310.
14. Stålnacke SR, Tessma M, Böhm B, Herlenius E. Cognitive development trajectories in preterm children with very low birth weight longitudinally followed until 11 years of age. *Front Physiol.* 2019;10:307.
15. Linsell L, Johnson S, Wolke D, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. *Arch Dis Child.* 2018;103:363–370.
16. Peacock JL, Marston L, Marlow N, Calvert SA, Greenough A. Neonatal and infant outcome in boys and girls born very prematurely. *Pediatr Res.* 2012;71:305–310.
17. Kolačko Š, Predović J, Kokot A, et al. Do gender, age, body mass and height influence eye biometrical properties in young adults? A pilot study. *Int J Environ Res Public Health.* 2021;18:11719.
18. Zhang H, Zhou J, Yang L, et al. Sex differences in ocular biometric measurements: a twin study. *Front Med.* 2022;9:936738.
19. Fieß A, Nauen H, Mildenberger E, et al. Ocular geometry in adults born extremely, very and moderately preterm with and without retinopathy of prematurity: results from the Gutenberg Prematurity Eye Study. *Br J Ophthalmol.* 2022;107:1125–1131.
20. Sun C, Ponsonby AL, Brown SA, et al. Associations of birth weight with ocular biometry, refraction, and glaucomatous endophenotypes: the Australian Twins Eye Study. *Am J Ophthalmol.* 2010;150:909–916.
21. Ojaimi E, Robaei D, Rochtchina E, Rose KA, Morgan IG, Mitchell P. Impact of birth parameters on eye size in a population-based study of 6-year-old Australian children. *Am J Ophthalmol.* 2005;140:535–537.
22. Ecsedy M, Kovacs I, Mihaltz K, et al. Scheimpflug imaging for long-term evaluation of optical components in Hungarian children with a history of preterm birth. *J Pediatr Ophthalmol Strabismus.* 2014;51:235–241.
23. Fieß A, Gißler S, Mildenberger E, et al. Anterior chamber angle in adults born extremely, very, and moderately preterm with and without retinopathy of prematurity—results of the Gutenberg Prematurity Eye Study. *Children (Basel).* 2022;9:281.
24. Fieß A, Hufschmidt-Merizian C, Gißler S, et al. Dry eye parameters and lid geometry in adults born extremely, very, and moderately preterm with and without ROP: results from the Gutenberg Prematurity Eye Study. *J Clin Med.* 2022;11:2702.
25. Voigt M, Fusch C, Olbertz D. Analyse des Neugeborenenkollektivs der Bundesrepublik Deutschland 12. Mitteilung: Vorstellung engmaschiger Perzentilwerte (-kurven) für die Körpermaße Neugeborener. *Geburtsh Frauenheilk.* 2006;66:956–970.
26. Fieß A, Pfisterer A, Gißler S, et al. Retinal thickness and foveal hypoplasia in adults born preterm with and without retinopathy of prematurity – The Gutenberg Prematurity Eye Study. *Retina.* 2022;42:1716–1728.
27. Fieß A, Brandt M, Mildenberger E, et al. Adults born small for gestational age at term have thinner peripapillary retinal nerve fiber layers than controls. *Eye Brain.* 2022;14:127–135.
28. Aghai ZH, Goudar SS, Patel A, et al. Gender variations in neonatal and early infant mortality in India and Pakistan: a secondary analysis from the Global Network Maternal Newborn Health Registry. *Reprod Health.* 2020;17:178.
29. Simchen MJ, Weisz B, Zilberberg E, et al. Male disadvantage for neonatal complications of term infants, especially in small-for-gestational age neonates. *J Matern Fetal Neonatal Med.* 2014;27:839–843.
30. Stevenson DK, Verter J, Fanaroff AA, et al. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. *Arch Dis Child Fetal Neonatal Ed.* 2000;83:F182–F185.
31. Wickremasinghe S, Foster PJ, Uranchimeg D, et al. Ocular biometry and refraction in Mongolian adults. *Invest Ophthalmol Vis Sci.* 2004;45:776–783.
32. Wagner-Schuman M, Dubis AM, Nordgren RN, et al. Race- and sex-related differences in retinal thickness and foveal pit morphology. *Invest Ophthalmol Vis Sci.* 2011;52:625–634.
33. Liu YT, Ma IH, Hsieh YT. Gender- and age-related differences in foveal pit morphology. *Indian J Ophthalmol.* 2024;72:S37–S41.
34. Stoica F, Chirita-Emandi A, Andreescu N, Stanciu A, Zimbru CG, Puiu M. Clinical relevance of retinal structure in children with laser-treated retinopathy of prematurity versus controls—using optical coherence tomography. *Acta Ophthalmol.* 2018;96:e222–e228.
35. O'Sullivan ML, Ying GS, Mangalesh S, et al. Foveal differentiation and inner retinal displacement are arrested in extremely premature infants. *Invest Ophthalmol Vis Sci.* 2021;62:25.
36. Park K-A, Oh SY. Analysis of spectral-domain optical coherence tomography in preterm children: retinal layer thickness and choroidal thickness profiles. *Invest Ophthalmol Vis Sci.* 2012;53:7201–7207.
37. Fieß A, Wagner FM, Urschitz MS, et al. Association of birth weight with foveolar thickness in adulthood: results from a population-based study. *Invest Ophthalmol Vis Sci.* 2021;62:9.
38. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-

control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology*. 2000;107:2224–2232.
39. Fieß A, Elbaz H, Korb CA, et al. Low birth weight is linked to age-related macular degeneration: results from the population-based Gutenberg Health Study (GHS). *Invest Ophthalmol Vis Sci*. 2019;60:4943–4950.
40. Nishi T, Ueda T, Mizusawa Y, et al. Effect of foveal morphology on visual acuity in 4–6-year-old children with retinopathy of prematurity: a J-CREST study. *Sci Rep*. 2022;12:16431.

4.3 Publikation III

Hartmann A, Scholz I, Hoffmann EM, Strzalkowska A, Lackner KJ, Münzel T, Wicke F, Schmidtmann I, Tüscher O, Schattenberg JM, Konstantinides S, Wild PS, Pfeiffer N, Schuster AK. Change of intraocular pressure over 5 years and its relationship to cardiovascular parameters – results from the Gutenberg Health Study. Investigative Ophthalmology & Visual Science (2024): https://doi.org/10.1167/iovs.65.1.12

Investigative Ophthalmology & Visual Science

Clinical and Epidemiologic Research

Change of Intraocular Pressure Over 5 Years and its Relationship to Cardiovascular Parameters: Results From the Gutenberg Health Study

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Received: May 15, 2023
Accepted: November 12, 2023
Published: January 4, 2024

Citation: Hartmann A, Scholz I, Hoffmann EM, et al. Change of intraocular pressure over 5 years and its relationship to cardiovascular parameters: Results from the Gutenberg Health Study. *Invest Ophthalmol Vis Sci.* 2024;65(1):12. https://doi.org/10.1167/iovs.65.1.12

Purpose. To investigate the longitudinal change in intraocular pressure (IOP) over 5 years and its relationship with cardiovascular parameters in a population-based sample in Germany.

Methods. The Gutenberg Health Study is a prospective, observational, single-center cohort study. The sample was equally stratified for sex, residence, and age decade. IOP was measured with noncontact tonometry at baseline and at 5-year follow-up. Cardiovascular parameters, including body mass index (BMI), systolic blood pressure, and diabetes status, were assessed. Participants without IOP measurement at one time point, who were taking IOP-lowering medications, or who had ophthalmic surgery during the 5-year follow-up interval were excluded, as well as those with glaucoma diagnosis. Univariable and multivariable linear regression analyses were conducted.

Results. This analysis included 9633 participants (48.9% female). The mean IOP increased from 14.04 ± 2.78 mmHg at baseline to 14.77 ± 2.92 mmHg at 5-year follow-up ($P < 0.001$). In multivariable linear regression analyses, an increase in BMI was associated with an increase in IOP over time ($P < 0.001$), whereas a higher baseline BMI was associated with a lower IOP change ($P < 0.001$). Higher age and male sex were associated with higher IOP change ($P < 0.001$). A change in systolic blood pressure was associated with IOP change, whereas baseline systolic blood pressure and diabetes status were not associated.

Conclusions. This population-based study found a relationship between IOP change over 5 years and BMI and systolic blood pressure change, respectively. These findings suggest the importance of monitoring cardiovascular risk factors in IOP management.

Keywords: intraocular pressure, blood pressure, body mass index, diabetes, epidemiology

Elevated intraocular pressure (IOP) is the leading and only therapeutically modifiable risk factor for the development and progression of glaucoma.[1,2] Cross-sectional studies have shown that cardiovascular parameters are further risk factors for open-angle glaucoma (OAG).[3,4] OAG diagnosis is associated with a lower body mass index (BMI),[5]

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arterial hypertension,[6] and diabetes mellitus.[7] Similarly, IOP is associated with BMI, arterial hypertension, and diabetes.[8] In addition, IOP is also associated with waist-to-hip ratio,[9] but this has not been shown previously in OAG.[10] A positive association between BMI and IOP has been demonstrated in several cross-sectional studies[11] but is considered to be of minor importance clinically.[8] Baisakhiya et al.[9] demonstrated a correlation between higher IOP and waist-to-hip ratio, BMI, and obesity. The authors hypothesized that the association between obesity and increased IOP is caused by fat accumulation in the periorbital space, which leads to increased episcleral venous pressure.

Arterial hypertension is also positively associated with glaucoma.[12] The positive association between elevated blood pressure and IOP has been shown in multiple cross-section studies.[13,14] It is well known that glaucoma prevalence is higher in subjects with diabetes.[15] Whether there is an association between higher IOP and diabetes has been investigated in cross-sectional studies.[16]

The literature about differences in IOP between women and men is inconsistent. Some studies have demonstrated a higher IOP in women,[17] whereas other studies have found a significantly higher IOP in men[18] or no sex-related difference in IOP at all.[19]

Concerning aging, a relationship between older age and higher IOP[14] has been reported in some studies. In contrast, others have shown no association with age[20] or even a negative relationship between IOP and age.[21]

Longitudinal studies on IOP are rare but allow us to investigate IOP change over time with regard to age, sex, and changes in cardiovascular risk factors. Han et al.[22] reported longitudinal changes in IOP in a Chinese study cohort over 4 years (2010–2014). The average change in IOP was an increase of 0.43 mmHg, positively correlated with older age. Study participants with increased blood pressure or BMI had IOP elevation over time.

The Gutenberg Health Study (GHS) offers the opportunity to gain insights into the change of IOP and its relationship with cardiovascular parameters over time in a large and population-based European cohort. With one of the largest samples in which IOP is observed over time, it allows confirmation of previously reported cross-sectional findings in a longitudinal population-based study design.

Methods

Study Sample

The GHS is a population-based, prospective, observational, single-center cohort study in the Rhine-Main Region in Germany. The sample was equally stratified for sex, residence (urban or rural), and age decade. At baseline, 15,010 individuals were included (2007–2012), and 12,423 were re-examined after 5 years (2012–2017). Participants without IOP measurement at one time point, who were taking IOP-lowering medications, or who had ophthalmic surgery during the 5-year follow-up interval were excluded, as well as those with glaucoma diagnosis.

Ophthalmic Parameters

During the initial examination, eye examinations were performed by medical staff. From the first follow-up at the study center, qualified study personnel took over this task. At both times, IOP was measured with noncontact tonometry and automatic air-puff control (NT 2000; Nidek Co., Tokyo, Japan). The mean of three measurements within a 3-mmHg range was obtained for each eye.[23] Most study participants were examined at a similar time at baseline and 5-year follow-up. In 98% of study participants, the time at follow-up examination did not differ by more than 2 hours from the time at the baseline examination. The time of year was also primarily consistent with baseline.

Cardiovascular Parameters

Characteristics of the study population included age, sex, body height, and body weight. Anthropometric measurements were performed using calibrated digital scales (Seca 862; Seca, Hamburg, Germany), a Seca measuring stick, and a waist-measuring tape.[8] Diabetes mellitus was defined as an established physician diagnosis using antidiabetics or HbA1c $\geq$ 6.5%. Arterial hypertension was defined as the use of antihypertensive medication, a systolic blood pressure >140 mmHg (HEM-705CP *II*; Omron, Mannheim, Germany[24]), diastolic blood pressure > 90 mmHg, or an established medical diagnosis. Further information, such as HbA1c level, was determined by using standardized measurement procedures.

Inclusion and Exclusion Criteria

For the selection of study participants, those without IOP measurement at one time point, who were taking IOP-lowering medications, or who had ophthalmic surgery during the 5-year follow-up interval were excluded (Supplementary Fig. S1).

Statistical Analysis

Descriptive analysis was conducted for primary and secondary variables. For categorical parameters, absolute and relative frequencies were computed. For continuous variables, means and standard deviations were calculated for approximately normally distributed data; otherwise, median and interquartile range were calculated. IOP change was computed as the difference between the 5-year follow-up and baseline measurements for the identical eye. Pearson correlation analysis was conducted for the right eyes to analyze the association of IOP change and cardiovascular parameters. Multivariable linear regression analyses were conducted with generalized estimating equations on a person level to account for two eyes of one subject. First, univariable association analysis was computed adjusted for age and sex. Second, the cardiovascular factors were included in one multivariable model. If the baseline value and the 5-year change of a cardiovascular factor were significant, an additional model with an interaction term was planned to be included. Data were processed with R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 9633 study participants were included. The mean age of the study population was 53.3 $\pm$ 10.5 years, and 48.9% were female. Table 1 shows the participants' characteristics at baseline; Supplementary Figure S1 shows the item non-responder analysis. The mean baseline IOPs in the right eye were 13.96 $\pm$ 2.96 mmHg in women and

Table 1. Participants' Characteristics (*N* = 9633, Baseline Examination) and Cardiovascular Parameters in the Gutenberg Health Study

	Overall	Men	Women
Anthropometric data (baseline)			
Participants, *n*	9633	4921	4712
Age (y), mean ± SD	53.30 ± 10.5	53.58 ± 10.6	53.02 ± 10.4
Age categories (y), mean ± SD			
35–44	2378 ± 24.7	1.169 ± 23.8	1.209 ± 25.7
45–54	2891 ± 30.0	1.471 ± 29.9	1.420 ± 30.1
55–64	2610 ± 27.1	1.326 ± 26.9	1.284 ± 27.2
65–74	1754 ± 18.2	955 ± 19.4	799 ± 17.0
Body weight (kg), mean ± SD	79.34 ± 16.2	87.1 ± 14.0	71.3 ± 14.4
Body height (cm), mean ± SD	171 ± 9.5	177.5 ± 6.9	164.2 ± 6.6
Cardiovascular parameters			
Arterial hypertension, *n* (%)	4412 (45.8)	2516 (51.1)	1896 (40.2)
Diabetes, *n* (%)	675 (7)	436 (8.9)	239 (5.1)
Change in diabetes over 5 years, %			
No diabetes	88.5	87.0	92.1
Newly diagnosed diabetes	3.7	4.1	2.8
Previous diabetes	0.9	0.7	1.0
Ongoing diabetes	6.9	8.1	4.1
HbA1c level, mean ± SD	5.51 ± 0.63	5.55 ± 0.66	5.47 ± 0.59
Systolic blood pressure (mmHg) , mean ± SD	130.16 ± 16.85	133.0 ± 15.6	127.2 ± 17.6
Diastolic blood pressure (mmHg) , mean ± SD	82.31 ± 9.27	83.84 ± 9.15	80.7 ± 9.13
Mean arterial pressure (mmHg), mean ± SD	98.26 ± 10.92	100.23 ± 10.37	96.19 ± 11.09
BMI (kg/m^2), mean ± SD	27.06 ± 4.78	27.6 ± 4.1	26.5 ± 5.3
Waist-to-hip ratio, mean ± SD	0.92 ± 0.09	0.98 ± 0.07	0.86 ± 0.07
Dyslipidemia, *n* (%)	3091 (32.1)	2030 (41.3)	1061 (22.5)
Smoking, *n* (%)	1803 (18.7)	973 (19.8)	830 (17.6)
Myocardial infarct, *n* (%)	197 (2.0)	154 (3.1)	830 (17.6)
Arterial fibrillation, *n* (%)	201 (2.1)	138 (2.8)	63 (1.3)
Chronic heart failure, *n* (%)	78 (0.8)	39 (0.8)	39 (0.8)
Coronary disease, *n* (%)	324 (3.4)	257 (5.2)	67 (1.4)
Peripheral disease, *n* (%)	251 (2.6)	141 (2.9)	110 (2.3)
LDL/HDL ratio, mean ± SD	2.58 ± 0.92	2.89 ± 0.92	2.25 ± 0.80
Ophthalmic parameters			
IOP (mmHg), right eye, mean ± SD	14.04 ± 2.78	14.10 ± 2.86	13.96 ± 2.69
IOP (mmHg), left eye, mean ± SD	14.19 ± 2.81	14.31 ± 2.89	14.06 ± 2.71
Central corneal thickness (μm), right eye, mean ± SD	552.04 ± 35.65	553.86 ± 35.42	550.14 ± 35.80
Central corneal thickness (μm), left eye, mean ± SD	555.64 ± 35.54	557.60 ± 35.46	553.59 ± 35.51

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Changes in Ophthalmic and Cardiovascular Parameters Over 5 Years

	Mean ± SD		
	Baseline (2007–2012)	Follow-Up (2012–2017)	Change Over 5 Years
IOP (mmHg), right eye	14.04 ± 2.78	14.77 ± 2.92	0.73 ± 2.04
IOP (mmHg), left eye	14.19 ± 2.81	14.85 ± 2.93	0.67 ± 2.04
Systolic blood pressure (mmHg)	130.16 ± 16.85	130.21 ± 16.51	0.05 ± 14.12
Diastolic blood pressure (mmHg)	82.31 ± 9.27	80.68 ± 9.31	−1.63 ± 8.30
BMI (kg/m^2)	27.06 ± 4.78	27.44 ± 4.98	0.38 ± 1.74
Waist-to-hip ratio	0.92 ± 0.09	0.92 ± 0.09	0.00 ± 0.06
HbA1c level (%)	5.51 ± 0.63	5.64 ± 0.61	0.13 ± 0.46

14.10 ± 2.86 mmHg in men; at 5-year follow-up, they were 14.65 ± 2.79 mmHg in women and 14.87 ± 3.03 mmHg in men. IOP increased in the right eye by 0.73 mmHg over 5 years.

During the 5 years, mean arterial blood pressure increased by 0.73 mmHg in women and decreased by 0.60 mmHg in men. The average BMI also increased more in women (0.49 kg/m^2) than in men (0.29 kg/m^2), whereas the increase in blood glucose levels was similar between both (0.12% and 0.13%, respectively). However, there were slightly more new diabetes diagnoses in men (4.1%) than in women (2.8%) (Tables 1, 2).

Among the excluded participants, the average age was 5 years older. There was a low frequency of participants with hypertension and slightly fewer people with diabetes. The other cardiovascular parameters showed comparable results. The IOP values were higher in the group of excluded participants (Supplementary Table S1). The mean change in IOP over 5 years (mean follow-up time, 5.04 ± 0.25 years) was 0.73 ± 2.04 mmHg in the right eye. The change in IOP was

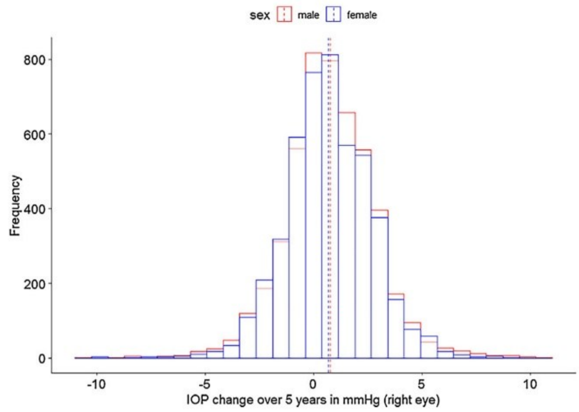

Figure 1. Distribution of IOP change over 5 years (right eye), based on the population-based Gutenberg Health Study ($N = 9590$ eyes; 2007–2017).

slightly higher in men (0.77 ± 2.11 mmHg) than in women (0.69 ± 1.96 mmHg; $P < 0.05$) (Fig. 1).

Univariable Analysis

Change in IOP was associated with age ($P < 0.001$) (Fig. 2A). Men showed a higher IOP change over 5 years than women ($P = 0.04$). IOP at baseline and IOP change over 5 years were associated; if the baseline IOP value was higher, the IOP change over 5 years tended to be lower (Fig. 2B, Table 3). The other results of univariable analysis showed an association between IOP change with several cardiovascular parameters. The strongest association was found with the 5-year changes in systolic, diastolic, and mean arterial blood pressure (Figs. 2C–2H, Table 3).

The boxplots in Figure 3 show the changes in IOP stratified for diabetes status. For newly diagnosed diabetics, the median is slightly higher than in the other groups ($P = 0.70$). Univariable analysis correlated ongoing diabetes and IOP change ($P = 0.04$). However, no further graphical evidence exists that the IOP change is higher in any group. Looking at diabetes status and the corresponding IOP change stratified by sex, we found that the median was slightly higher among women in the previously diagnosed group. In contrast, the median was highest among men in the newly diagnosed group.

Multivariable Regression Analysis

Associations between IOP change and baseline and change in cardiovascular risk factors were evaluated in multivariable linear regression analysis (Table 3). The average IOPs (baseline and follow-up) were included as a predictor variable because IOP change is connected to the IOP level. The goal was to make sure to observe correlations between IOP change and its relation to cardiovascular risk factors instead of looking at the IOP level and how it is connected to these risk factors. The results of the multivariable model were comparable to a model without IOP average as a predictor variable. Also, the regression analysis was performed including baseline IOP as predictor variable instead of IOP average; this analysis showed comparable results. Baseline BMI was negative, and changes in BMI over 5 years were positively associated with IOP changes. The baseline waist-to-hip ratio showed a positive association, but the 5-year change was not associated with IOP change. Systolic blood pressure was included in the regression model instead of diastolic blood pressure because systolic blood pressure showed a higher correlation with IOP change. This was also the case in other studies.[16] In addition, the pulse amplitude was included.

In multivariable regression analysis, a one-unit increase in BMI and a 10-mmHg increase in systolic blood pressure were associated with average increases in IOP of 0.07 mmHg and 0.02 mmHg, respectively. However, a higher baseline BMI was associated with a 0.03-mmHg lower IOP. Baseline pulse amplitude showed no significant association with IOP change over 5 years (Table 3). Per year of higher age, IOP change increased by 0.02 mmHg ($P < 0.001$). IOP change was lower in females (−0.12 mmHg; $P < 0.001$). As mean blood pressure over 5 years in the underlying cohort decreased in men but increased in women, the models for blood pressure were additionally stratified by sex. This hardly changed the effect estimates (Supplementary Table S2).

Baseline systolic blood pressure was not associated with IOP change, but a change of systolic blood pressure was positively associated with IOP change. Baseline pulse amplitude was not associated with IOP change; however, a change in pulse amplitude was. The baseline HbA1c level was not associated with IOP change, whereas the change of HbA1c level was positively associated with IOP change over 5 years.

When a stepwise backward regression analysis was performed, a correlation was observed between baseline systolic blood pressure and IOP change, in contrast to the multivariable model. The multivariable regression estimators shown previously changed little in the stepwise backward regression analysis model, and the previous shown associations remained consistent.

We analyzed the potential interaction between baseline BMI and BMI change over 5 years and did not find a statistical interaction ($P = 0.69$). Furthermore, we included baseline central corneal thickness (CCT) and change in CCT over 5 years. Between baseline and follow-up, the device for CCT measurement was changed. We first subtracted the equipment-related changes and then calculated the difference between baseline and follow-up. The results were comparable to the results obtained before. The results must nevertheless be viewed with caution due to the different measuring devices (Supplementary Table S3).

Discussion

This study investigated IOP changes with regard to age, sex, and changes in cardiovascular parameters over 5 years. Over these 5 years, IOP in the right eye increased by 0.73 mmHg. The main results of the multivariable regression analysis demonstrated that age and sex were associated with IOP change, with females having slightly lower IOP values than male participants. BMI change and change in systolic blood pressure were positively associated with IOP change, whereas baseline BMI and change in pulse amplitude were negatively associated. There was an association between change in HbA1c level with IOP change.

IOP values in this study population are similar to those of other European studies examining IOP in a large cohort.[25] The findings of this study regarding BMI and systolic blood pressure are like those of a Chinese longitudinal study on IOP change over 4 years. As participants' blood pressure and BMI increased, IOP increased.[22] Results from the Beijing Eye

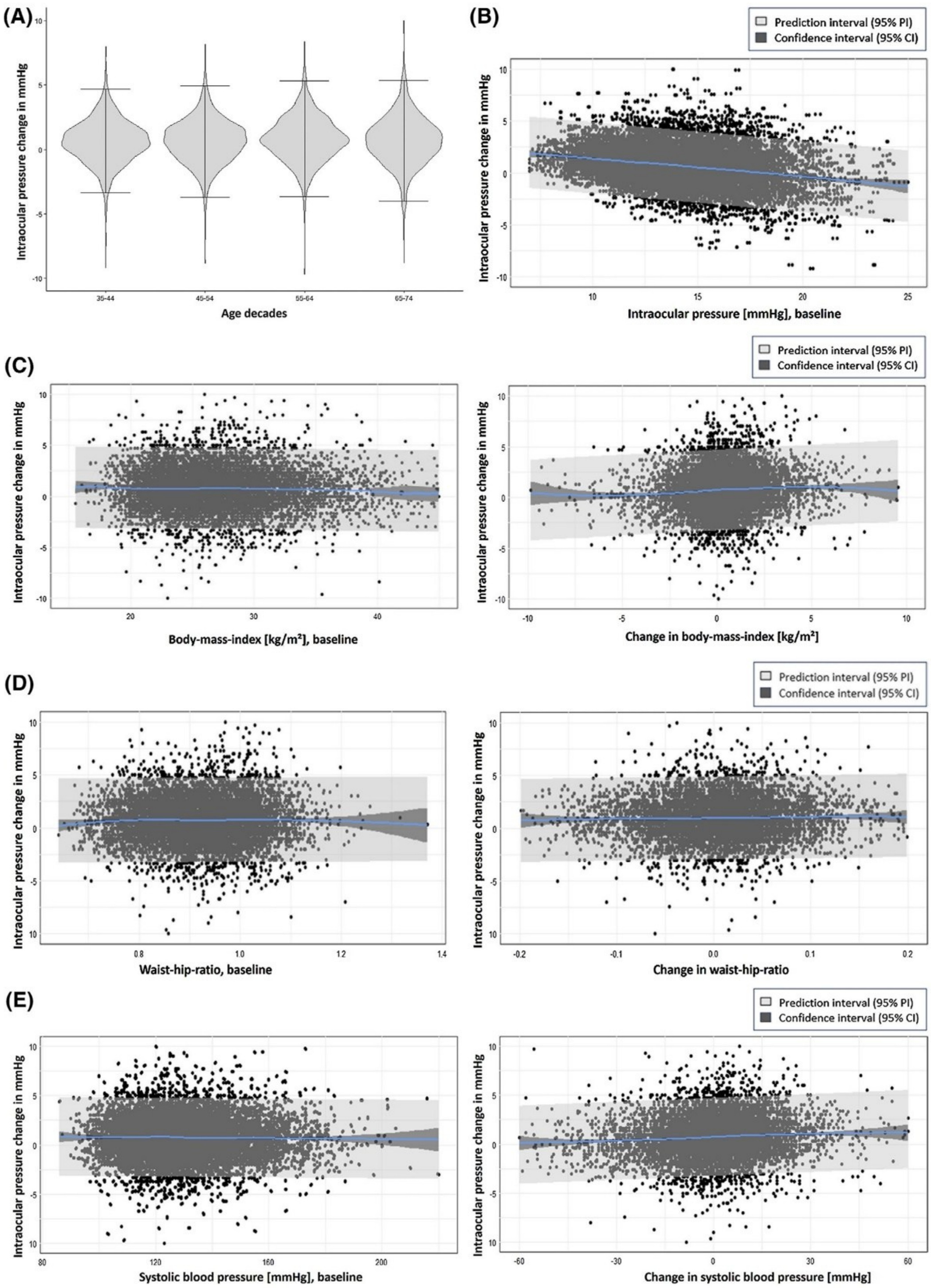

Figure 2. Association between IOP change over 5 years in the right eye and (**A**) age decades; (**B**) intraocular pressure (baseline); (**C**) BMI (baseline)/BMI change over 5 years; (**D**) waist-to-hip ratio (baseline)/waist-to-hip ratio change over 5 years; (**E**) systolic blood pressure (baseline)/systolic blood pressure change over 5 years; (**F**) diastolic blood pressure (baseline)/change of diastolic blood pressure; (**G**) pulse amplitude (baseline)/change of pulse amplitude; (**H**) percent of HbA1c level (baseline)/change of HbA1c level over 5 years. Results are based on the population-based Gutenberg Health Study ($N = 9590$ eyes; 2007–2017).

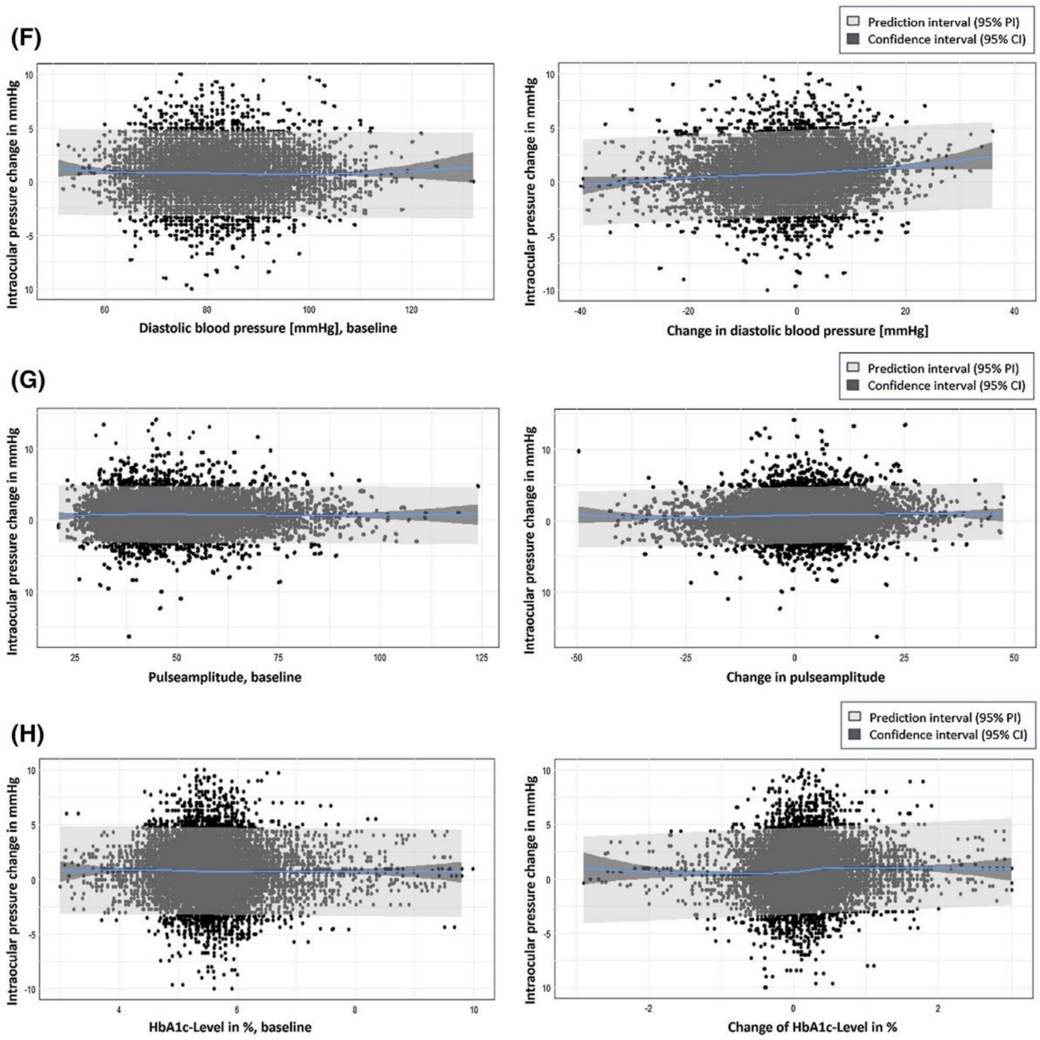

Figure 2. Continued.

study (2355 participants) support these findings, showing an association between change in IOP over 5 years and greater changes in mean blood pressure and BMI.[26]

The Beaver Dam Eye Study examined systemic blood pressure and IOP longitudinally over 5 years and found an association between changes in systemic blood pressure and IOP.[27] The underlying mechanism may be that higher systolic blood pressure increases aqueous humor production due to higher blood pressure in the ciliary artery.[28] Furthermore, the change in pulse amplitude was associated. This association additionally illustrates the influence of aqueous humor production on IOP, which is influenced by blood flow and pressure change within its arteries.[29]

Several cross-sectional studies have reported a similar relationship between BMI and IOP.[8,30] We showed that a change in BMI goes along with a subsequent increase in IOP. One hypothesis is that obesity increases oxidative stress, leading to degeneration of the trabecular meshwork and increased blood viscosity and episcleral venous pressure.[22] Furthermore, obesity can lead to endothelial and autonomic dysfunction. This can lead to altered blood flow to the eye and unstable perfusion.[31] Additionally, increased corticosteroid secretion in overweight individuals could potentially explain the association.[32]

Interestingly, baseline BMI was negatively associated with IOP change over 5 years. This may be explained by the fact that people with higher body weight have already experienced changes due to oxidative stress in the past with consecutive IOP elevation. Thus, the further elevation of IOP was less pronounced.

The baseline waist-to-hip ratio showed a univariable positive association with IOP change. This result is consistent with other cross-sectional studies.[8,9] This association could arise from the previous reasoning regarding the association between higher BMI and higher IOP, as a greater waist-to-hip ratio may also be a measure of overweight.

Cross-sectional studies have reported an association between diabetes and higher IOP.[16] The observed IOP

Table 3. Association Analysis Between Cardiovascular Risk Factors and a Change in IOP Over 5 Years

	Univariable				Multivariable			Stepwise Backwards Selection		
	B	95% CI	*P*	Pearson's Correlation (*R*)	*B*	95% CI	*P*	*B*	95% CI	*P*
Female sex, baseline	−0.05	−0.11 to 0.00	0.07	—	−0.12	−0.22 to −0.02	0.02	−0.14	−0.21 to −0.07	<0.001
Age, baseline	0.01	0.00–0.01	<0.001	0.04	0.02	0.01–0.02	<0.001	0.02	0.01–0.02	<0.001
IOP, average, baseline and follow-up	0.06	0.04–0.07	<0.001	0.08	0.09	0.08–0.11	<0.001	0.09	0.08–0.11	<0.001
BMI										
Baseline	−0.02	−0.02 to −0.01	<0.001	−0.03	−0.03	−0.04 to −0.02	<0.001	−0.02	−0.03 to −0.02	<0.001
5-year change	0.09	0.08–0.11	<0.001	0.08	0.07	0.05–0.09	<0.001	0.07	0.05-0.10	<0.001
Waist-to-hip ratio										
Baseline	1.20	0.63–1.76	<0.001	0.01	0.10	−0.59 to 0.80	0.77	—	—	—
5-year change	0.04	−0.03 to 0.11	0.26	0.03	0.53	−0.13 to 1.19	0.12	—	—	—
Systolic blood pressure (per 10 mmHg)										
Baseline	−0.00	−0.03 to 0.02	0.82	−0.02	−0.00	−0.01 to 0.00	0.20	−0.00	−0.01 to 0.00	0.002
5-year change	0.13	0.11–0.15	<0.001	0.09	0.02	0.01–0.02	<0.001	0.02	0.01–0.02	<0.001
Pulse amplitude (per 10 mmHg)										
Baseline	−0.03	−0.01 to 0.00	0.07	−0.01	−0.00	−0.01 to 0.00	0.49	—	—	—
Change	0.09	0.01–0.01	<0.001	0.06	−0.01	−0.02 to −0.01	0.00	−0.01	−0.02 to −0.01	<0.001
HbA1c										
Baseline	0.01	−0.05 to 0.08	0.72	−0.02	0.06	−0.01 to 0.12	0.10	—	—	—
Change	0.15	0.06–0.23	0.001	0.06	0.12	0.03–0.21	0.01	0.09	0.01–0.16	0.02

Data are from the German population-based Gutenberg Health Study (2007–2017; $N = 9633$ individuals). Linear regression analyses were performed using generalized estimating equation estimations. Dashed lines separating the three models. CI, confidence interval.

Figure 3. Association between IOP change in the right eye and diabetes status, based on the population-based Gutenberg Health Study ($N = 9590$; 2007–2017).

increase in cross-sectional studies might be due to elevated IOP in neovascular glaucoma, which is unlikely to occur early after the onset of diabetes. Another reason could be lower glucose control in diabetic patients, which may affect biomechanical properties of the cornea and may lead to increased IOP measures.[33] Another hypothesis suggests that autonomic dysfunction due to diabetes might increase IOP.[34,35] Evidence of an association between baseline and change in HbA1c level and IOP change was demonstrated in this study. This may be due to an increased glucose concentration in the aqueous humor. The aqueous humor flows through the trabecular meshwork and can lead to changes in its components. Evidence of an association between baseline and change in HbA1c level and IOP change was demonstrated in this study. This may be due to an increased glucose concentration in the aqueous humor. The aqueous humor flows through the trabecular meshwork and can lead to changes in its components and its biochemical properties due to the high glucose content.[36]

Higher IOP at an older age was reported to be associated with an increase in IOP in other studies investigating a similar age range.[14] We found a correlation between IOP increase and baseline age ($P < 0.001$); however, comparing IOP across various studies is difficult due to different age groups, ethnicities, and comorbidities. Older individuals tend to show more pronounced age-related ocular changes, including a decline in aqueous humor secretion and outflow facility, as well as alterations in corneal characteristics.[37,38]

Our results showed significant sex differences related to IOP and IOP change with higher values in men. Moreover, higher IOP values in men have been shown in other studies, as well[8,18]; however, some studies have shown opposite results.[17] The exact reasons for this sex difference are not well understood. A possible reason for the higher IOP values in men is that the higher testosterone levels in men may lead to higher IOP.[39] In turn, certain hormones could also lead to altered IOP in women. Fluctuations in hormone levels during the menstrual cycle in women are reported to lead to changes in IOP.[40] The larger corneal diameter in men may also lead to higher IOP measurements in men.[41]

Strengths and Limitations

This study analyzed data from a large population-based representative sample. The Gutenberg Health Study is one of the first to investigate the change in IOP and possible cardiovascular associations longitudinally over 5 years. However, our study has some limitations that must be considered. First, the included GHS subjects were mainly of Caucasian origin; therefore, the results cannot be generalized to other ethnicities. Additionally, IOP was measured only once, and we could not consider individual intra- and interday fluctuations. The GHS was able to examine most of the study participants at a similar time of day and the same season at baseline and 5-year examination. Although noncontact tonometry is commonly used to assess IOP in clinical settings, it is not entirely consistent with the Goldmann applanation tonometry, which is considered the reference standard. This difference may have influenced the results of this study.

Conclusions

This study reported a positive association between IOP change over 5 years and change in BMI and systolic blood pressure. A higher baseline BMI was associated with a lower IOP increase within 5 years. This suggests that alterations in BMI and systolic blood pressure can impact IOP over an extended period and that these cardiovascular parameters should be monitored in IOP management.

Acknowledgments

Supported by the Government of Rhineland–Palatinate (Stiftung Rheinland-Pfalz für Innovation, contract AZ 961-386261/733); by the research programs Wissen schafft Zukunft and Center for Translational Vascular Biology (CTVB) of the Johannes Gutenberg–University of Mainz and its contracts with Boehringer Ingelheim and Philips Medical Systems, including an unrestricted grant for the Gutenberg Health Study; by the Federal Ministry of Education and Research (BMBF 01EO1503; PSW); by the German Center for Cardiovascular Research (PSW and TM); and by the DIASyM research core (BMBF 161L0219; PSW)

Disclosure: **A. Hartmann**, None; **I. Scholz**, None; **E.M. Hoffmann**, Allergan (F), Carl Zeiss Meditec (F), Heidelberg Engineering (F), Novartis (F), Santen (F), Thea (F); **A. Strzalkowska**, None; **K.J. Lackner**, None; **T. Münzel**, None; **F.S. Wicke**, None; **I. Schmidtmann**, None; **O. Tüscher**, None; **J.M. Schattenberg**, Apollo Endosurgery (C), Bayer (C), Boehringer Ingelheim (C, R), Bristol Myers Squibb (C), Gilead Sciences (C, R), GSK (C), Intercept Pharmaceuticals (C), Ipsen (C), Inventiva Pharma (C), Madrigal (C), Merck Sharp & Dohme (C), Northsea Therapeutics (C), Novartis (C), Novo Nordisk (C), Pfizer (C), Roche (C), Sanofi (C), Siemens Healthcare (R), Siemens Healthineers (C); **S. Konstantinides**, None; **P.S. Wild**, None; **N. Pfeiffer**, Alcon (F), Boehringer Ingelheim (F), Ivantis (F), Novartis (F), Sanoculis (F), Santen (F), Thea (F); **A.K. Schuster**, Abbvie (F), Apellis (F), Bayer Vital (F), Heidelberg Engineering (F), Novartis (F), Santen (F)

References

1. Chan MPY, Broadway DC, Khawaja AP, et al. Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ*. 2017;358:j3889.
2. Schuster AK, Erb C, Hoffmann EM, Dietlein T, Pfeiffer N. The diagnosis and treatment of glaucoma. *Dtsch Arztebl Int*. 2020;117(13):225–234.
3. Orzalesi N, Rossetti L, Omboni S. Vascular risk factors in glaucoma: the results of a national survey. *Graefes Arch Clin Exp Ophthalmol*. 2007;245(6):795–802.
4. Cha S, Gu B, Sagong M, Son J, Kim M. Association between glaucoma and cardiovascular disease risk in Korean population based study. *Invest Ophthalmol Vis Sci*. 2016;57(12):2614.
5. Marshall H, Berry EC, Torres SD, et al. Association between body mass index and primary open angle glaucoma in three cohorts. *Am J Ophthalmol*. 2023;245:126–133.
6. Chung HJ, Hwang HB, Lee NY. The Association between primary open-angle glaucoma and blood pressure: two aspects of hypertension and hypotension. *Biomed Res Int*. 2015;2015:827516.
7. Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. *Ophthalmology*. 1997;104(4):712–718.
8. Hoehn R, Mirshahi A, Hoffmann EM, et al. Distribution of intraocular pressure and its association with ocular features and cardiovascular risk factors: the Gutenberg Health Study. *Ophthalmology*. 2013;120(5):961–968.
9. Baisakhiya S, Singh S, Manjhi P. Correlation between age, gender, waist-hip ratio and intraocular pressure in adult North Indian population. *J Clin Diagn Res*. 2016;10(12):CC05–CC08.
10. Yuan R, Liu K, Cai Y, He F, Xiao X, Zou J. Body shape and risk of glaucoma: a Mendelian randomization. *Front Med (Lausanne)*. 2022;9:999974.
11. Yoshida M, Ishikawa M, Karita K, et al. Association of blood pressure and body mass index with intraocular pressure in middle-aged and older Japanese residents: a cross-sectional and longitudinal study. *Acta Med Okayama*. 2014;68(1):27–34.
12. Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. *Am J Ophthalmol*. 2014;158(3):615–627.e9.
13. Chan MP, Grossi CM, Khawaja AP, et al. Associations with intraocular pressure in a large cohort: results from the UK Biobank. *Ophthalmology*. 2016;123(4):771–782.
14. Memarzadeh F, Ying-Lai M, Azen SP, Varma R, Los Angeles Latino Eye Study Group. Associations with intraocular pressure in Latinos: the Los Angeles Latino Eye Study. *Am J Ophthalmol*. 2008;146(1):69–76.
15. Zhao YX, Chen XW. Diabetes and risk of glaucoma: systematic review and a meta-analysis of prospective cohort studies. *Int J Ophthalmol*. 2017;10(9):1430–1435.
16. Tomoyose E, Higa A, Sakai H, et al. Intraocular pressure and related systemic and ocular biometric factors in a population-based study in Japan: the Kumejima study. *Am J Ophthalmol*. 2010;150(2):279–286.
17. Jeelani M, Taklikar RH, Taklikar A, Itagi V, Bennal A. Variation of intraocular pressure with age and gender. *Natl J Physiol Pharm Pharmacol*. 2014;4:57.
18. Liu X, Pan X, Ma Y, Jin C, Wang B, Ning Y. Variation in intraocular pressure by sex, age, and geographic location in China: a nationwide study of 284,937 adults. *Front Endocrinol (Lausanne)*. 2022;13:949827.
19. Yassin SA, Al-Tamimi ER. Age, gender and refractive error association with intraocular pressure in healthy Saudi participants: a cross-sectional study. *Saudi J Ophthalmol*. 2016;30(1):44–48.
20. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PTVM. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population: the Rotterdam Study. *Ophthalmology*. 1995;102(1):54–60.
21. Kawase K, Tomidokoro A, Araie M, Iwase A, Yamamoto T. Ocular and systemic factors related to intraocular pressure in Japanese adults: the Tajimi study. *Br J Ophthalmol*. 2008;92(9):1175–1179.
22. Han X, Yang T, Zhang J, et al. Longitudinal changes in intraocular pressure and association with systemic factors and refractive error: lingtou eye cohort study. *BMJ Open*. 2018;8(2):e019416.
23. Hohn R, Kottler U, Peto T, et al. The ophthalmic branch of the Gutenberg Health Study: study design, cohort profile and self-reported diseases. *PLoS One*. 2015;10(3):e0120476.

24. Höhn R, Mirshahi A, Zwiener I, Laubert-Reh D, Pfeiffer N. Hängt der Intraokulardruck mit dem Blutdruck zusammen? *Ophthalmologe*. 2013;110(3):218–223.
25. Khawaja AP, Springelkamp H, Creuzot-Garcher C, et al. Associations with intraocular pressure across Europe: the european eye epidemiology (E^3) Consortium. *Eur J Epidemiol*. 2016;31(11):1101–1111.
26. Wang YX, Xu L, Zhang XH, You QS, Zhao L, Jonas JB. Five-year change in intraocular pressure associated with changes in arterial blood pressure and body mass index. The Beijing Eye Study. *PLoS One*. 2013;8(10):e77180.
27. Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol*. 2005;89(3):284–287.
28. Hennis A, Wu S-Y, Nemesure B, Leske MC. Hypertension, diabetes, and longitudinal changes in intraocular pressure. *Ophthalmology*. 2003;110(5):908–914.
29. Ramos RF, Sumida GM, Stamer WD. Cyclic mechanical stress and trabecular meshwork cell contractility. *Invest Ophthalmol Vis Sci*. 2009;50(8):3826–3832.
30. Reddy A, Halenda K, Cromer P, et al. The association of intraocular pressure with obesity and cardiometabolic risk in a young farmworker population. *J Glaucoma*. 2021;30(1):24–31.
31. Zhao D, Kim MH, Pastor-Barriuso R, et al. A longitudinal study of association between adiposity markers and intraocular pressure: the Kangbuk Samsung Health Study. *PLoS One*. 2016;11(1):e0146057.
32. Schteingart DE, Conn JW. Characteristics of the increased adrenocortical function observed in many obese patients. *Ann N Y Acad Sci*. 1965;131(1):388–403.
33. Pérez-Rico C, Gutiérrez-Ortíz C, González-Mesa A, Zandueta AM, Moreno-Salgueiro A, Germain F. Effect of diabetes mellitus on Corvis ST measurement process. *Acta Ophthalmol*. 2015;93(3):e193–e198.
34. Ahmed MS, Ullah AY, Barman N, et al. Risk factors associated with elevated intraocular pressure: a population-based study in a rural community of Bangladesh. *BMJ Open Ophthalmol*. 2023;8(1):e001386.
35. Pimentel LG, Gracitelli CP, da Silva LS, Souza AK, Prata TS. Association between glucose levels and intraocular pressure: pre- and postprandial analysis in diabetic and nondiabetic patients. *J Ophthalmol*. 2015;2015:832058.
36. Hymowitz MB, Chang D, Feinberg EB, Roy S. Increased intraocular pressure and hyperglycemic level in diabetic patients. *PLoS One*. 2016;11(3):e0151833.
37. Augsburger A, Terry JE. Non-contact and Mackay-Marg tonometry: comparison in patients ages 7 to 85 years. *Am J Optom Physiol Opt*. 1977;54(1):31–34.
38. Becker B. The decline in aqueous secretion and outflow facility with age. *Am J Ophthalmol*. 1958;46(5, part 1):731–736.
39. Lee JS, Lee MH, Kim JH, Jo YJ, Shin JH, Park HJ. Cross sectional study among intraocular pressure, mean arterial blood pressure, and serum testosterone according to the anthropometric obesity indices in Korean men. *World J Mens Health*. 2021;39(4):697–704.
40. Adhikari A, Shet RV, Mandal R, Vaghela Y. Variations in intraocular pressure during different phases of menstrual cycle. *J Ophthalmic Res*. 2021;4:183–191.
41. Hoffmann EM, Lamparter J, Mirshahi A, et al. Distribution of central corneal thickness and its association with ocular parameters in a large central European cohort: the Gutenberg Health Study. *PLoS One*. 2013;8(8):e66158.

4.4 Publikation IV

Laspas P*, **Hartmann A*,** Scholz I, Hoffmann EM, Khawaja AP, Lackner KJ, Münzel T, Beutel ME, Schmidtmann I, Tüscher O, Schattenberg J, Pfeiffer N, Wild PS, Schuster AK. Change in systemic medication and its influence on intraocular pressure – results from the Gutenberg Health Study. Investigative Ophthalmology & Visual Science (2024):
https://doi.org/10.1167/iovs.65.14.4

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Clinical and Epidemiologic Research

Change in Systemic Medication and its Influence on Intraocular Pressure – Results From the Gutenberg Health Study

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Received: January 8, 2024
Accepted: September 25, 2024
Published: December 3, 2024

Citation: Laspas P, Hartmann A, Scholz I, et al. Change in systemic medication and its influence on intraocular pressure – Results from the Gutenberg Health Study. *Invest Ophthalmol Vis Sci.* 2024;65(14):4. https://doi.org/10.1167/iovs.65.14.4

Purpose. The purpose of this study was to investigate the relationship between the change in systemic medication and intraocular pressure (IOP) on a population-based level.

Methods. The Gutenberg Health Study is a population-based prospective observational cohort study in Germany. As part of the baseline examination (2007–2012) and 5-year follow-up examination (2012–2017), IOP was measured by non-contact tonometry. Systemic medication was recorded at both time points. Multivariable regression analyses were carried out to analyze associations. Moreover, we calculated the dose-response relationship for the dosage change of selective beta-blockers with IOP change over 5 years.

Results. The analysis population included 19,161 eyes of 9633 participants. IOP change was lower in participants with new intake of selective beta-blockers (−0.31 mm Hg, $P < 0.001$) and increased in those with discontinuation of selective beta-blocker intake (+0.28 mm Hg, $P = 0.02$). Associations between IOP change and statins and calcium channel blockers (CCBs) could be attributed to co-medications. There was a dose-response relationship for change in selective beta-blocker intake and change in IOP (−0.16 mm Hg/100 mg, $P = 0.02$).

Conclusions. Use of systemic selective beta-blockers is associated with an IOP change on a population level, whereas the association with other systemic medications on IOP change could be explained by co-medication use or change in blood pressure. Patients undergoing IOP monitoring and management should routinely be asked about changes in systemic medications.

Keywords: intraocular pressure (IOP), systemic medication, epidemiology

Investigative Ophthalmology & Visual Science

Advancing age, particularly above 75 years, is associated with various chronic illnesses. As a result, elderly individuals frequently use five or more drugs, referred to as polypharmacy.[1] Therefore, it is of importance to understand how systemic medications, commonly administrated in older patients, influence intraocular pressure (IOP). In particular, both selective and nonselective beta-blockers are utilized in the treatment of increased IOP. Nonselective beta-blockers, such as timolol and carteolol, inhibit both beta-1 and beta-2 receptors throughout the body. On the other hand, selective beta-blockers primarily target beta-1 receptors, with betaxolol being a notable example.[2]

Apart from beta-blockers, we focused on the possible effects of statins,[3] diuretics,[4] angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors,[5] calcium channel blockers (CCBs),[6] and various antidepressive drugs,[7] including monoamine reuptake inhibitors and selective serotonin reuptake inhibitors (SSRIs).[8] A recent cross-sectional meta-analysis of 11 European population-based studies showed an influence of beta-blockers on IOP, and potentially for loop diuretics, whereas other systemic medications were not associated with IOP alteration. This study also demonstrated that the intake of CCBs is associated with a higher prevalence of glaucoma. No other systemic medications were found to be related to glaucoma.[4] An analysis of the Rotterdam Study, involving 3842 participants, identified a higher incidence of open-angle glaucoma in those taking calcium channel antagonists, whereas beta-blockers showed a non-significant trend toward reducing the risk of developing glaucoma.[9] Drugs typically administrated locally for the reduction of IOP, such as beta-blockers, are also often given systemically for regulation of blood pressure and chronic heart failure.[10,11] For a long time, there was evidence[12] that the usage of such drugs have a measurable impact on IOP, even if their concentration in the eyes by systemic administration is lower than after topical application.

Various systemic drugs have been proposed to influence the development of ocular hypertension and glaucoma.[13]

Our study advances the understanding of the associations between changes in IOP and systemic medication use, overcoming several limitations of previous research. Unlike prior studies, which were predominantly cross-sectional, ours is the first, to our knowledge, that uses a longitudinal design. This approach allows us to track and analyze IOP changes over time within the same individuals, thereby offering a more detailed perspective on how systemic medications affect IOP.

Methods

The Gutenberg Health Study

The Gutenberg Health Study (GHS) is a prospective, monocentric cohort study based on the population of the city of Mainz and the district Mainz-Bingen in Germany.[14] The participants between the ages of 35 and 74 years were included stratified by sex, place of residence (urban/rural), and age decade. At baseline examination, 15,010 participants were included.[15]

The primary aim of this study was to provide new insights into risk stratification for various diseases in the general population, with special focus on the cardiovascular system.[14] The GHS database is currently the largest collection of data for eye diseases and associated risk factors in Germany and one of the largest worldwide. Recruitment started in 2007 and lasted until early 2012. The first follow-up examinations took place 5 years later, between 2012 and 2017, and included 12,423 participants. The GHS was conducted according to the principles of "Good Clinical Practice," the "Good Epidemiological Practice," and the Declaration of Helsinki.[16,17] Informed consent for participation was obtained from all participants. Approval for the conduction of the study was given by the Ethics Committee of the State Medical Association of Rhineland-Palatinate and the Data Protection Officer of the University Medical Center Mainz.

Measurement of Intraocular Pressure

Eye examinations were performed by medical staff and qualified personnel at the study center. IOP was measured with the Nidek NT-2000 (Nidek Co., Japan) non-contact tonometer. The mean value of three consecutive measurements per eye was assessed and this was considered as the measured IOP. All patients' examinations began with the right eye, followed by the left eye. Examination at baseline and at 5-year follow-up examination took place in the same season and at the same day and time (98% within 2 hours).

Assessment of Medication

Medication classes included in the study were chosen based on the prevalence of antihypertensive and cardiovascular drugs among the sample population. Participants were requested to bring the packaging of all their medications to their study visit to verify the medication intake. Drugs taken by participants were registered according to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization.[18] In Supplementary Table S1, we listed the active substances with ATC codes, for which an association with IOP change is suspected through previous cross-sectional studies.[4,19] Participants were grouped in those with no medication during the study, new intake, discontinued drug intake, and continuous intake during the study. An analysis was only performed if a drug was either newly received or discontinued in at least 100 participants, which corresponds to approximately 1% of the expected analysis population. For this reason, nonselective beta-blockers were not included in the statistical analysis, as they did not meet the minimum case threshold.

Within this study, the ATC codes C09B and C09D represent combination drugs; specifically, C09B refers to ACE inhibitors combined with other medications, and C09D to ARBs also in combination with other drugs. Before performing statistical analysis, these combinations were grouped into their corresponding drug classes.

Inclusion/Exclusion Criteria

The only inclusion criterion was having at least one IOP measurement in one eye at both time points of the study. Exclusion criteria were diagnosed glaucoma, taking antiglaucoma medication, or any eye surgery between both examinations.

Statistical Analysis

For descriptive analysis, absolute and relative frequencies were computed in categorical parameters. For continuous variables, mean and standard deviation were computed for approximately normal-distributed data, otherwise we used median and interquartile range. The change in IOP between baseline and follow-up was computed on eye level. Multivariable linear regression analyses were performed using generalized estimating equations (GEEs) to address the collinearity between the right and left eyes. The analysis incorporated medication classes categorized into four groups: new medication intake, discontinued intake, and continued intake, with "no medication use at both time points" serving as the reference category. Two models analyzing the medication classes separately were constructed (uni-medication models), each adjusting for a set of covariates. The first model included adjustments for age, sex, baseline body mass index (BMI), BMI difference, and diabetes. In the second model, systolic blood pressure difference was additionally incorporated. The adjustment variables were selected based on a previous analysis of the GHS regarding IOP. For this reason, baseline systolic blood pressure was not included in our analyses, as it did not demonstrate a significant association with IOP change in a multivariable context in our earlier univariable analysis.[20] Subsequently, multivariable models incorporating all medication classes were calculated (multi-medication models), adjusting for the same factors. Namely age, sex, baseline BMI, BMI difference, and diabetes in model 3, with an additional adjustment for systolic blood pressure difference in model 4.

In addition, we meticulously examined an effect modification for CCBs with an interaction term in the uni-medication analysis. In a previous cross-sectional study of the GHS, no significant association was found for this medication.[21] However, due to indications from the uni-medication analysis, we decided to investigate this potential association in more detail.

In an additional set of analyses, we included only participants who were taking a single class of the specified medications and excluded those who were on more than one class. This approach was adopted to ensure that the observed effects could be attributed as closely as possible to one medication class without the confounding influence of multiple medications. This way, we could better understand if the medication's effect on IOP stands on its own. Moreover, one analysis was conducted within sex-stratified subgroups to identify potential variations with usage of the multi-medication model. Finally, we calculated the dose-response relationship for the dosage change of beta-blockers (selective) with IOP change over 5 years in the right eye. Metoprolol was used as a reference for assigning weights to various beta-blocker subgroups. A table of equivalence dosage for various beta-blockers was used for standardization on Metoprolol dosage.[22]

R software version 4.0.3 (R Core Team) was used for the statistical evaluation. The analysis was conducted using the following R packages: ggplot2, tableone, ggpubr, and geepack.

Results

Analysis Population

Of the original cohort of 15,010 participants, we examined 12,423 at the 5-year follow-up examination. There were 1683 participants (11.21%) who dropped out of the study, 357 had died (2.38%) prior to the follow-up appointment, 447 (2.98%) could no longer be contacted, and 100 participants (0.67%) were excluded because they no longer met the health criteria for a visit at the study center.

Of those who took part at the 5-year follow-up, 1377 (11.08% of those examined at follow-up) had no IOP measurement in either eye at both time points. There were 1272 participants (10.24%) who were excluded because of the usage of topical eye medication, eye surgery during the 5-year interval, or newly diagnosed glaucoma.

Exclusion of participants with missing information on the systemic medication reduced the number of cases by 118 and by missing values regarding other analysis variables again by 23. Thus, the analysis population included 9633 individuals.

Participants' Characteristics

Of the analysis population, we included 19,161 eyes of 9633 participants. The description of the study population is shown in Table 1. The mean change in IOP was +0.73 (2.04) mm Hg for the right and +0.67 (2.04) mm Hg for the left eye over 5 years.

Because selective beta-blockers are a major focus of the analysis, we additionally compared the descriptive parameters between the groups using beta-blockers (new intake, discontinued intake, and continuous intake) and the group not taking these medications (Supplementary Table S2). The comparison revealed that individuals who have taken or are currently taking selective beta-blockers tend to be older and have a higher prevalence of conditions, such as arterial hypertension and diabetes. Furthermore, systolic and diastolic blood pressure, as well as BMI, were found to be higher compared to the group not using these medications.

Uni-Medication Analysis

Beta-Blockers. Five hundred eighty-six participants (6.1%) reported a new intake of selective β-adrenoceptor antagonists (beta-blockers), 934 participants (9.7%) had continuous intake of selective beta-blockers, and 207 participants (2.1%) stopped the intake of beta-blockers within the 5-year interval between examinations. Participants who were new on selective beta-blockers showed in model 1 (adjusted for age, sex, BMI baseline, BMI difference, and diabetes) a lower IOP change by an average of −0.39 mm Hg (95% confidence interval [CI] = −0.55 to −0.22, $P < 0.001$) over 5 years compared to the study participants without the intake of selective beta-blockers; Table 2. When discontinuing beta-blocker use, IOP change increased by 0.29 mm Hg (95% CI = 0.04 to 0.53, $P = 0.02$). We saw comparable results in model 2 with additional adjustment for 5-year differences of systolic blood pressure.

After exclusion of participants with other co-medications that could potentially influence IOP, namely ACE inhibitors, angiotensin II receptor blockers, diuretics, and calcium channel inhibitors, the association between the new intake or discontinuation of selective beta-blocker and IOP change was no longer evident; Supplementary Table S3. The number of cases of medication intake decreased significantly due to the elimination of co-medication (Supplementary Table S4).

The dosage change of selective beta-blockers showed a significant relationship between the dosage and IOP change in the right eye (B = −0.16 mm Hg/100 mg, $P = 0.02$; Fig. 1).

Table 1. Participants' Characteristics ($N = 9633$, Baseline Examination) Absolute Frequencies of the Intake Patterns of the Medications for Which we Calculated GEE Models

	Overall	Men	Women	Sex-Specific Difference, *P* Value
Anthropometric data (baseline)	9633	4921	4712	
Age, y, mean (SD)	53.30 (10.5)	53.58 (10.6)	53.02 (10.4)	0.009
Age categories: *n*				
35–44 y	2378 (24.7%)	1.169 (23.8%)	1.209 (25.7%)	
45–54 y	2891 (30.0%)	1.471 (29.9%)	1.420 (30.1%)	
55–64 y	2610 (27.1%)	1.326 (26.9%)	1.284 (27.2%)	
65–74 y	1754 (18.2%)	955 (19.4%)	799 (17.0%)	
Cardiovascular parameters				
Arterial hypertension	4412 (45.8%)	2516 (51.1%)	1896 (40.2%)	<0.001
Diabetes	675 (7%)	436 (8.9%)	239 (5.1%)	<0.001
Systolic blood pressure, mm Hg, mean (SD), baseline	130.16 (16.85)	133.0 (15.6)	127.2 (17.6)	<0.001
Systolic blood pressure, mm Hg, mean (SD), follow-up	130.21 (16.51)	132.42 (15.16)	127.91 (17.53)	<0.001
Diastolic blood pressure, mm Hg, mean (SD), baseline	82.31 (9.27)	83.84 (9.15)	80.7 (9.13)	<0.001
Diastolic blood pressure, mm Hg, mean (SD), follow-up	80.68 (9.31)	82.00 (9.24)	79.30 (9.17)	<0.001
Body-mass-index, kg/m^2, mean (SD), baseline	27.06 (4.78)	27.6 (4.1)	26.5 (5.3)	<0.001
Body-mass-index, kg/m^2, mean (SD), follow-up	27.44 (4.98)	27.92 (4.33)	26.95 (5.54)	<0.001
Ophthalmic parameters				
Intraocular pressure, mm Hg, right eye, mean (SD), baseline	14.04 (2.78)	14.10 (2.86)	13.96 (2.69)	0.01
Intraocular pressure, mm Hg, right eye, mean (SD), follow-up	14.77 (2.92)	14.87 (3.03)	14.65 (2.79)	<0.001
Intraocular pressure, mm Hg, left eye, mean (SD), baseline	14.19 (2.81)	14.31 (2.89)	14.06 (2.71)	<0.001
Intraocular pressure, mm Hg, left eye, mean (SD), follow-up	14.85 (2.93)	14.98 (3.03)	14.71 (2.83)	<0.001
Medication intake				
β-Adrenoceptor antagonists, selective: *n*				0.67
No intake	7.905 (82.1%)	4017 (81.6%)	3889 (82.5%)	
New intake	586 (6.1%)	303 (6.2%)	283 (6%)	
Discontinued intake	207 (2.1%)	110 (2.2%)	97 (2.1%)	
Continuous intake	934 (9.7%)	491 (10%)	443 (9.4%)	
β-Adrenoceptor antagonists, nonselective: *n*				1.00
No intake	9581 (99.5%)	4689 (95.3%)	4683 (99.4%)	
New intake	18 (0.2%)	6 (0.1%)	12 (0.3%)	
Discontinued intake	17 (0.2%)	8 (0.2%)	9 (0.2%)	
Continuous intake	17 (0.2%)	9 (0.2%)	8 (0.2%)	
Thiazide diuretics: *n*				<0.001
No intake	8.068 (83.8%)	4036 (82%)	4032 (85.6%)	
New intake	604 (6.3%)	339 (6.9%)	265 (5.6%)	
Discontinued intake	234 (2.4%)	141 (2.9%)	93 (2%)	
Continuous intake	727 (7.5%)	405 (8.2%)	322 (6.8%)	
Loop diuretics: *n*				0.34
No intake	9.359 (97.2%)	4766 (96.9%)	4593 (97.5%)	
New intake	154 (1.6%)	88 (1.8%)	66 (1.4%)	
Discontinued intake	33 (0.3%)	14 (0.3%)	19 (0.4%)	
Continuous intake	87 (0.9%)	53 (1.1%)	34 (0.7%)	
Angiotensin-converting enzyme (ACE) inhibitors: *n*				<0.001
No intake	7871 (81.7%)	3841 (78.1%)	4030 (85.5%)	
New intake	615 (6.4%)	379 (7.7%)	236 (5%)	
Discontinued intake	319 (3.3%)	186 (3.8%)	133 (2.8%)	
Continuous intake	828 (8.6%)	515 (10.5%)	313 (6.6%)	
Angiotensin II receptor blocker (ARB): *n*				<0.001
No intake	8051 (83.6%)	4060 (82.5%)	3991 (84.7%)	
New intake	730 (7.6%)	366 (7.4%)	364 (7.7%)	
Discontinued intake	103 (1.1%)	56 (1.1%)	47 (1%)	
Continuous intake	749 (7.8%)	439 (8.9%)	310 (6.6%)	
Calcium channel blocker: *n*				<0.001
No intake	8509 (88.3%)	4238 (86.1%)	4271 (90.6%)	
New intake	563 (5.8%)	332 (6.7%)	231 (4.9%)	
Discontinued intake	119 (1.2%)	70 (1.4%)	49 (1%)	
Continuous intake	442 (4.6%)	280 (5.7%)	161 (3.4%)	
HMG-CoA reductase inhibitors (statins): *n*				<0.001
No intake	8161 (84.7%)	4011 (81.5%)	4150 (88.1%)	
New intake	532 (5.5%)	328 (6.7%)	204 (4.3%)	
Discontinued intake	206 (2.1%)	122 (2.5%)	84 (1.8%)	
Continuous intake	734 (7.6%)	460 (9.3%)	274 (5.8%)	

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Table 1. Continued

	Overall	Men	Women	Sex-Specific Difference, *P* Value
Nonselective monoamine reuptake inhibitors: *n*				<0.001
No intake	9342 (97%)	4831 (98.2%)	4511 (95.7%)	
New intake	126 (1.3%)	38 (0.8%)	88 (1.9%)	
Discontinued intake	80 (0.8%)	32 (0.7%)	48 (1%)	
Continuous intake	85 (0.9%)	20 (0.4%)	65 (1.4%)	
Selective serotonin reuptake inhibitors: *n*				<0.001
No intake	9.337 (96.9%)	4817 (97.9%)	4520 (95.9%)	
New intake	125 (1.3%)	44 (0.9%)	81 (1.7%)	
Discontinued intake	88 (0.9%)	33 (0.7%)	55 (1.2%)	
Continuous intake	83 (0.9%)	27 (0.5%)	56 (1.2%)	
Other antidepressants: *n*				0.03
No intake	9.403 (97.6%)	4833 (98.2%)	4570 (97%)	
New intake	122 (1.3%)	45 (0.9%)	77 (1.6%)	
Discontinued intake	50 (0.5%)	19 (0.4%)	31 (0.7%)	
Continuous intake	58 (0.6%)	24 (0.5%)	34 (0.7%)	

Data from the German population-based Gutenberg Health Study (2007–2017, $N = 9633$).

Diuretics. Neither continuous, discontinued, nor new uptake of thiazide diuretics was associated with IOP change in any of the models.

Regarding loop diuretics, new intake was associated with a lower IOP change in model 1 (B = −0.35, 95% CI = −0.69 to −0.00, $P = 0.05$), but not after adjustment for a change in systolic blood pressure.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blocker. Continuous intake of ACE inhibitors was associated with a lower IOP change by an average of −0.20 mm Hg (95% CI = −0.34 to −0.06, $P = 0.01$). This association remained in model 2 with −0.17 mm Hg IOP change (95% CI = −0.32 to −0.03, $P = 0.01$) after adjustment for change in systolic blood pressure. Discontinuation of these drugs showed no influence on IOP change. The new intake of angiotensin II receptor blockers was associated with a lower IOP change in model 1 (B = −0.15 mm Hg, 95% CI = −29 to 0.00, $P = 0.05$), however, not after adjustment for a change in systolic blood pressure.

When excluding the effect of co-medication, the association between new intake or continuous intake of ACE inhibitors and IOP change was not present.

Calcium Channel Inhibitors. New intake of calcium channel inhibitors was associated with a decrease in IOP of −0.42 mm Hg (95% CI = −0.58 to −0.26, $P < 0.001$) on average. Similarly, in model 2, the IOP change was associated with new intake of calcium channel inhibitors (B = −0.29 mm Hg, 95% CI = −0.45 to −0.13, $P < 0.001$). The continuous intake or stop of medication showed no association with IOP change.

The negative association between the new intake of calcium channel inhibitors and IOP change disappeared in model 1 and model 2, when participants with a co-medication were excluded (model 1: B = −0.06, $P = 0.77$ and model 2: B = 0.01, $P = 0.96$).

We investigated the potential effect modification within the medication groups involving CCBs. Notably, an effect modification was evident when examining the discontinuation of angiotensin II receptor blockers and the new intake of CCBs in both model 1 (B = −1.40, $P = 0.002$) and model 2 (B = −1.36, $P = 0.004$).

Statins. Concerning statins, new usage was associated with a lower IOP change of −0.27 mm Hg (95% CI = −0.44 to −0.09, $P = 0.003$) in model 1 and −0.21 mm Hg in model 2 (95% CI = −0.39 to −0.04, $P = 0.02$). Continuous intake as well as discontinuation of the drug was not associated with IOP change. After exclusion of co-medication, new intake of statins and IOP change were not associated (model 1: B = −0.03, $P = 0.87$ and model 2: B = −0.01, $P = 0.96$).

Antidepressants. Regarding nonselective monoamine reuptake inhibitors, participants who continuously took the medication had a positive IOP change compared to those without intake (B = 0.44, 95% CI = 0.01 to 0.88, $P = 0.05$) in model 2. New intake and discontinuation of these drugs showed no effect on IOP change.

Concerning SSRIs, there was a significant association with IOP change for discontinuation of the drug with an increasing IOP of 0.43 mm Hg over 5 years (95% CI = 0.12 to 0.74, $P = 0.01$) in model 2.

The association between continuous use of nonselective monoamine reuptake inhibitors with IOP change was not observed when participants with co-medication were excluded (model 1: B = 0.44, $P = 0.08$ and model 2: B = 0.41, $P = 0.11$). Furthermore, the association between discontinuation of SSRIs remained evident in model 2 after exclusion of co-medication (model 1: B = 0.38, 95% CI = −0.02 to 0.77, $P = 0.06$ and model 2: B = 0.39, 95% CI = −0.01 to 0.78, $P = 0.05$).

Multi-Medication Modeling. Models 3 and 4 demonstrated a significant association with changes in IOP over 5 years concerning the new intake and the discontinuation of selective beta-blockers (Fig. 2, Supplementary Table S5). The new intake of selective beta-blockers was associated with a decrease in IOP over 5 years (B = −0.28, $P = 0.001$), whereas discontinuation was associated with an increase (B = 0.33, $P = 0.01$).

Continuous use of ACE inhibitors was also linked to a negative change in IOP pressure over 5 years (B = −0.18, $P = 0.03$). Furthermore, a negative association was observed with the new intake of CCBs (B = −0.25, $P = 0.003$). In the case of nonselective monoamine reuptake

Table 2. Uni-Medication Association Analysis Between Systemically Acting Drugs and a Change in Intraocular Pressure Over 5 Years

	Model 1		Model 2	
Reference: No Medication	IOP Change Over 5 y in mm Hg (95% CI)	P Value	IOP Change Over 5 y in mm Hg (95% CI)	P Value
Selective beta-blockers				
New intake	−0.39 (−0.55 to −0.22)	<0.001	−0.31 (−0.48 to −0.15)	<0.001
Discontinued	0.29 (0.04 to 0.53)	0.02	0.28 (0.04 to 0.53)	0.02
Continuous intake	−0.13 (−0.25 to 0.00)	0.05	−0.11 (−0.24 to 0.01)	0.08
Thiazide diuretics				
New intake	−0.08 (−0.24 to 0.08)	0.33	0.07 (−0.09 to 0.24)	0.38
Discontinued	−0.16 (−0.41 to 0.09)	0.22	−0.22 (−0.47 to 0.03)	0.09
Continuous intake	−0.07 (−0.22 to 0.07)	0.33	−0.05 (−0.20 to 0.09)	0.48
Loop diuretics				
New intake	−0.35 (−0.69 to 0.00)	0.05	−0.24 (−0.58 to 0.11)	0.18
Discontinued	−0.12 (−0.83 to 0.60)	0.75	−0.14 (−0.85 to 0.57)	0.69
Continuous intake	−0.08 (−0.42 to 0.25)	0.62	−0.04 (−0.37 to 0.29)	0.81
ACE inhibitors				
New intake	−0.14 (−0.29 to 0.01)	0.07	−0.02 (−0.17 to 0.13)	0.77
Discontinued	−0.13 (−0.34 to 0.08)	0.23	−0.13 (−0.34 to 0.08)	0.22
Continuous intake	−0.20 (−0.34 to −0.06)	0.01	−0.17 (−0.32 to −0.03)	0.01
Angiotensin II receptor blockers				
New intake	−0.15 (−29 to 0.00)	0.05	−0.04 (−0.17 to 0.13)	0.62
Discontinued	−0.04 (−0.34 to 0.08)	0.86	−0.10 (−0.34 to 0.08)	0.61
Continuous intake	−0.02 (−0.32 to −0.03)	0.76	0.01 (−0.32 to −0.03)	0.93
Calcium channel blocker				
New intake	−0.42 (−0.58 to −0.26)	<0.001	−0.29 (−0.45 to −0.13)	<0.001
Discontinued	0.20 (−0.14 to 0.54)	0.26	0.13 (−0.21 to 0.47)	0.44
Continuous intake	−0.06 (−0.26 to 0.14)	0.56	−0.01 (−0.21 to 0.18)	0.90
Statins				
New intake	−0.27 (−0.44 to −0.09)	0.003	−0.21 (−0.39 to −0.04)	0.02
Discontinued	−0.01 (−0.26 to 0.25)	0.96	−0.01 (−0.27 to 0.25)	0.95
Continuous intake	−0.05 (−0.21 to 0.11)	0.53	−0.02 (−0.18 to 0.13)	0.78
Nonselective monoamine reuptake inhibitors				
New intake	0.23 (−0.06 to 0.52)	0.13	0.23 (−0.06 to 0.52)	0.12
Discontinued	0.26 (−0.10 to 0.62)	0.16	0.24 (−0.12 to 0.60)	0.19
Continuous intake	0.42 (−0.02 to 0.86)	0.06	0.44 (0.01 to 0.88)	0.05
Selective serotonin reuptake inhibitors				
New intake	0.11 (−0.43 to 0.22)	0.51	−0.09 (−0.41 to 0.23)	0.57
Discontinued	0.43 (0.13 to 0.74)	0.01	0.43 (0.12 to 0.74)	0.01
Continuous intake	0.23 (−0.19 to 0.66)	0.29	0.26 (−0.16 to 0.68)	0.23
Other antidepressants				
New intake	0.10 (−0.41 to 0.23)	0.59	0.10 (−0.41 to 0.23)	0.58
Discontinued	0.47 (0.12 to 0.74)	0.09	0.45 (0.12 to 0.74)	0.10
Continuous intake	0.47 (−0.16 to 0.68)	0.09	−0.09 (−0.16 to 0.68)	0.68

Data from the German population-based Gutenberg Health Study (2007–2017, $N = 9633$ individuals). Linear GEE models were calculated. Model 1 controlling for age, sex, BMI baseline, BMI difference, and diabetes. Model 2 controlling for age, sex, BMI baseline, BMI difference, diabetes, and systolic blood pressure difference.

inhibitors, their continuous use was associated with an increase in IOP (B = 0.45, $P = 0.04$). A positive association was also observed between discontinuation of selective serotonin reuptake inhibitors and IOP change (B = 0.34, $P = 0.05$).

In addition, we stratified the regression models by sex, revealing sex-specific differences in the previously mentioned associations (Supplementary Table S6). In men, an association was observed between changes in IOP over 5 years and the new intake of CCBs, continuous use of ACE inhibitors, and the continuous use of nonselective monoamine reuptake inhibitors.

In contrast, among women, we observed associations between changes in IOP over 5 years and the new intake of selective beta-blockers, as well as the initiation or discontinuation of other antidepressants.

Discussion

This study analyzed changes in IOP over a 5-year period and its association with systemic medication. IOP change was associated with various medications in uni-medication analysis, including selective beta-blockers, diuretics, ACE inhibitors, angiotensin II receptor blockers, CCBs, statins, and antidepressants. In the multi-medication model, the new intake and discontinuation of beta-blockers, as well as the continuous intake of ACE inhibitors, the new intake of CCBs and the discontinuation of SSRIs, were still associated with IOP changes in the general population.

The observed association between the new intake of selective beta-blockers and IOP change over a 5-year period aligns with various cross-sectional studies that investigated this relationship.[4,21,23] The association was present both

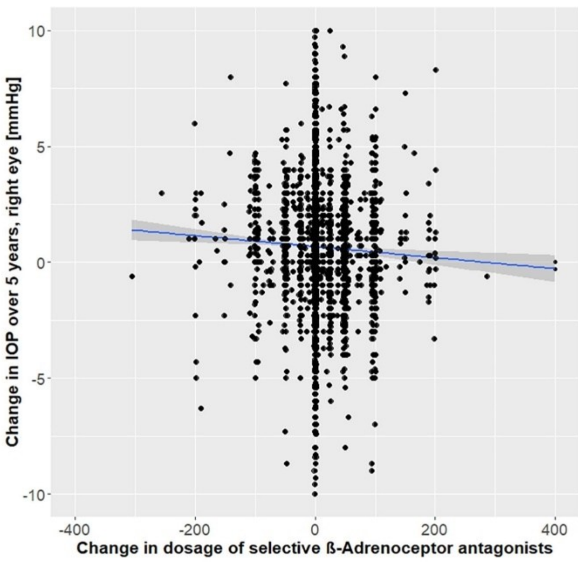

Figure 1. Dose-response relationship between change in dosage of selective beta-blockers and IOP change. Data from the German population-based Gutenberg Health Study (2007–2017). The dosage of selective beta-blockers was standardized to a common scale based on the equivalent dose of metoprolol.

in the uni-medication model and in the multi-medication model with all co-medications. In addition, we found a dose-response relationship of selective beta-blocker usage and IOP change. First reports about a dose-response influence of beta-blockers on IOP go back to 1976, when in 12 patients a dose-response relationship between propranolol (nonselective beta-blocker) and IOP was found.[24] The use of oral beta-blockers has been shown to reduce IOP in several studies.[25,26] Wettrell et al. investigated the effects of three adrenergic beta-blockers on healthy eyes. The authors demonstrated that a significant reduction in IOP was achieved immediately following the administration of the minimum oral dose. This reduction persisted for the entire duration of the treatment period, which lasted 8 days.[26] A further study, which examined the effect of orally administered beta-blockers on 46 individuals, showed that a reduction in IOP occurred both after 3 hours and after 24 hours, which was in the range of 20% to 40%.[25] Beyond the impact of beta-blockers on IOP, additional research has demonstrated that the use of oral selective beta-blockers may also reduce the risk of developing glaucoma.[9,27] Owen et al. conducted a case-control study involving 8778 cases diagnosed with or treated for glaucoma and matched them with 8778 glaucoma-free controls. The study found a lower prevalence of selective beta-blocker usage among the glaucoma cases compared to the controls.[27] Further, we showed that discontinuation of beta-blockers led to an increase in IOP. Beta-blockers are mostly used for the treatment of cardiovascular diseases[28–30] and can be classified into selective (cardioselective) ones, which inhibit β1-adrenoceptors, and nonselective beta-blockers, which inhibit both β1 and β2 adrenoceptors.[31,32] Given that beta-adrenoceptors are present in various tissues within the eye, including the ciliary body, and play a significant role in the regulation of aqueous humor production, beta-blockers have a targeted effect in this context. Specifically, these receptors contribute to the regulation of aqueous humor production by influencing the rate of fluid secretion.[33,34] Beta-blockers function by binding to these receptors, thereby inhibiting their activity. This inhibition reduces the secretion of aqueous humor from the ciliary epithelium, leading to a decrease in IOP.[35] The association of selective beta-blocker intake and IOP changes is no longer visible after excluding co-medication in the sensitivity analysis. This is likely due to the significantly reduced number of cases. In a previous cross-sectional study of the GHS, a descriptively lower IOP in case of the use of selective beta-blockers was observed (−0.12 mm Hg, $P = 0.054$), nevertheless, the difference was not statistically significant.[21] This is likely due to the fact that a smaller number of participants could be included in the longitudinal study, resulting in lower statistical power. Additionally, we have a comparatively lower average age, which could also lead to a reduction in medication use.

In our analysis, an association between the new intake of statins with IOP change was observed. In the multi-medication model, which integrated all co-medications, the previously observed association ceased to exist. This suggests the involvement of at least one more medication, likely due to its blood pressure-lowering effect. This finding is consistent with other studies that showed no association between usage of statins and IOP.[21,23] Khawaja et al.[23] initially demonstrated an association between IOP and statins in their cross-sectional study. However, this association could also be explained by the concurrent use of systemic beta-blockers.

An association was observed between the new intake of ACE inhibitors and a lower IOP in both the uni-medication and multi-medication model. However, this association was no longer evident in the sensitivity analysis, which could also be attributed to the reduced number of cases. A prior cross-sectional analysis from the GHS did not find this association between baseline IOP and ACE inhibitors.[21] However, a significant IOP reduction has been demonstrated in experimental animal models with the administration of topical ACE inhibitors, and it is suspected that this modification increases the uveoscleral outflow.[5,36] A clinical study in patients with ocular hypertension or primary open angle glaucoma showed a lower IOP following the topical application of ACE inhibitors.[37] With respect to angiotensin II receptor blockers, the potential association with IOP change could be explained by co-medications, which is in line with other cross-sectional studies.[21,23]

Although an association with a lower IOP change in case of new intake of CCBs was demonstrated, this association could also be explained by co-medication. Our effect medication analysis revealed that angiotensin II receptor blockers appeared to be the main contributing factors for this finding. This result is consistent with previous literature, which reported no association between CCBs and IOP.[4,23]

Last, we found an association between discontinuation of SSRIs and an increase in IOP change in uni-medication and multi-medication analysis, as well as after exclusion of co-medication. It has been shown that in some patients with depression, the reason for discontinuing SSRI intake was the occurrence of unspecified visual disturbances.[7] Several articles describe the association between SSRIs on IOP.[7,38] The reviews describe that limited numbers of case reports have suggested that an adverse event associated with the use of this drug might be angle-closure. This could suggest a possible association between changes in IOP and the usage of this medication.[7] However, the causality between taking the drug

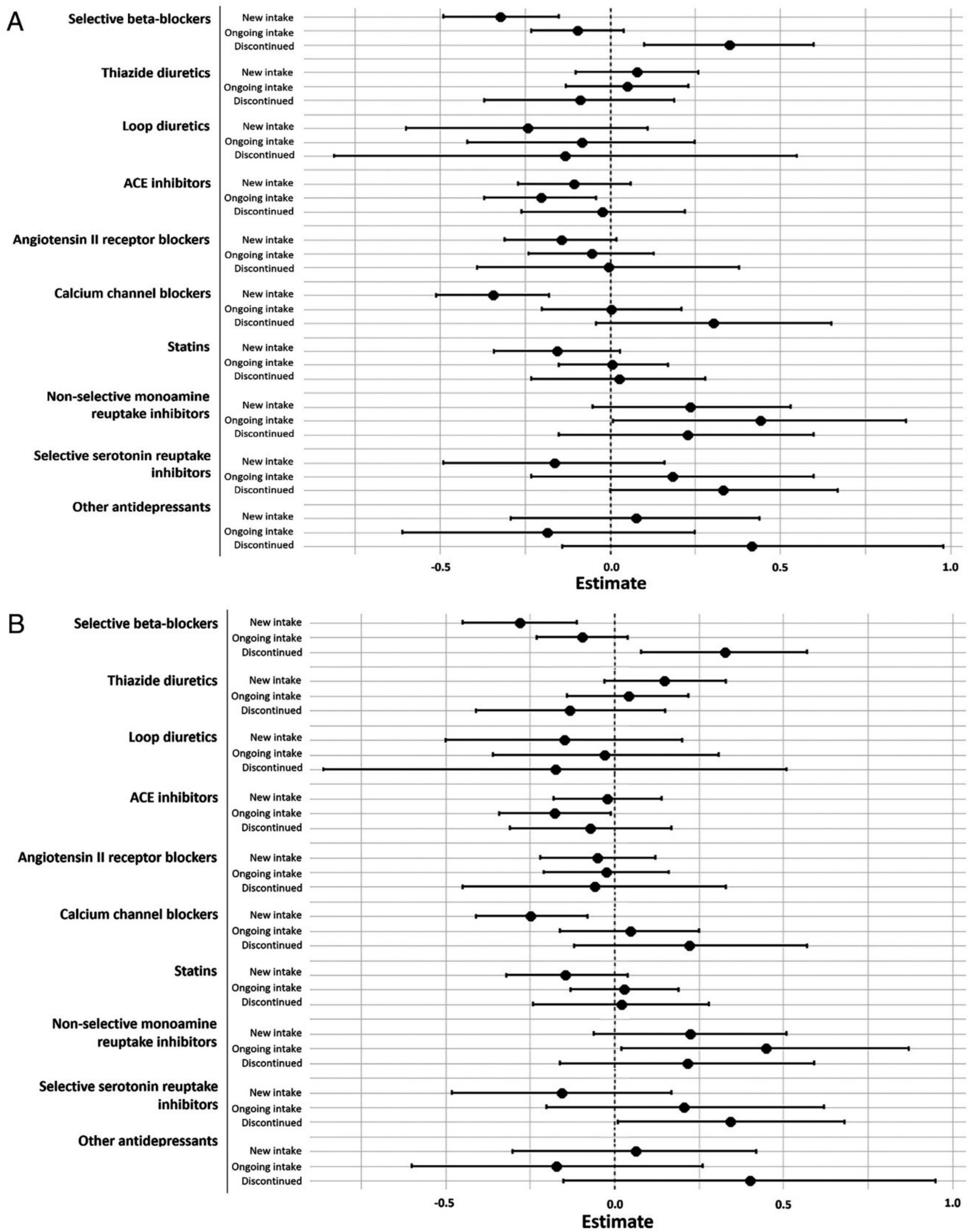

Figure 2. Associations between systemically acting drugs and a change in intraocular pressure over 5 years. Data from the German population-based Gutenberg Health Study (2007–2017, $N = 9633$ individuals, multi-medication analysis). Linear GEE models were calculated. (**A**) Model 3 controlling for co-medication, age, sex, baseline body mass index, body mass index difference over 5 years, and diabetes. (**B**) Model 4 controlling for co-medication, age, sex, baseline body mass index, body mass index difference over 5 years, diabetes, and systolic blood pressure difference over 5 years. Detailed data in Supplementary Table S5.

and the occurrence of angle-closure has not been proven. Given that our results were only marginal after exclusion of co-medication, this finding should be interpreted with caution.

In women, IOP changes were associated with "other antidepressants" like mirtazapine. Studies indicate that women generally respond better to serotonergic antidepressants, although postmenopausal women show poorer responses,[39–41] whereas there are also studies contradicting these findings.[42–45] To our knowledge, there are no studies specifically examining sex differences in the effects of antidepressants on IOP. Furthermore, there was a significant association between selective beta-blockers and the change in IOP in women, which was not significant in men. This effect is likely due to different baseline characteristics, as literature suggests a similar response to the medication in women and men.[46] Moreover, sex differences in drug metabolism and hormonal influences could contribute to the observed variations.[47] There is a need for further studies comparing the effects of medications on IOP between sexes.

In 2023, a meta-analysis of 11 population-based studies was conducted, exploring the impact of various medications on glaucoma and IOP. Similar to findings in this study, an association was observed between lower IOP and the use of systemic beta-blockers (both selective and nonselective), whereas no association was found with CCBs, ACE inhibitors, angiotensin II receptor blockers, statins, or antidepressants. A weak association with high-ceiling diuretics was identified, but it was nonsignificant after adjusting for other systemic medications.[4] These findings are in line with our results, except for the association with ACE inhibitors which was seen in our study. Another literature-based meta-analysis from 2023 including 10 cross-sectional and case-control studies also identified an association between lower IOP and the treatment with beta-blockers, although there was no association with CCBs, ACE inhibitors, angiotensin receptor blockers, or diuretics.[48]

Our investigation significantly advances the field's comprehension of the interactions between systemic medication use and IOP changes, thereby addressing critical gaps highlighted in earlier studies. Our longitudinal study design marks a departure from prior cross-sectional analyses, providing us with the unique capability to track IOP changes over time within the same individuals. This approach grants us a richer, more intricate view into the mechanisms by which systemic medications can affect IOP.

Strengths and Limitations

This study analyzed data from a large population-based representative sample. This analysis uniquely investigates the impact of new, discontinued, and continuous intake of systemic medications on IOP. One of the strengths of our approach is the longitudinal design, allowing us to compare within-individual differences over time, which provides a clearer picture of the medication effects and natural variations in IOP. Moreover, this study is among the first to examine how co-medications may drive IOP changes, offering insights into the complex interactions between various cardiovascular drugs. These aspects underscore the study's significant step forward from previous research, by providing a nuanced understanding of IOP dynamics in a large, well-characterized cohort.

However, our study has some limitations. First, the included GHS participants mainly were of Caucasian origin. Therefore, the results cannot be generalized to other ethnicities. Additionally, whereas IOP measurements were taken three times per eye during each visit to enhance accuracy, these measurements were all conducted within a short time frame. Therefore, although the average of these three readings was used to increase the reliability of the data, we could not account for potential intra- and inter-day fluctuations in IOP. To minimize environmental effects, the GHS aimed to examine the study participants at a similar time of day and the same season at baseline and 5-year examination. Furthermore, although noncontact tonometry is commonly used to assess IOP in clinical settings, it is not entirely consistent with Goldmann applanation tonometry, which is considered as reference standard. Within the GHS, tonometry was measured with the same device at baseline and follow-up examination to minimize a systemic bias due to different measurement techniques. Although our study excluded participants with diagnosed glaucoma, it did include individuals with narrow angles, a factor that should be considered when interpreting the impact on IOP and medication effects. Last, this was an exploratory study, and no adjustment for multiple testing was conducted, which should also be taken into account when interpreting the study data.

Conclusions

In summary, there was an approximate 0.7 mm Hg increase in IOP over a 5-year period in the population aged 35 to 74 years. New intake of systemic selective beta-blockers was associated with a reduction in IOP. Discontinuation of systemic beta-blockers led to an increase in IOP, whereas associations between IOP changes and statins, or CCBs could be attributed to the influence of co-medications.

Acknowledgments

The Gutenberg Health Study is funded through the Government of Rhineland-Palatinate ("Stiftung Rheinland-Pfalz für Innovation," contract AZ 961-386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study.

A. P. Khawaja is supported by a UK Research and Innovation Future Leaders Fellowship, an Alcon Research Institute Young Investigator Award and a Lister Institute for Preventive Medicine Award. This research was supported by the NIHR Biomedical Research Centre at Moorfields Eye Hospital and the UCL Institute of Ophthalmology.

Disclosure: **P. Laspas**, None; **A. Hartmann**, None; **I. Scholz**, None; **E.M. Hoffmann**, None; **A.P. Khawaja**, AbbVie (C), Aerie (C), Allergan (C), Google Health (C), Heidelberg Engineering (C), Novartis (C), Reichert (C), Santen (C), Thea (C), A. K. G. Schuster holds the professorship for ophthalmic healthcare research endowed by "Stiftung Auge" and financed by "Deutsche Ophthalmologische Gesellschaft" and "Berufsverband der Augenärzte Deutschlands e.V."; **K.J. Lackner**, None; **T. Münzel**, None; **J.G. Kerahrodi**, None; **I. Schmidtmann**, None; **O. Tüscher**, None; **J.M. Schattenberg**, Apollo Endosurgery (C), Bayer (C), Boehringer Ingelheim (C), BMS (C), Gilead Sciences (C), GSK (C), Intercept Pharmaceuticals (C), Ipsen (C), Inventiva Pharma (C), Madrigal (C), MSD (C), Northsea Therapeutics (C), Novartis (C), Novo Nordisk (C), Pfizer (C), Roche (C), Sanofi (C), Siemens Healthineers (C); **N. Pfeiffer**, Novartis (F), Ivantis (F), Santen (F), Thea (F), Boehringer Ingelheim Deutschland GmbH & Co. KG (F), Alcon (F), Sanoculis (F); **S. Konstantinides**, None; **P.S. Wild** is funded by the Federal Ministry of Education and Research (BMBF 01EO1503) and he and T. Münzel are principal investigators of the German Center for Cardiovascular Research (DZHK). P. S. Wild is principal investigator of the DIASyM research core (BMBF 161L0219); **A.K.-G. Schuster**, AbbVie (F), Apellis (F), Bayer Vital (F), Heidelberg Engineering (F), Novartis (F), Santen (F)

References

1. Drenth-van Maanen AC, Wilting I, Jansen PAF. Prescribing medicines to older people - how to consider the impact of ageing on human organ and body functions. *Br J Clin Pharmacol*. 2020;86:1921–1930.
2. Brooks AM, Gillies WE. Ocular beta-blockers in glaucoma management. Clinical pharmacological aspects. *Drugs Aging*. 1992;2:208–221.
3. Kim ML, Sung KR, Shin JA, Young Yoon J, Jang J. Statins reduce TGF-beta2-modulation of the extracellular matrix in cultured astrocytes of the human optic nerve head. *Exp Eye Res*. 2017;164:55–63.
4. Vergroesen JE, Schuster AK, Stuart KV, et al. Association of systemic medication use with glaucoma and intraocular pressure: the European Eye Epidemiology Consortium. *Ophthalmology*. 2023;130:893–906.
5. Ho H, Shi Y, Chua J, et al. Association of systemic medication use with intraocular pressure in a multiethnic Asian population: the Singapore epidemiology of eye diseases study. *JAMA Ophthalmol*. 2017;135:196–202.
6. Quill B, Irnaten M, Docherty NG, et al. Calcium channel blockade reduces mechanical strain-induced extracellular matrix gene response in lamina cribrosa cells. *Br J Ophthalmol*. 2015;99:1009–1014.
7. Costagliola C, Parmeggiani F, Sebastiani A. SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs*. 2004;18:475–484.
8. Zheng W, Dryja TP, Wei Z, et al. Systemic medication associations with presumed advanced or uncontrolled primary open-angle glaucoma. *Ophthalmology*. 2018;125:984–993.
9. Müskens RP, de Voogd S, Wolfs RC, et al. Systemic antihypertensive medication and incident open-angle glaucoma. *Ophthalmology*. 2007;114:2221–2226.
10. Nabil S. Comparison of international guidelines for managing chronic heart failure with reduced ejection fraction. *Curr Probl Cardiol*. 2023;48:101867.
11. Hanna J, Ghazi L, Yamamoto Y, et al. Excessive blood pressure response to clonidine in hospitalized patients with asymptomatic severe hypertension. *Am J Hypertens*. 2022;35:433–440.
12. Phillips CI, Howitt G, Rowlands DJ. Propranolol as ocular hypotensive agent. *Br J Ophthalmol*. 1967;51:222–226.
13. Wu A, Khawaja AP, Pasquale LR, Stein JD. A review of systemic medications that may modulate the risk of glaucoma. *Eye (Lond)*. 2020;34:12–28.
14. Wild PS, Zeller T, Beutel M, et al. Die Gutenberg Gesundheitsstudie. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*. 2012;55:824–830.
15. Hohn R, Kottler U, Peto T, et al. The ophthalmic branch of the Gutenberg Health Study: study design, cohort profile and self-reported diseases. *PLoS One*. 2015;10:e0120476.
16. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomed Imaging Interv J*. 2008;4:e5.
17. Hoffmann W, Latza U, Baumeister SE, et al. Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology. *Eur J Epidemiol*. 2019;34:301–317.
18. WHO Expert Committee. The selection and use of essential medicines. *World Health Organ Tech Rep Ser*. 2007;958:1–162, back cover.
19. Wang H-Y, Tseng P-T, Stubbs B, et al. The risk of glaucoma and serotonergic antidepressants: a systematic review and meta-analysis. *J Affect Disord*. 2018;241:63–70.
20. Hartmann A, Scholz I, Hoffmann EM, et al. change of intraocular pressure over 5 years and its relationship to cardiovascular parameters: results from the Gutenberg Health Study. *Invest Ophthalmol Vis Sci*. 2024;65:12.
21. Hohn R, Mirshahi A, Nickels S, et al. Cardiovascular medication and intraocular pressure: results from the Gutenberg Health Study. *Br J Ophthalmol*. 2017;101:1633–1637.
22. Arzneimittel Kommission. Vergleichstabelle: Betablocker. 2020. Available at: https://www.abda.de/fileadmin/user_upload/assets/Arzneimittelkommission/Aequivalenzdosistabellen/Betablocker_Vergleichstabelle.pdf.
23. Khawaja AP, Chan MP, Broadway DC, et al. Systemic medication and intraocular pressure in a British population: the EPIC-Norfolk Eye Study. *Ophthalmology*. 2014;121:1501–1507.
24. Wettrell K, Pandolfi M. Early dose response analysis of ocular hypotensive effects of propranolol in patients with ocular hypertension. *Br J Ophthalmol*. 1976;60:680–683.
25. Williamson J, Atta HR, Kennedy PA, Muir JG. Effect of orally administered nadolol on the intraocular pressure in normal volunteers. *Br J Ophthalmol*. 1985;69:38–40.
26. Wettrell K, Pandolfi M. Effect of oral administration of various beta-blocking agents on the intraocular pressure in healthy volunteers. *Exp Eye Res*. 1975;21:451–456.
27. Owen CG, Carey IM, Shah S, et al. Hypotensive medication, statins, and the risk of glaucoma. *Invest Ophthalmol Vis Sci*. 2010;51:3524–3530.
28. do Vale GT, Ceron CS, Gonzaga NA, Simplicio JA, Padovan JC. Three generations of β-blockers: history, class differences and clinical applicability. *Curr Hypertens Rev*. 2019;15:22–31.
29. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation*. 1986;73:503–510.
30. Brodde OE. The functional importance of beta1 and beta2 adrenoceptors in the human heart. *Am J Cardiol*. 1988;62:24C–29C.
31. Brooks AM, Gillies WE. Ocular β-blockers in glaucoma management. Clinical pharmacological aspects. *Drugs Aging*. 1992;2:208–221.
32. Metra M, Nodari S, Boldi E, Cas LD. Selective or nonselective β-adrenergic blockade in patients with congestive heart failure. *Curr Cardiol Rep*. 2000;2:252–257.
33. Grüb M, Mielke J. Aqueous humor dynamics. *Der Ophthalmologe: zeitschrift der Deutschen Ophthalmologischen Gesellschaft*. 2004;101:357–365.
34. Nathanson JA. Adrenergic regulation of intraocular pressure: identification of beta 2-adrenergic-stimulated adenylate cyclase in ciliary process epithelium. *Proc Natl Acad Sci USA*. 1980;77:7420–7424.
35. Coakes RL, Brubaker RF. The mechanism of timolol in lowering intraocular pressure: in the normal eye. *Arch Ophthalmol*. 1978;96:2045–2048.
36. Watkins RW, Baum T, Cedeno K, et al. Topical ocular hypotensive effects of the novel angiotensin converting enzyme inhibitor SCH 33861 in conscious rabbits. *J Ocul Pharmacol*. 1987;3:295–307.
37. Constad WH, Fiore P, Samson C, Cinotti AA. Use of an angiotensin converting enzyme inhibitor in ocular hyperten-

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sion and primary open-angle glaucoma. *Am J Ophthalmol*. 1988;105:674–677.

38. Costagliola C, Parmeggiani F, Semeraro F, Sebastiani A. Selective serotonin reuptake inhibitors: a review of its effects on intraocular pressure. *Curr Neuropharmacol*. 2008;6:293–310.
39. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry*. 2000;157:1445–1452.
40. Khan A, Brodhead AE, Schwartz KA, Kolts RL, Brown WA. Sex differences in antidepressant response in recent antidepressant clinical trials. *J Clin Psychopharmacol*. 2005;25:318–324.
41. Yang SJ, Kim SY, Stewart R, et al. Gender differences in 12-week antidepressant treatment outcomes for a naturalistic secondary care cohort: the CRESCEND study. *Psychiatry Res*. 2011;189:82–90.
42. Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J Clin Psychiatry*. 2001;62:869–877.
43. Thiels C, Linden M, Grieger F, Leonard J. Gender differences in routine treatment of depressed outpatients with the selective serotonin reuptake inhibitor sertraline. *Int Clin Psychopharmacol*. 2005;20:1–7.
44. Gougoulaki M, Lewis G, Nutt DJ, Peters TJ, Wiles NJ, Lewis G. Sex differences in depressive symptoms and tolerability after treatment with selective serotonin reuptake inhibitor antidepressants: secondary analyses of the GENPOD trial. *J Psychopharmacol*. 2021;35:919–927.
45. Sramek JJ, Murphy MF, Cutler NR. Sex differences in the psychopharmacological treatment of depression. *Dialogues Clin Neurosci*. 2016;18:447–457.
46. Wilmes N, van Luik EM, Vaes EWP, et al. Exploring sex differences of beta-blockers in the treatment of hypertension: a systematic review and meta-analysis. *Biomedicines*. 2023;11:1494.
47. Chang TKH, Waxman DJ. Sex Differences in Drug Metabolism. Part I. Basics overview of drug metabolism. *Encyclopedia of Drug Metabolism and Interactions*. 2012. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/9780470921920.edm004?msockid=359f1086d8a066af24f10589d9b26701.
48. Leung G, Grant A, Garas AN, Li G, Freeman EE. A systematic review and meta-analysis of systemic antihypertensive medications with intraocular pressure and glaucoma. *Am J Ophthalmol*. 2023;255:7–17.

4.5 Publikation V

Hartmann A, Grabitz SD, Hoffmann EM, Wild PS, Schmidtmann I, Lackner KJ, Beutel ME, Münzel T, Tüscher O, Schattenberg JM, Pfeiffer N, and Schuster AK. Intraocular Pressure and Its Relation to Climate Parameters—Results From the Gutenberg Health Study. Investigative Ophthalmology & Visual Science (2023): https://doi.org/10.1167/iovs.64.7.15

Investigative Ophthalmology & Visual Science

Clinical and Epidemiologic Research

Intraocular Pressure and Its Relation to Climate Parameters—Results From the Gutenberg Health Study

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Received: January 13, 2023
Accepted: May 3, 2023
Published: June 8, 2023

Citation: Hartmann A, Grabitz SD, Hoffmann EM, et al. Intraocular pressure and its relation to climate parameters—results from the Gutenberg Health Study. *Invest Ophthalmol Vis Sci.* 2023;64(7):15. https://doi.org/10.1167/iovs.64.7.15

Purpose. To investigate the association between intraocular pressure (IOP) and climate parameters.

Methods. The Gutenberg Health Study (GHS) is a population-based cohort study in Mainz, Germany. Participants underwent two comprehensive ophthalmologic examinations (baseline visit and five-year follow up) including non-contact tonometry, objective refraction, pachymetry, perimetry, and fundus imaging in the time frame of 2007 to 2017. The respective climate parameters were assessed at the University Mainz including temperature, air humidity, and air pressure. Associations of IOP and climatic parameters were computed using component models and cross-correlation plots. Multivariable regression analysis was performed to adjust for age, sex, body mass index, diabetes, central corneal thickness, and systolic blood pressure. To further explore the link between systolic blood pressure, temperature, and IOP, an effect mediation analysis was conducted.

Results. A total of 14,632 participants (age 55 ± 11 years at baseline, 49.1% female) were included in this analysis. Mean IOP was 14.24 ± 2.8 mm Hg at baseline. There was a similar periodic change in IOP and in temperature, as shown in the component models. IOP was not associated with air humidity. In univariable and multivariable regression analyses we found a significant association between lower IOP during the summer months with higher air temperature ($B = -0.011$, $P < 0.001$). This could be partially explained in mediation analysis by lower systolic blood pressure at higher air temperature. Furthermore, IOP was associated with air pressure in univariable ($B = 0.005$, $P = 0.04$.) and multivariable models ($B = 0.006$, $P = 0.03$).

Conclusions. There is a periodic annual change of IOP with higher values in winter and lower values in summer supporting the hypothesis of an impact of environmental temperature on IOP, which is partly mediated by lower systolic blood pressure in summer.

Keywords: intraocular pressure, environmental factors, seasonality, time series analysis

The major modifiable risk factor for development and progression of open-angle glaucoma is elevated intraocular pressure (IOP).[1] Knowledge of IOP, its distribution in the general population over different time courses, and influencing factors play an important role in the diagnosis and treatment of glaucoma.[2]

Several studies analyzed time-of-day and yearly fluctuations.[3–7] It has already been proven that patients with

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glaucoma have high IOP fluctuations. Few studies have investigated daily IOP variations in healthy subjects. Fluctuations were also seen in these patients, but these were smaller compared to in glaucoma patients.[8,9] Larger fluctuations occur at night because of the lying sleeping position.[10] Studies that attempted to characterize a daily IOP pattern concluded that there is no uniform pattern in healthy subjects.[11–13]

Furthermore, little is known about possible environmental factors influencing IOP on large studies or on population-based level. A former study from the 1980s found an association between IOP and air pressure: increased air pressure led to lower IOP.[14] However, a multiple regression analysis taking into account interindividual variations showed only a negligible influence of atmospheric pressure on IOP.[14] An experimental study in healthy volunteers showed that an air pressure increase to two bars over 40 minutes led to a significant decrease of IOP from 11.8 mm Hg to 10.7 mm Hg.[15] A possible association between IOP and air humidity is barely investigated and showed no significant correlation.[14]

With respect to air temperature, a study of healthy Chinese showed an IOP change over the time course of one year, indicated that IOP is higher on cold days and lower on warm days.[12] Also, other studies showed differences of IOP in winter and summer.[4,12,16–21]

The Gutenberg Health Study (GHS) offers the opportunity to gain new insights into potential environmental factors influencing IOP. The study population is one of the largest population-based samples, in which IOP, climate parameters and anthropometric parameters are observed over a period of 10 years.

Methods

Procedure and Study Sample

The GHS is a population-based, prospective, observational single-center cohort study in the Rhine-Main Region in Germany. The sample was equally stratified for sex, residence (urban or rural), and for age-decade. At baseline, 15,010 individuals were included (2007–2012), and 12,423 were re-examined after five years (2012–2017).

Ophthalmic Parameters

IOP was measured with a noncontact tonometry and automatic air-puff control (NT 2000; Nidek, Inc., San Jose, CA, USA), the mean of three measurements within a 3 mm Hg range was obtained for each eye. The date and time of the measurement was recorded. IOP measurements were mainly performed between 11:00 and 18:00 hours. First, the right eye was measured three times followed by the left eye. If there was a difference of more than 3 mm Hg between the three measurements, the measurement was immediately repeated. For further calculations, the mean IOP value of the right and left eye was used. Further information on the lens status were determined with slit-lamp examination at baseline examination[22] and Scheimpflug imaging at follow-up examination.[23] Pachymetry was measured with Pachycam (Oculus, Wetzlar, Germany) at baseline and Pentacam HR (Oculus) at follow-up examination. Glaucoma status was determined on optic disc photographs and using frequency doubling technology perimetry according to a modified definition of the Glaucoma classification according to International Society of Geographical and Epidemiological Ophthalmology (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1771026/).[24]

Climate Parameters

Climate parameters were provided by the "Institute for Atmospheric Physics (Johannes Gutenberg University)." Air pressure, humidity, and temperature were continuously measured, and daily mean, minimum, and maximum values were provided. In addition, the GHS also provided data on measured temperature inside and outside the study center.

General Parameters

Characteristics of the study population including age, sex, height, weight, and body mass index (BMI) were surveyed. Diabetes mellitus was defined as an established diagnosis, use of anti-diabetics, or HbA1c $\geq$ 6.5%, arterial hypertension as use of antihypertensive medication, systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or an established diagnosis. Further information, such as the HbA1c-level, were determined by using standardized measurement procedures.

Statistical Analysis

Descriptive analysis was conducted for primary and secondary variables. For categorical parameters, absolute and relative frequencies were computed. For continuous variables, mean and standard deviation were calculated for approximately normal-distributed data, otherwise median and interquartile range were calculated.

For IOP analysis, the mean value from both eyes was used, if available. Population-based IOP distribution within the day, daily IOP averages, and the IOP distribution over the year with monthly averages were computed.

To analyze the association of IOP and climate parameters, time series diagrams (the component models) were created that highlight the seasonal component, as well as the trend. The component model is subject to the assumption that not all time series are stationary. They are therefore subject to a trend, seasonality and thus variance, which is not constant. To analyze the nonstationary time series in more detail, it is decomposed into several components.[25] In the analysis, the time series was decomposed into the following four components: observed values, trend, seasonal component, and random data. Time series were then adjusted for trend and tested for a significant relationship using a cross-correlation function. One function of time series is to be able to recognize possible correlations in successive temporal intervals. This is illustrated by the autocorrelation, which shows possible correlation between the temperature and the subsequent values of the IOP in the following correlation plot.[25,26] The lags in the correlation plot establish periods of time between the two time series. The observations in one time series are tested against lagged values in the other time series.[25] An association between IOP and the temporal component was additionally examined using cosinor analysis ("cosinor package" in R).[27]

Univariable and multivariable linear regression analyses were conducted to analyze the association between IOP and climate parameters (air temperature, air humidity, air pressure) on individual participant level (repeated measures were modeled with generalized estimating equations). Analyses were adjusted for potential confounding factors (age, sex, diabetes, BMI), and in addition an effect mediation for systolic blood pressure was conducted. The mediation analysis helps to speculate why an independent variable is possibly associated with another variable. We looked at an intervening variable (mediator = systolic blood pressure) that could possibly be the reason for the present association. The percentage of the mediator causing the association is calculated.[28]

As sensitivity analyses, glaucoma patients, those with a prescription of IOP lowering therapy were excluded and only participants with phakic lens status were included. The study population was stratified by sex, and stratified on age decades. Data were processed with the statistical program R (version: 4.0.3 (2020-10-10)).

Results

Overall, 14.632 study participants were included. The mean age of the study population was 55 ± 11.11 years, and 49.5% were female. Table 1 shows the participants' characteristics at baseline. The mean IOP was 14.11 ± 2.69 mm Hg in women and 14.37 ± 2.87 mm Hg in men.

Table 1. Participants' Characteristics (*N* = 14,632, Baseline Examination) and Climatic Parameter in the Gutenberg Health Study

	Overall	Men	Women
Anthropometric data	14,632	7390	7242
Age (y), mean (SD)	55 (11.1)	55.22 (11.1)	54.77 (11.1)
Weight (kg), mean (SD)	79.72 (16.58)	87.28 (14.36)	72.01 (15.08)
Height (cm), mean (SD)	170.44 (9.5)	176.98 (7.08)	163.79 (6.61)
BMI, mean (SD)	27.38 (5.02)	27.86 (4.29)	26.88 (5.62)
Medical history			
Systolic blood pressure (mm Hg), mean (SD)	131.30 (17.42)	133.86 (16.22)	128.69 (18.20)
Arterial hypertension	7261 (49.7%)	4026 (54.5%)	3235 (44.7%)
Diabetes	1364 (9.3%)	841 (11.4%)	523 (7.2%)
Ophthalmic parameters			
IOP (mm Hg), mean (SD)	14.24 (2.79)	14.37 (2.87)	14.11 (2.69)
Glaucoma (ISGEO)	128 (1.1%)	63 (1.0%)	65 (1.1%)
Central corneal thickness (μm)	553.76 (35.28)	556.19 (35.1)	551.30 (35.29)
Spherical equivalent (diopters), mean (SD)	−0.42 (2.44)	−0.44 (2.36)	−0.40 (2.51)
Lens status (phakic)	14,055 (96.1%)	7106 (96.2%)	6936 (95.8%)
Local eye medication			
Sympathomimetics	37 (0.3%)	20 (0.3%)	17 (0.2%)
Parasympathomimetics	8 (0.1%)	2 (0.0%)	6 (0.1%)
Carbonic anhydrase inhibitors	46 (0.3%)	20 (0.3%)	26 (0.4%)
Beta blocking agents	202 (1.4%)	103 (1.4%)	99 (1.4%)
Prostaglandin analogues	95 (0.7%)	48 (0.7%)	47 (0.7%)
Climatic parameters			
Temperature in F° and C° , mean	50.34°F/10.19°C		
Air humidity, mean	80%		
Air pressure (mB), mean	1000.3		

SD, Standard deviation; ISGEO, Glaucoma classification according to International Society of Geographical and Epidemiological Ophthalmology (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1771026/).

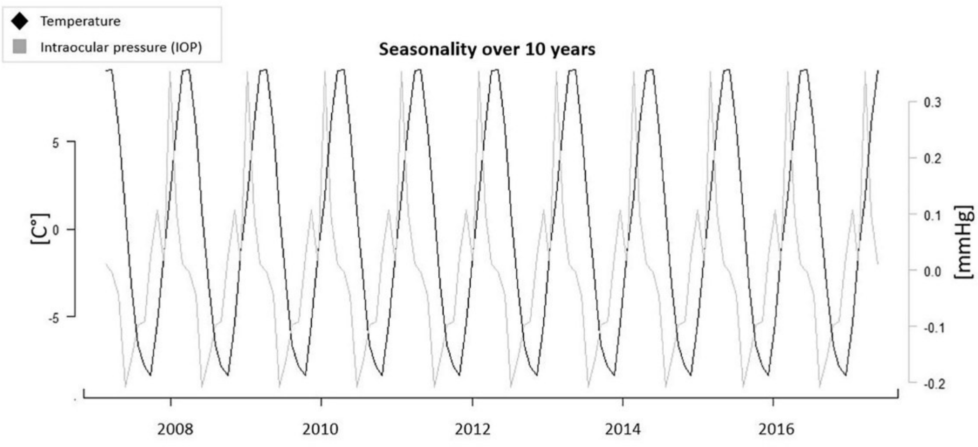

Figure 1. Seasonal component of average temperature and IOP in time series analysis (monthly averages): data from the Gutenberg Health Study (2007–2017) and Department of Astrophysics (2007–2017).

Time Series Analysis

IOP time series over 10 years with monthly averages showed that IOP is subject to seasonality (Fig. 1). The time series of temperature also shows a seasonal component (Fig. 1). Looking at the two time series, an almost inverse relationship between both time series can be seen: at high temperature, the IOP is low and the other way round. The smaller peak of the IOP seasonality arises from a small number of IOP measurements in December, because the study center is not open the whole month. The other components of time series analysis are shown in Supplementary Figures S1 and S2.

Data from the GHS study center also demonstrated seasonality in the measured outdoor temperature (Supplementary Fig. S3a). This was not the case for the indoor temperature (Supplementary Fig. S3b).

The correlation between temperature and IOP is also reflected in the correlation plot of both time series (Fig. 2a) in crude analysis and after removing the trend component (Fig. 2b), although there is a minor correlation after also removing the seasonal component (Fig. 2c). Component models were also created for variables that have been shown to influence IOP. Systolic blood pressure showed a matching seasonality compared to IOP (higher values in winter, lower values in summer). The correlation plots between the outdoor temperature of the GHS and IOP showed comparable results (Supplementary Fig. S4).

Furthermore, we conducted a cosinor analysis to examine the association between IOP and temporal patterns. Our results revealed significant temporal relationship between the 52-week IOP data and both the amplitude (B = 0.12, $P < 0.05$) and acrophase (B = 1.04, $P < 0.05$) within the 52 weeks of a year demonstrating a periodic distribution of IOP.

Associations Between Climate Parameters and IOP

There was a significant association between air temperature and IOP ($r = -0.17$, $P < 0.0001$; Fig. 3a). Higher average daily temperature was associated with a lower IOP. IOP peak was recorded in February (14.9 ± 0.48 mm Hg) and lowest IOP in July (14.3 ± 0.43 mm Hg).

A univariable correlation was also found between air pressure and IOP ($r = 0.07$, $P = 0.031$, Fig. 3b) and air humidity and IOP ($r = 0.07$, $P = 0.031$, Fig. 3c). Linear regression analysis showed in univariable analysis an association between IOP and air temperature and air pressure as climate parameters, whereas in multivariable model with adjustment for potential confounders air temperature and air pressure remained associated with IOP (Table 2).

We further found a significant association of lower systolic blood pressure and higher air temperature (−0.08, 95% confidence interval [CI] = −0.1 to −0.06, $P < 0.001$). Mediation analysis revealed that the relationship between IOP and air temperature is approximately 77% mediated by the lower systolic blood pressure. In the regression model with both temperature and systolic blood pressure, the association between IOP and air temperature remains (−0.0088, 95% CI = −0.01 to 0.00, $P < 0.0012$) significant. In the multivariable model with adjusting for potential confounders the association remains robust. Sensitivity analyses (exclusion of subjects with glaucoma disease, exclusion of subjects with IOP surgery or IOP-lowering medication, only inclusion of participants with phakic lens status) showed comparable results.

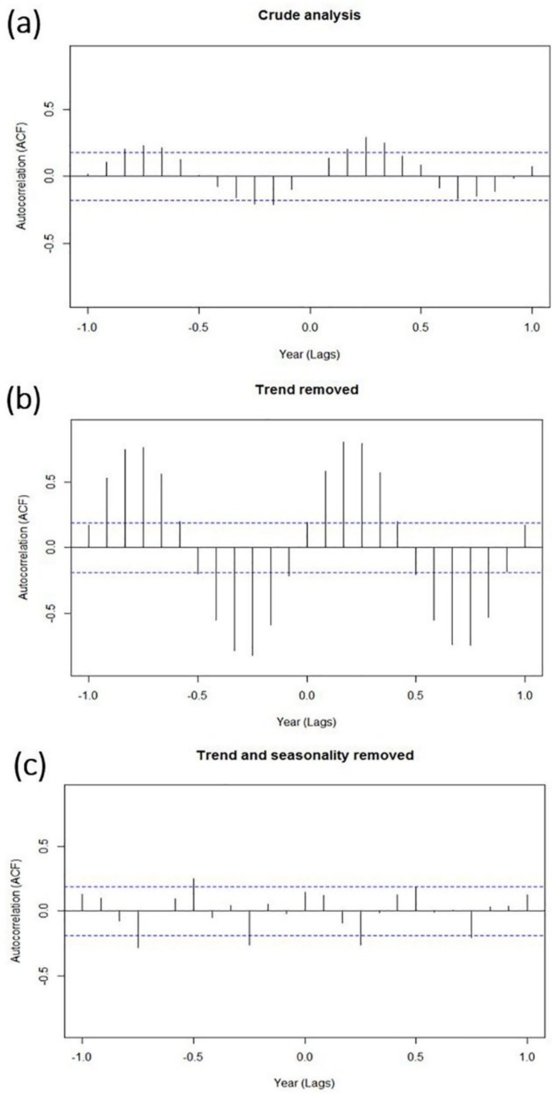

Figure 2. Correlation plot between IOP and air temperature. (**a**) Crude analysis, (**b**) after removing of the trend component, and (**c**) after removing the seasonal component as well.

Within Day IOP Distribution

Within day distribution of IOP (measured between 7:00-18:00) showed no significant difference over the day (Fig. 4), with women showing slightly lower values than men (Supplementary Fig. S5).

Discussion

This study analyzed the relationship between IOP and climate parameters in a large population-based sample over the course of 10 years. We found a periodic change of IOP over the year through the time series and cosinor analysis with higher values in winter and lower values in summer.

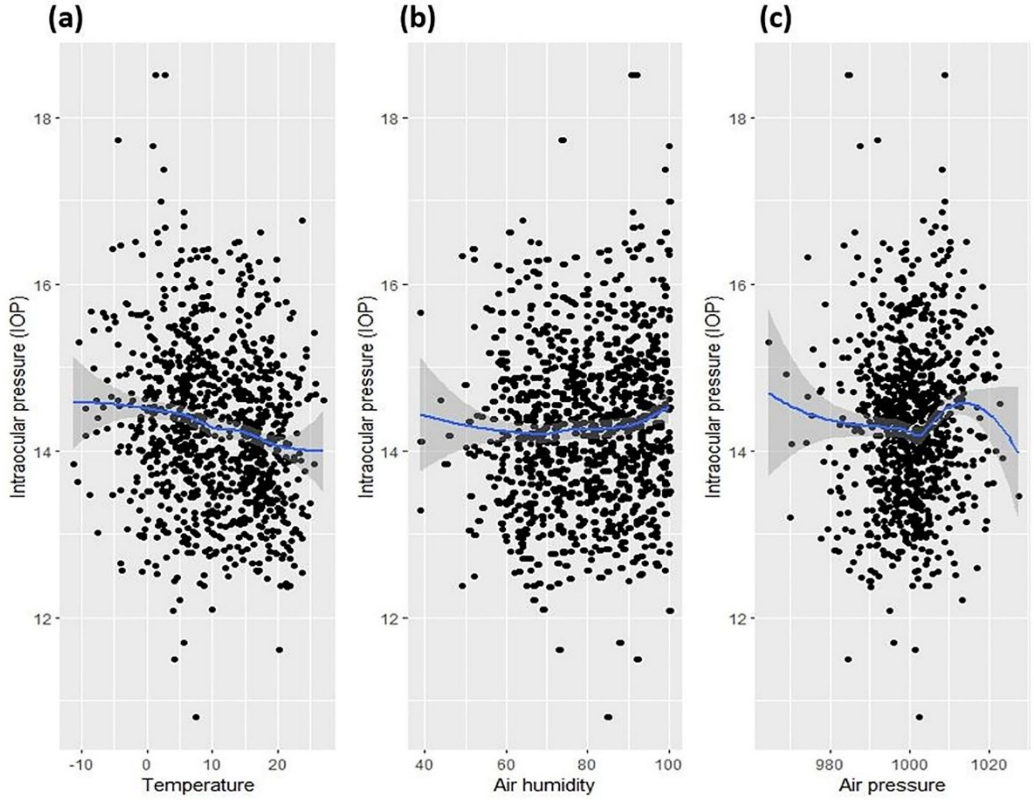

Figure 3. Scatterplot between IOP and air temperature (**a**), air humidity (**b**), and air pressure (**c**). Results from the population-based Gutenberg Health Study (n = 14,632) from baseline examination (2007–2012). The *blue line* illustrates the LOESS line.

Table 2. Multivariable Linear Regression Analysis (With Generalized Estimating Equations) of Climate Parameters With IOP

	Univariable, Unadjusted			Multivariable, Adjustment for Age, Sex, BMI, CCT, and Diabetes			Multivariable, Adjustment for Age, Sex, BMI, CCT, Diabetes, and Systolic Blood Pressure		
	B	95% CI	*P* Value	B	95% CI	*P* Value	B	95% CI	*P* Value
Air temperature	−0.011	−0.02 to −0.01	<0.001	−0.016	−0.02 to −0.01	<0.001	−0.013	−0.02 to 0.01	<0.001
Air humidity	0.002	0.00–0.01	0.16	0.002	0.00–0.01	0.38	0.002	[0.00–0.01]	0.26
Air pressure	0.005	0.00–0.01	0.04	0.006	0.00–0.01	0.03	0.006	[0.00–0.01]	0.02

CCT, central corneal thickness.
Data from the Gutenberg Health Study (2007–2017).

This association can in part be explained by lower blood pressure values at higher air temperature.

Our findings are supported by other studies in healthy subjects[4,17,18]: One study with 103 healthy Chinese participants found an IOP difference of 1.4 ± 0.7 mm Hg between winter and summer, with higher IOP in winter months.[3] Analyses in this subject area in Chicago, Illinois, United States, recorded an IOP peak in December/January (15.7 ± 3.7/15.7 ± 3.8 mm Hg) and lowest IOP in September (14.5 ± 3.1 mm Hg).[20] A study using results from the UK Biobank of 110,573 participants demonstrated seasonality of IOP with lower values in summer and higher values in winter.[29] In this study IOP peak was recorded in February (14.9 ± 0.48 mm Hg) and lowest IOP in July (14.3 ± 0.43 mm Hg).

One retrospective cohort study analyzed a 20-year period through medical records showing significant seasonal changes over the entire period.[17] Similarly, studies examining glaucoma patients concluded that IOP is subject to periodic IOP changes.[4,17,18]

The question arises how this seasonality of IOP might be explained. The present study showed that there is a significant relationship between IOP and air temperature. Seasonality of IOP and temperature showed an almost inverse relationship. Both seasonality curves partially overlap, most likely because the IOP does not react immediately to temperature change but with a time lag. The association was evident in both the correlation plot and the regression analysis, as well as after adjustment for possible confounders. Effect mediation analysis revealed that systolic blood pressure

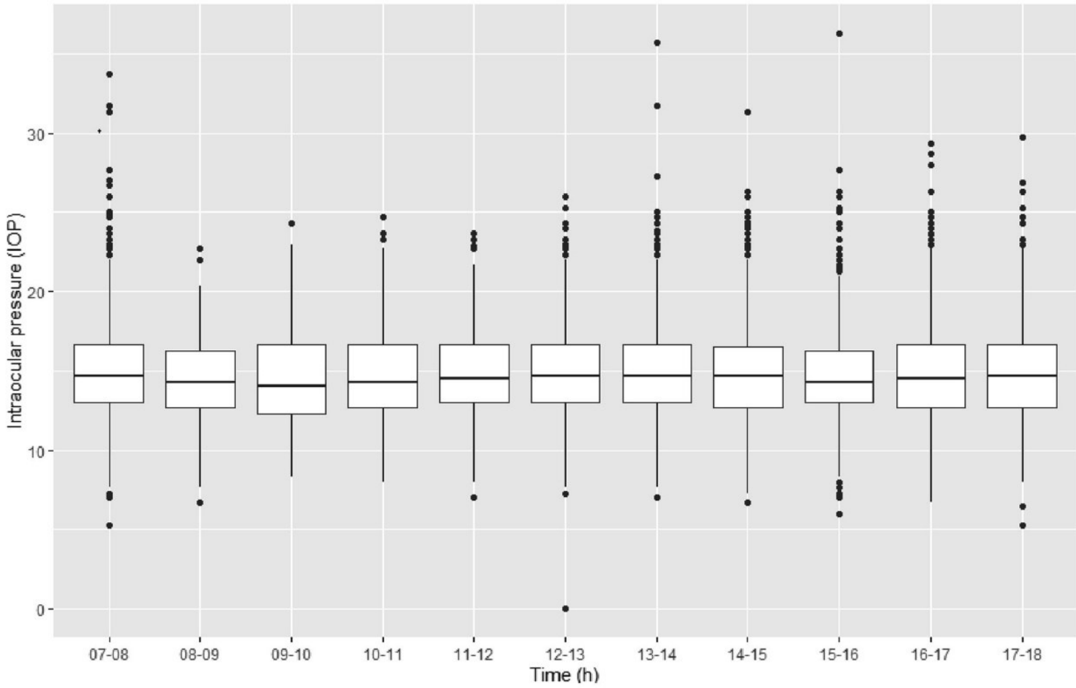

Figure 4. Within day distribution of IOP. Results from the population-based Gutenberg Health Study (n = 14,632), data from baseline examination (2007–2012).

partly mediates this association. Similar to our study data, other studies demonstrated the seasonality of systolic blood pressure with higher values in winter and lower values in summer time.[30–33] The association between IOP and systolic blood pressure has been proven by multiple studies,[34–37] each of these studies indicated that an increase in systolic blood pressure was also associated with an increase in IOP. Temperature and systolic blood pressure showed a relationship in several studies: at high temperatures blood pressure is lower, whereas at low temperatures blood pressure is reported to be higher.[31,38,39] The underlying explanation for this phenomenon is that lower temperature cause temporary constriction of blood vessels, resulting in increased resistance to blood flow and consequently higher blood pressure.[40] It has been hypothesized by several studies that high systolic blood pressure affects aqueous humor by ultrafiltration, which increases IOP.[41–43] Our effect mediation results show that IOP is partially altered because of a change in systolic blood pressure caused by outdoor temperature. However, in our cohort, systolic blood pressure did not fully explain the association of IOP and air temperature.

Little is known about a possible relationship between air humidity and IOP. We didn't find an association between air humidity and IOP in this analysis. Similar results on this subject demonstrating no relationship were reported in another study.[14] With respect to atmospheric pressure, IOP was associated in univariable and multivariable analysis.

This result is partly consistent with the literature on this topic. One study in Germany examined 109 patients with chronic glaucoma or ocular hypertension and found a correlation between IOP and atmospheric pressure. However, a multiple regression analysis showed that the influence of atmospheric pressure on IOP is negligible when taking interindividual variations into account.[14]

One experimental study showed that an increase of air pressure to two bars over 40 minutes in a hyperbaric chamber led to a significant decrease of IOP.[15] This atmospheric pressure corresponds to a dive at a depth of 10 meters. However, this study evaluated the short-term effects of massive air pressure changes and thus is not comparable to the natural slow and much smaller fluctuations. Air pressure regularly fluctuates by approximately 0.003 bars during the day.[44]

Strengths and Limitations

This study analyzed data from a large population-based representative sample. The study contributes results to better understanding of characteristics of IOP over time course and its relation to climate parameters as an environmental influence factor. Compared to other studies on this topic, the large study population and the long observation time of 10 years offer the possibility of obtaining representative findings. Furthermore, the large study sample offers the opportunity to explore the link between systolic blood pressure, temperature, and IOP.

However, there are some limitations of our study, which need to be considered. The included GHS subjects mainly consist of Caucasian origin. Therefore no generalizability to other ethnicities is given. IOP measurement by noncontact tonometry can be recognized as a limitation, although the application of noncontact tonometry is widely used in the clinics but not in full agreement with the reference standard Goldmann applanation tonometry. Moreover, there are IOP measurement techniques incorporating biomechanical properties such as the ocular response analyzer,[45,46] which would allow us to further investigate potential influence of temperature on IOP because of a change in biomechanical characteristics. To reduce this potential influence, we adjusted for central corneal thickness in our statistical analysis. In addition, only daily data on climate parameters were available limiting the time series analysis.

Conclusion

In conclusion, this study demonstrates periodic change of IOP over the time course of 10 years in a population-based sample: IOP is higher in winter and lower in summer time. IOP is associated with air temperature showing an inverse but similar pattern of seasonality. Part of the effect of air temperature on IOP could be explained by systolic blood pressure as an effect mediation.

Acknowledgments

The Gutenberg Health Study is funded through the Government of Rhineland-Palatinate ("Stiftung Rheinland-Pfalz für Innovation", contract AZ 961-386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study.

Disclosure: **A. Hartmann,** None; **S.D. Grabitz,** None; **E.M. Hoffmann,** Allergan (F), Heidelberg Engineering (F), Santen (F), Novartis (F), Thea (F), Carl Zeiss Meditec (F); **P.S. Wild,** Federal Ministry of Education and Research (BMBF 01EO1503) (R); **I. Schmidtmann,** None; **K.J. Lackner,** None; **M.E. Beutel,** None; **T. Münzel,** None; **O. Tüscher,** None; **J.M. Schattenberg,** None; **N. Pfeiffer,** Novartis (F), Ivantis (F), Santen (F), Thea (F), Boehringer Ingelheim Deutschland GmbH & Co. KG (F), Alcon (F), Sanoculis (F); **A.K. Schuster,** Allergan (F), Bayer Vital (F), Heidelberg Engineering (F), Novartis (F), Santen (F), "Stiftung Auge" (R); "Deutsche Ophthalmologische Gesellschaft" (R), "Berufsverband der Augenärzte Deutschlands e.V" (R)

References

1. Hashemi H, Khabazkhoob M, Emamian MH, Shariati M, Yekta A, Fotouhi A. Distribution of intraocular pressure and its determinants in an Iranian adult population. *Int J Ophthalmol.* 2016;9:1207–1214.
2. McMonnies CW. The importance of and potential for continuous monitoring of intraocular pressure. *Clin Exp Optom.* 2017;100:203–207.
3. Saccà SC, Rolando M, Marletta A, Macrí A, Cerqueti P, Ciurlo G. Fluctuations of intraocular pressure during the day in open-angle glaucoma, normal-tension glaucoma and normal subjects. *Ophthalmologica.* 1998;212:115–119.
4. Terauchi R, Ogawa S, Noro T, et al. Seasonal fluctuation in intraocular pressure and retinal nerve fiber layer thinning in primary open-angle glaucoma. *Ophthalmology Glaucoma.* 2021;4:373–381.
5. Bengtsson B, Leske MC, Hyman L, Heijl A. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. *Ophthalmology.* 2007;114:205–209.
6. Drance SM. The significance of the diurnal phasic variation of intraocular pressure in normal and glaucomatous eyes. *Trans Can Opthalmolog Soc.* 1960;23:131–140.
7. Medeiros FA, Weinreb RN, Zangwill LM, et al. Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. *Ophthalmology.* 2008;115:934–940.
8. Agnifili L, Mastropasqua R, Frezzotti P, et al. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. *Acta Ophthalmol.* 2015;93: e14–e21.
9. Aref AA. What happens to glaucoma patients during sleep? *Curr Opin Ophthalmol.* 2013;24:162–166.
10. Liu JH, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. *Invest Ophthalmol Vis Sci.* 1999;40:2912–2917.
11. Realini T, Weinreb R, Wisniewski S. Diurnal Intraocular Pressure Patterns are Not Repeatable in the Short Term in Healthy Individuals. *Ophthalmology.* 2010;117:1700–1704.
12. Liao N, Xie YQ, Mao GY, et al. Observation seasonal variation of intraocular pressure in young healthy volunteers. *Int J Ophthalmol.* 2022;15:59–64.
13. Song YK, Lee C-K, Kim J, Hong S, Kim CY, Seong GJ. Instability of 24-hour intraocular pressure fluctuation in healthy young subjects: a prospective, cross-sectional study. *BMC Ophthalmology.* 2014;14:127.
14. Jonas J, Guggenmoos-Holzmann I, Brambring D, Schmitz-Valckenberg P. [Weather influences on intraocular pressure in patients with chronic glaucoma or ocular hypertension]. *Klin Monbl Augenheilkd.* 1986;189:445–449.
15. Van de Veire S, Germonpre P, Renier C, Stalmans I, Zeyen T. Influences of atmospheric pressure and temperature on intraocular pressure. *Invest Ophthalmol Vis Sci.* 2008;49:5392–5396.
16. Cheng J, Xiao M, Xu H, et al. Seasonal changes of 24-hour intraocular pressure rhythm in healthy Shanghai population. *Medicine.* 2016;95:e4453.
17. Ikeda Y, Mori K, Ueno M, et al. Seasonal variation and trend of intraocular pressure decrease over a 20-year period in normal-tension glaucoma patients. *Am J Ophthalmol.* 2022;234:235–240.
18. Kuze M, Ayaki M, Yuki K, et al. Seasonal variation of intraocular pressure in glaucoma with and without dry eye. *Sci Rep.* 2020;10:13949.
19. Mansouri K, Gillmann K, Rao HL, Weinreb RN. Weekly and seasonal changes of intraocular pressure measured with an implanted intraocular telemetry sensor. *Br J Ophthalmol.* 2021;105:387–391.
20. Morettin CE, Roberts DK, Newman TL, et al. Time-of-year variation in intraocular pressure. *J Glaucoma.* 2021;30:952–962.
21. Qureshi IA, Xi XR, Lu HJ, Wu XD, Huang YB, Shiarkar E. Effect of seasons upon intraocular pressure in healthy population of China. *Korean J Ophthalmol.* 1996;10:29–33.
22. Schuster AK, Pfeiffer N, Schulz A, et al. The impact of pseudophakia on vision-related quality of life in the general population—The Gutenberg Health Study. *Aging (Albany NY).* 2017;9:1030–1040.
23. Schuster AK, Nickels S, Pfeiffer N, et al. Frequency of cataract surgery and its impact on visual function-results from the German Gutenberg Health Study. *Graefes Arch Clin Exp Ophthalmol.* 2020;258:2223–2231.
24. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol.* 2002;86:238–242.
25. Schlittgen R, Sattarhoff C. *Angewandte Zeitreihenanalyse mit R.* Berlin: De Gruyter Oldenbourg, 2020.

26. Ward MP, Iglesias RM, Brookes VJ. Autoregressive models applied to time-series data in veterinary science. *Front Vet Sci*. 2020;7:604.
27. Cornelissen G. Cosinor-based rhythmometry. *Theor Biol Med Model*. 2014;11:16.
28. Gunzler D, Chen T, Wu P, Zhang H. Introduction to mediation analysis with structural equation modeling. *Shanghai Arch Psychiatry*. 2013;25:390–394.
29. Chan MP, Grossi CM, Khawaja AP, et al. Associations with intraocular pressure in a large cohort: results from the UK Biobank. *Ophthalmology*. 2016;123:771–782.
30. Lewington S, Li L, Sherliker P, et al. Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank. *J Hypertens*. 2012;30:1383–1391.
31. Woodhouse PR, Khaw KT, Plummer M. Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. *J Hypertens*. 1993;11:1267–1274.
32. Narita K, Hoshide S, Kario K. Seasonal variation in blood pressure: current evidence and recommendations for hypertension management. *Hypertens Res*. 2021;44:1363–1372.
33. Stergiou GS, Palatini P, Modesti PA, et al. Seasonal variation in blood pressure: Evidence, consensus and recommendations for clinical practice. Consensus statement by the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. *J Hypertens*. 2020;38:1235–1243.
34. Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol*. 2005;89:284–287.
35. Bakke EF, Hisdal J, Semb SO. Intraocular Pressure Increases in Parallel with Systemic Blood Pressure during Isometric Exercise. *Invest Ophthalmol Vis Sci*. 2009;50:760–764.
36. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PTVM. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population: the Rotterdam Study. *Ophthalmology*. 1995;102:54–60.
37. Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. *Am J Ophthalmol*. 2014;158:615–627.e9.
38. Barnett AG, Sans S, Salomaa V, Kuulasmaa K, Dobson AJ. The effect of temperature on systolic blood pressure. *Blood Press Monit*. 2007;12:195–203.
39. Alpérovitch A, Lacombe J-M, Hanon O, et al. Relationship between blood pressure and outdoor temperature in a large sample of elderly individuals: the three-city study. *Arch Intern Med*. 2009;169:75–80.
40. Nakagami H, Akiyama H, Otsuka H, Iwamae A, Yamada H. Blood pressure fluctuations and the indoor environment in a highly insulated and airtight model house during the cold winter season. *Hypertens Res*. 2022;45:1217–1219.
41. Yasukawa T, Hanyuda A, Yamagishi K, et al. Relationship between blood pressure and intraocular pressure in the JPHC-NEXT eye study. *Sci Rep*. 2022;12:17493.
42. Bulpitt CJ, Hodes C, Everitt MG. Intraocular pressure and systemic blood pressure in the elderly. *Br J Ophthalmol*. 1975;59:717–720.
43. Shiose Y. The aging effect on intraocular pressure in an apparently normal population. *Arch Ophthalmol*. 1984;102:883–887.
44. Mentzer AP. What is the range of barometric pressure? Available at: https://sciencing.com/range-barometric-pressure-5505227.html. Accessed December 2, 2022.
45. Hoffmann EM, Lamparter J, Mirshahi A, et al. Distribution of central corneal thickness and its association with ocular parameters in a large central European cohort: the Gutenberg health study. *PLoS One*. 2013;8:e66158.
46. McCann P, Hogg RE, Wright DM, et al. Comparison of Goldmann applanation and Ocular Response Analyser tonometry: intraocular pressure agreement and patient preference. *Eye*. 2020;34:584–590.

4.6 Publikation VI

Hartmann A, Grabitz SD, Wild PS, Lackner KJ, Münzel T, Ghaemi Kerahrodi J, Singer S, Geschke K, Schattenberg JM, Konstantinides S, Pfeiffer N, Schuster AK. Gender-specific changes in vision-related quality of life over time – results from the Gutenberg Health Study. Graefe's Archive for Clinical and Experimental Ophthalmology (2025): https://doi.org/10.1007/s00417-025-06741-9

Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-025-06741-9

BASIC SCIENCE

Gender-specific changes in vision-related quality of life over time – results from the population-based Gutenberg Health Study

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Received: 6 May 2024 / Revised: 23 October 2024 / Accepted: 14 January 2025

Abstract

Purpose To investigate potential gender- and age-specific changes over time in vision-related quality of life (VRQoL) on a population-based level. Further, factors associated with changes in VRQoL will be explored.

Methods The Gutenberg Health Study is a population-based, prospective, observational, single-center cohort study in Germany. VRQoL was quantified at baseline and 5-year follow-up using the visual function scale (VFS) and socio-emotional scale (SES-VRQoL). VFS and SES-VRQoL are calculated using the "National Eye Institute 25-Item Visual Functioning Questionnaire" (NEI-VFQ-25). Both scales range from 0 to 100, 0 corresponds to the sum that would be achieved if a participant had answered all items with the worst performance, and 100 corresponds to the sum of all items answered with the best possible performance. Distance-corrected visual acuity was measured in both eyes. Univariable and multivariable linear regression analyses were conducted to identify ophthalmic and sociodemographic predictors of VRQoL.

Results A total of 10,152 participants (mean age 54.2 years; 49.2% female) were included in the analysis. The mean visual functioning decreased from 89.6 (IQR: 81.3, 95.1) at baseline to 85.9 (IQR: 79.2, 92.6) at 5-year follow-up in the VFS ($p<0.001$). Participants' socio-emotional well-being remained the same from baseline to 5-year follow-up in the SES-VRQoL. In multivariable linear regression analysis, older age (0.03, $p=0.002$) and female gender (-1.00, $p<0.001$) were associated with a VFS change. Higher baseline socioeconomic status was associated with a slightly positive increase in VFS (0.07, $p=0.001$). Deterioration of visual acuity in the better and worse-seeing eye was associated with negative VFS change over 5 years (better-seeing eye: -5.41, $p<0.001$, worse-seeing eye: -7.35, $p<0.001$). Baseline socioeconomic status was associated with SES-VRQoL change (0.06, $p<0.001$). The negative change in visual acuity showed an association with negative SES-VRQoL in the better (-4.15, $p<0.001$) and worse-seeing eye (-3.75, $p<0.001$). Stratification of the regression models by age and gender showed greater reductions in VFS scores with visual acuity changes in participants aged 65 years or older and a more pronounced decrease in female participants over 5 years.

Conclusions This study demonstrated an association between visual acuity change and change in VRQoL over 5 years, with a greater decrease in female participants and participants aged 65 years or older. The better-seeing eye and the worse-seeing eye both had an impact on changes in VRQoL.

Key messages

What is known

- Previous studies have predominantly used cross-sectional designs to investigate the correlation between visual acuity and vision-related quality of life, with limited insights into how visual acuity changes over time affect vision-related quality of life in a large cohort.

What is new

- This study demonstrates that visual acuity changes significantly impact VRQoL over a 5-year period, with a notable decrease observed in female participants and those aged 65 years or older.
- Analysis reveals both the better-seeing and worse-seeing eye contribute to changes in VRQoL, highlighting the necessity of comprehensive visual assessments in both eyes for a more accurate understanding of VRQoL outcomes.

Extended author information available on the last page of the article

Published online: 11 February 2025

Keywords Quality of life · Visual acuity · Visual impairment · Gender factors · Healthy ageing · VFQ-25

Introduction

Subjective perception of difficulties due to vision and their impact on daily life activities are important when assessing the burden of ophthalmic diseases. Patient-reported outcomes analyzing vision-related functioning and quality of life are gaining importance in evaluating therapeutic interventions and are included as primary outcomes in clinical studies. Vision-related quality of life (VRQoL) describes how vision affects the life of a person and their satisfaction with vision ability [1].

To date, VRQoL has been mostly examined in cross-sectional studies. These cross-sectional studies showed worse VRQoL in the presence of visual impairment (VI) compared to no VI [1–3]. Several studies have demonstrated that loss of visual functioning and VI is associated with a decline in VRQoL [3–5]. VI can lead to emotional or physical difficulties resulting in limitations in social life [6]. In addition, higher age and lower socioeconomic status is associated with lower VRQoL [7, 8].

Few studies have examined gender-related differences in VRQoL in cross-sectional studies: one study found slightly worse VRQoL in women [9]. The Gutenberg Health Study (GHS) has previously reported gender-specific differences in VRQoL in a cross-sectional approach with worse VRQoL in women [3, 10]. When examining gender-related differences in health-related quality of life (HRQoL), numerous studies consistently report lower scores for women [11–14]. A study from the United States, which analyzed four national datasets, found that women had worse HRQoL outcomes compared to men, with sociodemographic and socioeconomic disparities partially accounting for these differences [13]. Similarly, another study demonstrated that women had significantly worse HRQoL than men across all subscales, even after adjusting for factors such as age and chronic conditions [11].

However, it is unknown to date whether the course of VRQoL over time also differs between genders. Possible gender differences could be due to a higher prevalence of blindness in women [15], a difference in socioeconomic status [16] or different symptom reporting [17].

Several studies found that VRQoL decreases with age [1, 8, 18]. Thus, it may be important to implement screening measures early to detect VI and counteract a decrease in VRQoL early on [8]. Concerning visual acuity, both the better-seeing and worse-seeing eye have an influence on VRQoL: the better-seeing eye has a stronger influence and the worse eye has a minor influence on the VRQoL, thus the function of both eyes should also be included in clinical decision-making processes [3].

McKean-Cowdin et al. examined changes in visual acuity and HRQoL in a population-based cohort study with 3,169 individuals in La Puente, California (age: 40 years or older). A decreased visual acuity over 4 years was linked to decreased visual functionality and overall well-being [19].

Cross-sectional studies reported that individuals with lower socioeconomic status also have worse VRQoL [20, 21]. It may be important to provide more counseling and information to these individuals in the clinical context to increase awareness of eye disease. It is also important to reach this group of people in prevention programs [20, 21].

This study focuses on changes in VRQoL over time and evaluates whether there are gender-, age- or socioeconomic-specific differences in this regard on a population-based level. Further, the association between the change in VRQoL with the change in visual acuity of the better and worse-seeing eye is evaluated.

Method

Study sample

The GHS is a population-based, prospective, observational, single-center cohort study in the Rhine-Main-Region in Germany. The sampling was stratified for gender, residence (urban or rural) and age-decade. At baseline, 15,010 individuals were included (in the years 2007–2012) and 12,423 of them were re-examined after 5 years (2012–2017). The inclusion criteria for the current analysis were the availability of NEI-VFQ-25 (National Eye Institute Visual Function Questionnaire) scores at baseline and at 5-year follow-up to be able to calculate the change of VFQ-25 scores for each study participant. This reduced the number of subjects to 10,152 participants.

Ophthalmic parameters

Objective refraction and distance-corrected visual acuity were measured in both eyes with Humphrey Automated Refractor/Keratometer at baseline and 5-year follow-up. Distance corrected visual acuity was measured with built-in Snellen charts, ranging from 20/400 to 40/20. The values were transformed to LogMar for statistical analysis. Spherical equivalent was measured through the following calculation: spherical equivalent value plus half of the cylindrical power [3]. A short interview was conducted before the eye examination to assess a potential history of eye disease.

The WHO definition of VI was used to categorize visual acuity into no, mild, and moderate/severe vision impairment groups.

Quality of life and socioeconomic status

Vision-related quality of life was assessed using the NEI-VFQ-25 questionnaire [22]. The questionnaire was completed using both eyes and reading glasses if needed. Socioeconomic status was calculated according to Lampert and Kroll [23], this score consists of the following factors: highest education (school/vocational training), position in occupation, and income. With regard to occupation, participants were asked what occupation was currently held or, in the case of unemployment/retirement, what occupation was previously held. The survey also asked for a classification of the occupation into an occupational group (self-employed, academics in the liberal professions such as doctors, lawyers, officials, employees, trainees, or assisting family members). Regarding income, the survey asked about the households' net monthly income. The household size was considered and the net income was adjusted for the individual person. Status was defined as a socioeconomic status range between 3 (lowest) and 21 (highest) socioeconomic status [23].

Statistical analysis

A descriptive analysis was conducted and stratified by gender to examine potential gender differences at baseline time point. For categorical parameters, absolute and relative frequencies were computed. For continuous variables, mean and standard deviation were calculated for approximately normal-distributed data, otherwise median and interquartile range. We calculated the "visual functioning scale (VFS)" and "socioemotional scale (SES-VRQoL)". This is relevant to counteract limitations of the questionnaire (e.g. influenced by multidimensionality) [24]. Scales were based on Rasch-transformed individual-level NEI-VFQ-25 data, as used in several other studies [25, 26]. The questionnaire is composed of 25 questions and includes 12 subscales: general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The VFS and SES-VRQoL were calculated based on the principal component analysis approach of Pseudovs. et al. [24]. Both scales were then converted to a 0–100 point scale, where 0 represents the sum a participant would achieve if all items were answered with the worst possible performance, and 100 represents the sum for the best possible performance. This conversion to a 0–100 scale was done to ensure comparability with other studies.

We investigated the factors associated with changes in the VFS over a five-year period. The analysis included several independent variables, namely gender (reference: male participants), age, baseline VFS, socioeconomic status, and visual acuity in both the better- and worse-seeing eye. Both univariable and multivariable linear regression models were employed to assess how each factor is related to changes in VFS, both individually and while controlling for other variables.

In a separate linear regression analysis, the same independent variables were used to examine their influence on changes in the SES-VRQoL.

We created additional models with stratification by age group (<65 years versus ≥ 65 years). Finally, the models were calculated separated for women and men to examine gender-related differences and additionally a gender specific interaction analysis was conducted.

Data were processed with the statistical program R (version: 4.0.3 (2020–10-10)).

Results

The mean age of the study population was 54.2 ± 10.8 years at baseline, and 49.2% were female (Table 1). VFS was slightly higher in men than in women at baseline (89.59 vs. 89.56).

During the 5 years, visual acuity decreased by 0.05 LogMAR in women and by 0.03 LogMAR in men. VFS decreased more in women (−1.3) than in men (−0.9; $p = 0.05$) (Fig. 1a). SES-VRQoL scores changed barely over 5 years for both men and women (Fig. 1b). Socioeconomic status decreased overall by −0.19 (SD: 1.93), and decreased significantly more for women (−0.26 (SD: 1.96) vs. −0.12 (SD: 1.90)). Over the period from baseline to the five-year follow-up, the number of eyes with VI increased (Table S1).

Figure 2 shows the change in VFS over five years for participants with no VI at baseline. In participants with no VI over time, VFS decreased slightly, while a change from no VI at baseline to mild VI at a 5-year follow-up was associated with a more significant decrease in VFS, which was even more pronounced with a change from no VI at baseline to moderate/severe VI over the 5 years.

Table 2 illustrates how changes in VI status over five years influence the VFS scores of the study participants. Specifically, it categorizes individuals based on their VI status in the better-seeing eye at baseline and at the five-year follow-up. The table shows how VFS scores change depending on whether participants' vision remained stable, improved, or worsened over this period. Participants who consistently had no VI in the better-seeing eye over 5 years showed a slight worsening of VFS over five years by −1.08 VFS score points. Moreover, those with no VI in the better-seeing eye at baseline and a change to mild or moderate VI at 5-year follow-up had decreasing VFS scores.

Table 1 Participants' characteristics (*N* = 10,152, baseline) and quality of life parameters. Data from the German population-based Gutenberg Health Study (2007–2012)

	Overall	Men	Women
	10,152	5161	4991
Age [y], mean (SD)	54.2 (10.8)	54.5 (10.9)	53.8 (10.7)
Age categories, n (%)			
35–44	2349 (23.1)	1144 (22.2)	1205 (24.1)
45–54	2863 (28.2)	1438 (27.9)	1425 (28.6)
55–64	2734 (26.9)	1386 (26.9)	1348 (27.0)
65–74	2206 (21.7)	1193 (23.1)	1013 (20.3)
Ophthalmic parameters			
Visual acuity [logMar], better eye, mean (SD)	0.03 (0.09)	0.02 (0.09)	0.04 (0.09)
Visual acuity [logMar], worse eye, mean (SD)	0.11 (0.22)	0.10 (0.22)	0.12 (0.22)
Spherical equivalent [diopters], right eye, mean (SD)	−0.50 (2.49)	−0.53 (2.42)	−0.47 (2.57)
Spherical equivalent [diopters], left eye, mean (SD)	−0.49 (2.50)	−0.53 (2.45)	−0.45 (2.55)
Glaucoma (ISGEO definition), n (%)	72 (0.9)	41 (1.0)	31 (0.8)
History of eye surgery, n (%)	692 (6.8)	326 (6.3)	366 (7.3)
General health and socioeconomic status			
Arterial hypertension, n (%)	4792 (47.2)	2719 (52.7)	2073 (41.6)
BMI [kg/m^2], mean (SD)	27.1 (4.8)	27.7 (4.2)	26.4 (5.3)
Socioeconomic status, mean (SD)	13.5 (4.3)	14.2 (4.4)	12.7 (4.1)
Vision-related quality of life			
Visual functioning scale, median [IQR]	89.57 [81.30, 95.10]	89.59 [84.02, 95.10]	89.56 [81.25, 94.49]
Socioemotional scale, median [IQR]	100 [95.07, 100.00]	100 [94.62, 100.00]	100 [95.07, 100.00]

y years, *SD* standard deviation

Participants whose vision worsened from mild VI at baseline to moderate/severe VI at follow-up experienced a small improvement in VFS scores (+0.83 points). Study participants with improvement in VI categories in the better-seeing eye showed improvement in VFS scores. Participants who initially had moderate/severe VI in the better-seeing eye at baseline and an improvement to no VI at 5-year follow-up showed an increase in VFS scores of 14.8 points (Table 2), however, this VI change in the better-seeing eye was only the case in 9 participants. Supplemental Fig. 1 demonstrates the change in visual acuity (LogMAR) and the change in the VFS over five years for the better-seeing eye (a) and the worse-seeing eye (b). In both cases, a negative association is evident, indicating that a decline in visual acuity corresponds with a decrease in VFS. Outliers (1.31%, *n* = 118) were identified, showing no visual acuity decline greater than 0.1 LogMAR in either eye over five years, a change not considered clinically relevant [27], yet experiencing a high deterioration in VFS of more than 15 points, which normally corresponds with a significant decline in visual acutiy [28]. At baseline, this group reported better general health, but a significantly worse general health status was observed at follow-up. Additionally, the group was significantly younger, had a higher proportion of female participants, and showed a greater decline in SES-VRQoL (Suppl. Table 2).

Linear regression analysis

Gender and age were associated with VFS change, with a higher VFS reduction in female participants compared to male participants (Table 3). Baseline socioeconomic status was associated with change in VFS but change in socioeconomic status was not associated with change in VFS.

The baseline visual acuity in the better-seeing and worse-seeing eye, both were univariable positively associated with VFS change over 5 years due to collinearity with lower VFS at baseline. In the multivariable regression model, there was a negative association for the change of VFS with associated with the change of visual acuity in the better- and worse-seeing eye over 5 years.

Additionally, associations between the change of SES-VRQoL with visual acuity (baseline/change) and socioeconomic status (baseline/change) were evaluated in multivariable regression analysis (Table 4). Female gender and age were not associated with the SES-VRQoL. Baseline socioeconomic status was positively associated with the change in SES-VRQoL scores, while change in socioeconomic status over 5 years was not associated in the multivariable model. Baseline and changes in visual acuity were associated with a reduction in SES-VRQoL scores over 5 years.

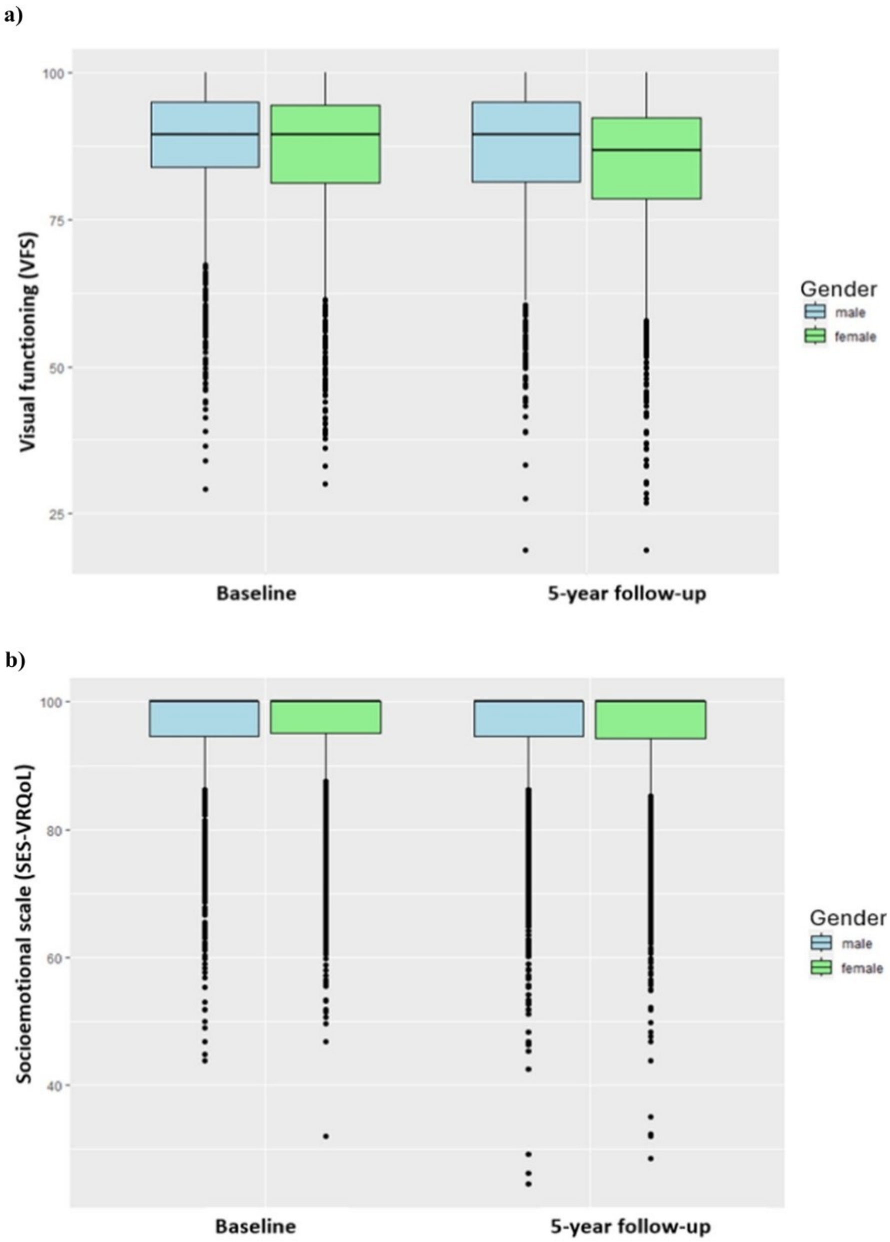

Fig. 1 **a** Visual functioning scale (VFS) at baseline and 5-year follow-up stratified by gender and **b**) socioemotional scale (SES-VRQoL) at baseline and 5-year follow-up stratified by gender. Data from the German population-based Gutenberg Health Study (2007–2017)

We additionally stratified the regression models for patients under 65 years of age and participants 65 years and older in two subgroups. Regarding the change in VFS, in both age groups, the visual acuity in the better-/worse-seeing eye was associated with a change in VFS.

The impact of changes in visual acuity on the VFS change was higher in the older age group: a greater reduction in VFS over 5 years due to change in visual acuity was observed for the better- and worse-seeing eye. Baseline socioeconomic status was only associated in the younger group, while change in socioeconomic status was not associated with VFS change (Suppl. Table 3a and Suppl. Table 3b).

Moreover, we stratified the regression models for female and male participants. Female participants showed a greater decrease in VFS scores over 5 years associated with visual acuity change. An association between baseline visual acuity in the worse-seeing eye and change in VFS was also related to female and male participants (Suppl. Table 4a and Suppl. Table 4b). Furthermore, we analyzed the potential interaction between gender and VFS change over 5 years.

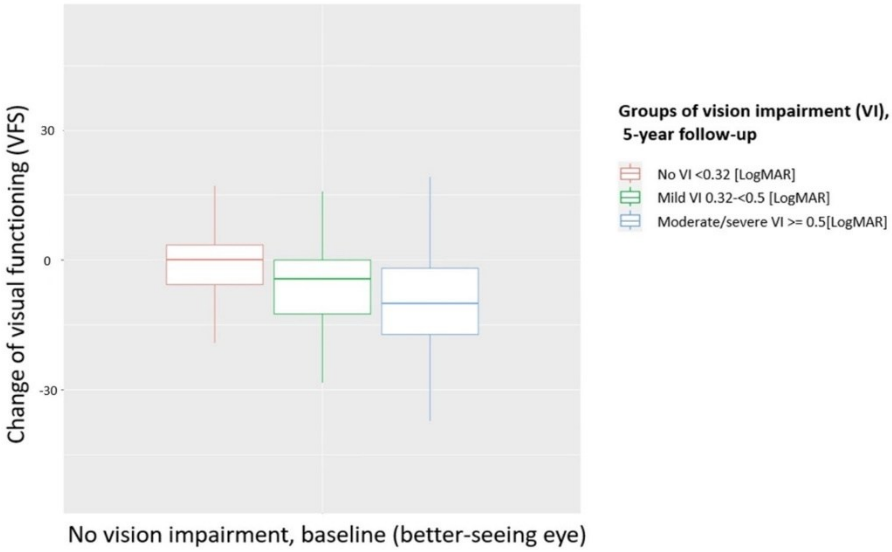

Fig. 2 Change of visual functioning scale (VFS) over 5 years with no vision impairment at baseline (better-seeing eye, (n=9,875)). Grouped into the follow-up vision impairment groups of the better-seeing eye (no (n=8,997), mild (n=83), and moderate/severe (n=51)). Results from the population-based Gutenberg Health Study (2007–2017)

Table 2 Change of NEI-VFQ-25 visual functioning scale (VFS) scores by categories of vision impairment (VI) at baseline and 5-year follow-up (better-seeing eye) of the German population-based Gutenberg Health Study (GHS), time frame of 2007–2017

	Better-seeing eye, 5-year follow-up			
	Change of VFS over 5 years	No VI (n = 8,997)	Mild VI (n = 83)	Moderate/severe VI (n = 51)
Better-seeing eye, Baseline	No VI (n = 9,875)	−1.08 points	−5.17 points	−8.96 points
	Mild VI (n = 28)	+14.79 points	−5.53 points	+0.83 points
	Moderate/severe VI (n = 32)	+14.76 points	+4.72 points	−5.45 points

VFS visual functioning scale

Table 3 Association analysis between gender, age, visual acuity (in the better-/worse-seeing eye) and socioeconomic status with the change in the visual functioning scale (VFS) over 5 years. Data from the German population-based Gutenberg Health Study (2007–2017)

	Univariable			Multivariable		
Dependent variable: Change of VFS	B	95%-CI	p-value	B	95%-CI	p-value
Gender, female						
Baseline	−0.37	[−0.74–0.01]	0.05	−1.00	[−1.35- −0.64]	<0.001
Age						
Baseline	0.07	[0.05–0.09]	<0.001	0.03	[0.01–0.05]	0.002
VFS						
Baseline	−0.41	[−0.43- −0.40]	<0.001	−0.45	[−0.47- −0.43]	<0.001
Socioeconomic status						
Baseline	−0.01	[−0.06–0.03]	0.56	0.07	[0.03–0.11]	0.001
5-year change	−0.20	[−0.30- −0.11]	<0.001	−0.06	[−0.15–0.03]	0.22
Visual acuity, better-seeing eye						
Baseline	11.30	[9.22–13.39]	<0.001	−3.16	[−5.69- −0.63]	0.01
5-year change	−5.97	[−7.21–4.72]	<0.001	−5.41	[−6.69- −4.13]	<0.001
Visual acuity, worse-seeing eye						
Baseline	3.22	[2.38–4.05]	<0.001	−3.41	[−4.52- −2.29]	<0.001
5-year change	−10.88	[−12.53- −9.23]	<0.001	−7.35	[−9.18- −5.52]	<0.001

VFS Visual functioning scale; reference group for gender is male participants

Table 4 Association analysis between gender, age, visual acuity (in the better-/worse-seeing eye) and socioeconomic status with a change in socioemotional scale (SES-VRQoL) over 5 years. Data from the German population-based Gutenberg Health Study (2007–2017)

	Univariable			Multivariable		
Dependent variable: Change of SES-VRQoL	B	95%-CI	p-value	B	95%-CI	p-value
Gender, female						
Baseline	−0.24	[−0.51–0.04]	0.09	0.04	[−0.22–0.30]	0.77
Age						
Baseline	−0.01	[−0.02–0.01	0.31	−0.01	[−0.02–0.01]	0.31
SES-VRQoL						
Baseline	0.06	[0.03–0.09]	<0.001	−0.48	[−0.50- −0.46]	<0.001
Socioeconomic status						
Baseline	0.06	[0.03–0.09]	<0.001	0.06	[0.03–0.10]	<0.001
5-year change	−0.08	[−0.15- −0.01]	0.02	−0.03	[−0.10–0.04]	0.43
Visual acuity, better-seeing eye						
Baseline	−0.46	[−2.03–1.11]	0.56	−7.21	[−9.08- −5.35]	<0.001
5-year change	−3.96	[−4.92- −3.00]	<0.001	−4.15	[−5.14- −3.16	<0.001
Visual acuity, worse-seeing eye						
Baseline	0.70	[0.06–1.33]	0.03	−1.41	[−2.24–0.58]	<0.001
5-year change	−5.38	[−6.61- −4.16]	<0.001	−3.75	[−5.11- −2.39]	<0.001

SES-VRQoL socioemotional scale; reference category for gender is male participants

Univariable analyses showed an association between the interaction factor of gender and 5-year change in visual acuity in the better-seeing and worse-seeing eyes with respect to change in VFS over 5 years ($p < 0.001$), while not in the multivariable model (Suppl. Table 5).

Discussion

This study investigated VFS and SES-VRQoL change over 5 years and its association concerning age, gender, changes in socioeconomic status, and changes in visual acuity in the better- and worse-seeing eye. Participants who improved from moderate/severe VI to no VI over the 5-year period experienced a substantial improvement in VFS scores (+ 14.76 points). Moreover, the descriptive results demonstrated a small improvement in VFS scores (+ 0.83 points) in participants whose vision worsened from mild VI at baseline to moderate/severe VI in the better-seeing eye at the 5-year follow-up. This finding is unexpected, but it may be explained by psychological adjustment to VI [29]. As participants adjust to their condition over time, their perceived quality of life may stabilize or even improve, despite the objective worsening of their vision. Due to the small number of participants ($n = 4$), this result should be interpreted with caution.

The results demonstrated that changes in visual acuity were associated with VFS change with a higher decrease in older participants and female participants. In general, individuals aged 65 years or older had a smaller decline in VFS over 5 years. This can be explained by the fact that participants of higher age may already have had a decline in VFS in the previous years, which means that it is now less pronounced. Higher baseline socioeconomic status led to a slight positive change in VFS. In the multivariable regression analysis, an association was found regarding visual acuity: a lower baseline visual acuity leads to lower VFS. Moreover, there was a negative association between change in visual acuity in the better- and worse-seeing eye with VFS change. Female participants showed a more significant decrease in VFS scores over 5 years associated with visual acuity change. Socioeconomic status at baseline was positively associated with SES-VRQoL change, but change in socioeconomic status was not associated with SES-VRQoL change over 5 years. Visual acuity in the better-seeing eye at baseline was accompanied by an increase in SES-VRQoL over 5 years. Change in visual acuity in the better- and worse-seeing eye over 5 years was associated with change in SES-VRQoL. Age and gender were not associated with SES-VRQoL change.

A population-based study showed a VFS value of 88.5 for men and 88.1 for women (adjusted for age), in our study the values are slightly higher with 89.59 for men and 89.56 for women at baseline [30]. The findings of this study regarding the change in VFS and change in visual acuity are like those of a longitudinal study examining VFS change over 4 years. The authors reported that decreased visual acuity is associated with decreased VRQoL [19]. The Submacular Surgery Trials Research Group said that NEI-VFQ scores were sensitive to changes in visual acuity (over 2 years).

The study demonstrated that a 4-point change in the overall NEI-VFQ score was assessed to be the minimal clinically important difference (MCID) [31]. Several other clinical and population-based studies demonstrated that a decrease in visual acuity or VI leads to changes in VRQoL [1, 4, 32, 33]. In our analysis over 5 years, the change in visual acuity of the worse-seeing eye resulted in a slightly more significant reduction in VRQoL than that of the better-seeing eye. VFS decreased by seven score points in the worse-seeing eye over 5 years per 1 LogMar; while in the group of persons 65 years and older, the reduction in the worse-seeing eye was −13.24.

Cross-sectional studies have reported an association between older age and reduced VRQoL [8]. Our study also indicated that in individuals 65 years of age or older, the reduction in VFS scores due to a change in visual acuity was higher than that in individuals aged < 65 years. In general, the decline in VI is part of the aging process, accompanied by several factors leading to lower visual functioning. Projection of light onto the retina changes with age: biochemical processes alter the cornea, lens opacity, and the ability to accommodate. Furthermore, sensory information processing is impaired. For example, the number of neurons in the ganglion cell layer of the retina and the number of rods in parafoveal vision decrease [34]. Some studies have shown that the typical age-related changes limit mobility and consequently have a negative impact on the quality of life [35–37].

Our findings demonstrate an association between gender and change in VFS. Other studies have also found that female participants were associated with lower VRQoL [38, 39]. There may be several reasons for this finding. One reason could be that women generally have a higher risk of VI in all age groups compared to men [40–42]. Inequalities in diagnosing and treating ophthalmic diseases could be an underlying reason for this. A study in Spain showed that women are less able to pay for private services and, thus, must wait longer for treatment [43]. Biological differences may also be a relevant factor: sex hormones, e.g. due to menopause, may play a role in the prevalence of diseases in ophthalmology, such as glaucoma and age-related macular degeneration [44]. Some mental disorders are more common in women, like depression [45]. This could also be a reason, as they lead to lower self-care, making doctor visits more difficult [46].

Several cross-sectional studies have reported an association between low socioeconomic status and lower VRQoL [20, 47, 48]. This could be based on the fact that a higher level of education leads to a better understanding of eye diseases, earlier consultation of an ophthalmologist in case of symptoms, and different psychological handling of a limitation in vision due to a better understanding [49, 50]. Thus, prevention programs should reach especially people with lower socioeconomic status, which now is the opposite. This is because people with higher educational background tend to think more about their health and, therefore, attend prevention programs more likely [51]. Our study also indicated a slight improvement in VFS and SES-VRQoL scores over 5 years due to a higher socioeconomic status at baseline. Furthermore, an association is also possible, because two integral dimensions of the questionnaire are mental health and social functioning; both dimensions have been associated with socioeconomic status in the past [52–54].

In a clinical setting, the NEI-VFQ-25 questionnaire could be an appropriate method for assessing the success of treatment and surgical interventions. Patients after cataract surgery showed significant improvements of VRQoL [55, 56].

Strengths and limitations

This study analyzed data from a large population-based representative sample. The GHS is one of the first studies to investigate the change in VRQoL using Rasch-transformed data derived from the NEI-VFQ-25 questionnaire. While previous studies have examined these relationships, the added value of our research lies in its longitudinal design in a large cohort, which tracks changes over a 5-year period. However, our study has some limitations that need to be considered. First, the GHS subjects mainly consist of Caucasian origin. Therefore, the results cannot be generalized to other ethnicities. Second, we utilized a conventional Rasch-based scoring method for the NEI VFQ-25 in this study. The recently developed NEI VFQ-25C approach by Goldstein et al. [57], which applies advanced Rasch analysis for improved precision and comparability in a unidimensional scale, could provide additional insights and is worth considering in future studies. Unfortunately, this approach was not feasible in our study, as not all questions required for the NEI VFQ-25C scoring were included in our questionnaire. Third, the number of subjects with VI in the general population is relatively low. Thus, the results show the change on a population-based level rather than in a clinical setting.

Conclusion

This study supports existing research on the association between visual acuity and VRQoL, with a more pronounced decline observed in females and participants aged 65 years and older. Importantly, by employing a longitudinal approach over a 5-year period, our findings add new insights to the existing body of literature, highlighting the significant impact of both the better-seeing and worse-seeing eyes on changes in VRQoL.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00417-025-06741-9.

Funding Open Access funding enabled and organized by Projekt DEAL. The Gutenberg Health Study is funded through the government of Rhineland-Palatinate („Stiftung Rheinland-Pfalz für Innovation ", contract AZ 961–386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study.

Declarations

Ethical approval The Gutenberg Health Study was conducted according to the principles of "Good Clinical Practice," the "Good Epidemiological Practice," and the Declaration of Helsinki. All participants gave their written informed consent to participation. The Medical Ethics Commission of Rhineland-Palatinate and local and Gutenberg-University of Mainz data protection officials reviewed and approved the study (ethics committee review number 837.020.07(5555)).

Conflict of interest All authors: The Gutenberg Health Study is funded through the Government of Rhineland-Palatinate („Stiftung Rheinland-Pfalz für Innovation ", contract AZ 961–386261/733), the research programs "Wissen schafft Zukunft" and "Center for Translational Vascular Biology (CTVB)" of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and PHILIPS Medical Systems, including an unrestricted grant for the Gutenberg Health Study.
Schuster AK holds the professorship for ophthalmic healthcare research endowed by „Stiftung Auge " and financed by „Deutsche Ophthalmologische Gesellschaft " and „Berufsverband der Augenärzte Deutschlands e.V." Schuster AK received financial and research support by Abbvie, Apellis, Bayer Vital, Heidelberg Engineering, Novartis, Santen.
Wild PS is funded by the Federal Ministry of Education and Research (BMBF 01EO1503) and he and Münzel T are PI of the German Center for Cardiovascular Research (DZHK). Wild PS is principal investigator of the DIASyM research core (BMBF 161L0219).
Pfeiffer N receives financial support by Novartis, Ivantis, Santen, Thea, Boehringer Ingelheim Deutschland GmbH & Co. KG, Alcon, Sanoculis.
Schattenberg JM consulted with Apollo Endosurgery, Bayer, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers. Research Funding: Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH.
Singer S received honoraria from Lilly for the review of papers submitted to their quality-of-life-prize.
The remaining authors report no conflict of interest.

References

1. Yibekal BT, Alemu DS, Anbesse DH et al (2020) Vision-related quality of life among adult patients with visual impairment at University of Gondar, Northwest Ethiopia. J Ophthalmol 2020:9056097. https://doi.org/10.1155/2020/9056097
2. Panigrahi A, Nageswar Rao G, KumariKonar A (2021) Vision-related quality of life and its sociodemographic correlates among individuals with visual impairments. J Vis Impair Blindness 115:319–328. https://doi.org/10.1177/0145482x211028938
3. Nickels S, Schuster AK, Elflein H et al (2019) Vision-related quality of life considering both eyes: results from the German population-based Gutenberg Health Study (GHS). Health Qual Life Outcomes 17:98. https://doi.org/10.1186/s12955-019-1158-1
4. Adigun K, Oluleye TS, Ladipo MM et al (2014) Quality of life in patients with visual impairment in Ibadan: a clinical study in primary care. J Multidiscip Healthc 7:173–178. https://doi.org/10.2147/jmdh.S51359
5. Finger RP, Fenwick E, Marella M et al (2011) The impact of vision impairment on vision-specific quality of life in Germany. Invest Ophthalmol Vis Sci 52:3613–3619. https://doi.org/10.1167/iovs.10-7127
6. Parrish RK II, Gedde SJ, Scott IU et al (1997) Visual function and quality of life among patients with glaucoma. Arch Ophthalmol 115:1447–1455. https://doi.org/10.1001/archopht.1997.01100160617016
7. Frost A, Eachus J, Sparrow J et al (2001) Vision-related quality of life impairment in an elderly UK population: associations with age, sex, social class and material deprivation. Eye (Lond) 15:739–744. https://doi.org/10.1038/eye.2001.241
8. Man REK, Gan ATL, Fenwick EK et al (2021) The differential impact of age on vision-related quality of life across the visual impairment spectrum. Ophthalmology 128:354–363. https://doi.org/10.1016/j.ophtha.2020.07.046
9. Bertelmann T, Feltgen N, Scheffler M et al (2016) Vision-related quality of life in patients receiving intravitreal ranibizumab injections in routine clinical practice: baseline data from the German OCEAN study. Health Qual Life Outcomes 14:132. https://doi.org/10.1186/s12955-016-0536-1
10. Nickels S, Schuster AK, Singer S et al (2017) The National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) - reference data from the German population-based Gutenberg Health Study (GHS). Health Qual Life Outcomes 15:156. https://doi.org/10.1186/s12955-017-0732-7
11. Hajian-Tilaki K, Heidari B, Hajian-Tilaki A (2017) Are gender differences in health-related quality of life attributable to sociodemographic characteristics and chronic disease conditions in elderly people? Int J Prev Med 8:95. https://doi.org/10.4103/ijpvm.IJPVM_197_16
12. Gallicchio L, Hoffman SC, Helzlsouer KJ (2007) The relationship between gender, social support, and health-related quality of life in a community-based study in Washington County, Maryland. Qual Life Res 16:777–786. https://doi.org/10.1007/s11136-006-9162-4
13. Cherepanov D, Palta M, Fryback DG et al (2010) Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. Qual Life Res 19:1115–1124. https://doi.org/10.1007/s11136-010-9673-x
14. Jörngården A, Wettergen L, von Essen L (2006) Measuring health-related quality of life in adolescents and young adults: Swedish normative data for the SF-36 and the HADS, and the influence

of age, gender, and method of administration. Health Qual Life Outcomes 4:91. https://doi.org/10.1186/1477-7525-4-91
15. Courtright P (2009) Gender and blindness: Taking a global and a local perspective. Oman J Ophthalmol 2:55–56. https://doi.org/10.4103/0974-620x.53032
16. Fang R, Yu Y-F, Li E-J et al (2022) Global, regional, national burden and gender disparity of cataract: findings from the global burden of disease study 2019. BMC Public Health 22:2068. https://doi.org/10.1186/s12889-022-14491-0
17. Barsky AJ, Peekna HM, Borus JF (2001) Somatic symptom reporting in women and men. J Gen Intern Med 16:266–275. https://doi.org/10.1046/j.1525-1497.2001.00229.x
18. Harutyunyan T, Giloyan A, Petrosyan V (2017) Factors associated with vision-related quality of life among the adult population living in Nagorno Karabagh. Public Health 153:137–146. https://doi.org/10.1016/j.puhe.2017.09.004
19. McKean-Cowdin R, Varma R, Hays RD et al (2010) Longitudinal changes in visual acuity and health-related quality of life: the Los Angeles Latino Eye study. Ophthalmology 117:1900–1907, 1907.e1901. https://doi.org/10.1016/j.ophtha.2010.01.059
20. Kuo YS, Liu CJ, Cheng HC et al (2017) Impact of socioeconomic status on vision-related quality of life in primary open-angle glaucoma. Eye (Lond) 31:1480–1487. https://doi.org/10.1038/eye.2017.99
21. Chatziralli IP, Sergentanis TN, Peponis VG et al (2013) Risk factors for poor vision-related quality of life among cataract patients. Evaluation of baseline data. Graefes Arch Clin Exp Ophthalmol 251:783–789. https://doi.org/10.1007/s00417-012-2194-2
22. Mangione CM, Lee PP, Gutierrez PR et al (2001) Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 119:1050–1058. https://doi.org/10.1001/archopht.119.7.1050
23. Lampert T, Kroll LE (2009) Die Messung des sozioökonomischen Status in sozialepidemiologischen Studien. In: Richter M, Hurrelmann K (eds) Gesundheitliche Ungleichheit: Grundlagen, Probleme, Perspektiven. VS Verlag für Sozialwissenschaften, Wiesbaden, pp 309–334
24. Pesudovs K, Gothwal VK, Wright T et al (2010) Remediating serious flaws in the National Eye Institute Visual Function Questionnaire. J Cataract Refract Surg 36:718–732. https://doi.org/10.1016/j.jcrs.2009.11.019
25. Dougherty BE, Bullimore MA (2010) Comparison of scoring approaches for the NEI VFQ-25 in low vision. Optom Vis Sci 87:543–548. https://doi.org/10.1097/OPX.0b013e3181e61bd8
26. Petrillo J, Cano SJ, McLeod LD et al (2015) Using classical test theory, item response theory, and Rasch measurement theory to evaluate patient-reported outcome measures: a comparison of worked examples. Value Health 18:25–34. https://doi.org/10.1016/j.jval.2014.10.005
27. Rosser DA, Cousens SN, Murdoch IE et al (2003) How sensitive to clinical change are ETDRS logMAR visual acuity measurements? Invest Ophthalmol Vis Sci 44:3278–3281. https://doi.org/10.1167/iovs.02-1100
28. Coleman AL, Yu F, Ensrud KE et al (2010) Impact of age-related macular degeneration on vision-specific quality of life: Follow-up from the 10-year and 15-year visits of the Study of Osteoporotic Fractures. Am J Ophthalmol 150:683–691. https://doi.org/10.1016/j.ajo.2010.05.030
29. Bergeron CM, Wanet-Defalque M-C (2013) Psychological adaptation to visual impairment: The traditional grief process revised. Br J Vis Impair 31:20–31. https://doi.org/10.1177/0264619612469371
30. Chia E-M, Mitchell P, Ojaimi E et al (2006) Assessment of vision-related quality of life in an older population subsample: The Blue Mountains Eye Study. Ophthalmic Epidemiol 13:371–377. https://doi.org/10.1080/09286580600864794
31. Submacular Surgery Trials Research Group (2007) Evaluation of minimum clinically meaningful changes in scores on the national eye institute visual function questionnaire (NEI-VFQ) SST report number 19. Ophthalmic Epidemiol 14:205–215. https://doi.org/10.1080/09286580701502970
32. Sugar EA, Venugopal V, Thorne JE et al (2017) Longitudinal vision-related quality of life for patients with noninfectious uveitis treated with fluocinolone acetonide implant or systemic corticosteroid therapy. Ophthalmology 124:1662–1669. https://doi.org/10.1016/j.ophtha.2017.05.015
33. Varma R, Wu J, Chong K et al (2006) Impact of severity and bilaterality of visual impairment on health-related quality of life. Ophthalmology 113:1846–1853. https://doi.org/10.1016/j.ophtha.2006.04.028
34. Andersen GJ (2012) Aging and vision: changes in function and performance from optics to perception. Wiley Interdiscip Rev Cogn Sci 3:403–410. https://doi.org/10.1002/wcs.1167
35. Wahl H-W, Schilling O, Oswald F et al (1999) Psychosocial consequences of age-related visual impairment: Comparison with mobility-impaired older adults and long-term outcome. J Gerontol: Ser B 54B:P304–P316. https://doi.org/10.1093/geronb/54B.5.P304
36. Wahl HW, Heyl V, Oswald F et al (1998) Deteriorating vision in the elderly: double stress? Ophthalmologe 95:389–399. https://doi.org/10.1007/s003470050286
37. Bergholz R, Dutescu RM, Steinhagen-Thiessen E et al (2019) Ophthalmologic health status of an aging population-data from the Berlin Aging Study II (BASE-II). Graefes Arch Clin Exp Ophthalmol 257:1981–1988. https://doi.org/10.1007/s00417-019-04386-z
38. Rausch-Koster PT, Rennert KN, Heymans MW et al (2022) Predictors of vision-related quality of life in patients with macular oedema receiving intra-vitreal anti-VEGF treatment. Ophthalmic Physiol Opt 42:849–857. https://doi.org/10.1111/opo.12984
39. Sturrock BA, Xie J, Holloway EE et al (2015) The influence of coping on vision-related quality of life in patients with low vision: a prospective longitudinal study. Invest Ophthalmol Vis Sci 56:2416–2422. https://doi.org/10.1167/iovs.14-16223
40. Evans JR, Fletcher AE, Wormald RPL et al (2002) Prevalence of visual impairment in people aged 75 years and older in Britain: results from the MRC trial of assessment and management of older people in the community. Br J Ophthalmol 86:795–800. https://doi.org/10.1136/bjo.86.7.795
41. Abou-Gareeb I, Lewallen S, Bassett K et al (2001) Gender and blindness: a meta-analysis of population-based prevalence surveys. Ophthalmic Epidemiol 8:39–56. https://doi.org/10.1076/opep.8.1.39.1540
42. Rius Ulldemolins A, Benach J, Guisasola L et al (2018) Why are there gender inequalities in visual impairment? Eur J Pub Health 29:661–666. https://doi.org/10.1093/eurpub/cky245
43. García-Corchero JD, Jiménez-Rubio D (2022) Waiting times in healthcare: equal treatment for equal need?. Int J Equity Health 21:184. https://doi.org/10.1186/s12939-022-01799-x
44. Korpole NR, Kurada P, Korpole MR (2022) Gender difference in ocular diseases, risk factors and management with specific reference to role of sex steroid hormones. J Midlife Health 13:20–25. https://doi.org/10.4103/jmh.jmh_28_22
45. Salk RH, Hyde JS, Abramson LY (2017) Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. Psychol Bull 143(8):783–822. https://doi.org/10.1037/bul0000102
46. Chen C, Chen Y, Huang Q et al (2022) Self-care ability of patients with severe mental disorders: based on community patients investigation in Beijing, China. Front Public Health 10:847098. https://doi.org/10.3389/fpubh.2022.847098
47. Habsyiyah H, Lestari D, Ariawan I et al (2015) Relationship of socioeconomic factors with vision-related quality of life on severe

low vision and blind population in Indonesia. Med J Indones 24:245. https://doi.org/10.13181/mji.v24i4.1245
48. Nutheti R, Shamanna BR, Nirmalan PK et al (2006) Impact of impaired vision and eye disease on quality of life in Andhra Pradesh. Invest Ophthalmol Vis Sci 47:4742–4748. https://doi.org/10.1167/iovs.06-0020
49. Levinger N, Beykin G, Grunin M et al (2021) Socioeconomic status and visual outcome in patients with neovascular age-related macular degeneration. Eur J Ophthalmol 31:1094–1100. https://doi.org/10.1177/1120672120920783
50. Nesemann JM, Morocho-Alburqueque N, Quincho-Lopez A et al (2023) Association of vision impairment and blindness with socioeconomic status in adults 50 years and older from Alto Amazonas, Peru. Eye 37:434–439. https://doi.org/10.1038/s41433-021-01870-x
51. Pampel FC, Krueger PM, Denney JT (2010) Socioeconomic disparities in health behaviors. Annu Rev Sociol 36:349–370. https://doi.org/10.1146/annurev.soc.012809.102529
52. Zhang Y, Su D, Chen Y et al (2022) Effect of socioeconomic status on the physical and mental health of the elderly: the mediating effect of social participation. BMC Public Health 22:605. https://doi.org/10.1186/s12889-022-13062-7
53. Li J, Wang J, Li JY et al (2020) How do socioeconomic status relate to social relationships among adolescents: a school-based study in East China. BMC Pediatr 20:271. https://doi.org/10.1186/s12887-020-02175-w
54. Reiss F, Meyrose AK, Otto C et al (2019) Socioeconomic status, stressful life situations and mental health problems in children and adolescents: Results of the German BELLA cohort-study. PLoS One 14:e0213700. https://doi.org/10.1371/journal.pone.0213700
55. Miura G, Baba T, Tatsumi T et al (2021) Effects of cataract surgery on vision-related quality of life in patients with retinitis pigmentosa and the predictive factors of quality of life improvement. Biomed Res Int 2021:3846867. https://doi.org/10.1155/2021/3846867
56. Javed U, McVeigh K, Scott NW et al (2015) Cataract extraction and patient vision-related quality of life: a cohort study. Eye 29:921–925. https://doi.org/10.1038/eye.2015.70
57. Goldstein JE, Bradley C, Gross AL et al (2022) The NEI VFQ-25C: Calibrating items in the National Eye Institute Visual Function Questionnaire-25 to enable comparison of outcome measures. Transl Vis Sci Technol 11:10. https://doi.org/10.1167/tvst.11.5.10

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4.7 Publikation VII

Hartmann A, Bertram B, Siebelmann S, Böhm M, Faber H, Zhour A, Schuster AK. Berufliche Zukunftsperspektive von Augenärzten unter 49 Jahren**.** Eine Umfrage in Deutschland aus dem Jahr 2022. Die Ophthalmologie (2023): https://doi.org/10.1007/s00347-022-01806-0

Die Ophthalmologie
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Originalien

Ophthalmologie 2023 · 120:726–733
https://doi.org/10.1007/s00347-022-01806-0
Eingegangen: 7. November 2022
Überarbeitet: 22. Dezember 2022
Angenommen: 28. Dezember 2022
Online publiziert: 2. Februar 2023

Berufliche Zukunftsperspektive von Augenärzten unter 49 Jahren

Eine Umfrage in Deutschland aus dem Jahr 2022

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Hintergrund

Augenerkrankungen wie die altersassoziierte Makuladegeneration, die diabetische Retinopathie, das Glaukom und die Katarakt stellen häufige Augenerkrankungen dar und zeigen einen deutlichen Anstieg mit dem Alter. Folglich steigt die Anzahl an Personen mit Augenerkrankungen in Deutschland [5], und es ist von einem steigenden Versorgungsbedarf in der Augenheilkunde auszugehen [6]. Laut einem Bericht der Bundesärztekammer lag die Anzahl der Augenärzte in Deutschland am 31.12.2021 bei 7974, größtenteils sind die Augenärzte im ambulanten Sektor tätig ($n = 6602$), insbesondere in der Niederlassung [2]. Insgesamt zeigt sich eine Zunahme an Augenärzten, jedoch nimmt die Versorgungskapazität nur im geringen Maße zu [10]. Die bedarfsgerechte Versorgung stellt weiterhin eine Herausforderung für die Augenheilkunde dar [3, 9].

Um die Fachdisziplin der Augenheilkunde weiterzuentwickeln und die Versorgung in der Bevölkerung perspektivisch zu sichern, haben junge Augenärzte eine wesentliche Bedeutung. Es wird angenommen, dass ca. 29 % der in der gesetzlichen Krankenversicherung (GKV) tätigen Augenärzte in den nächsten 5 Jahren das Rentenalter erreichen bzw. bereits erreicht haben [1]. Um diesen Punkt näher zu beleuchten, werden Daten einer Umfrage zur Zukunftsperspektive von Augenärzten unter 49 Jahren ausgewertet, hierunter zählen Fachärzte und Weiterbildungsassistenten der Augenheilkunde. Die derzeitige Beschäftigungsform und zukünftige berufliche Vorstellungen wie die gewünschte Beschäftigungsform, Tätigkeitsfelder im OP-Bereich, der Arbeitsumfang und Einstellungen zu spezifischen Aspekten der Augenheilkunde in Deutschland werden erfragt.

Material und Methoden

Wir werteten Daten einer Umfrage des Berufsverbands der Augenärzte Deutschlands e.V. aus, die unter seinen Mitgliedern, wie auch unter denen der Deutschen Ophthalmologischen Gesellschaft durchgeführt wurde. Alle Mitglieder bis 49 Jahre wurden mittels eines online-basierten Fragebogens in die Umfrage einbezogen (Zeitraum: 07.04.2022–15.05.2022). Die Ethikkommission der Landesärztekammer Rheinland-Pfalz stimmte der wissenschaftlichen Auswertung zu. Die Umfrage wurde mit einem sehr ähnlichen Fragenkatalog bereits im Jahr 2016 durchgeführt. Die erneute Erhebung sollte auch mögliche Unterschiede zwischen den Ansichten und Einstellungen sichtbar machen. Abgefragt wurden demografische Daten wie das Alter, Geschlecht und der derzeitige Ausbildungsstand (Weiterbildungsassistent, Facharzt, seit wann). Die derzeitige Beschäftigungsstelle (Wo arbeiten Sie derzeit?: Arzt in Universitäts-Augenklinik, Arzt in anderer Augenklinik, angestellter Arzt in Praxis, angestellter Arzt in medizinischem Versorgungszentrum [MVZ], selbstständiger Arzt in Praxis, in anderer ärztlicher Tätigkeit, nicht ärztlich berufstätig) sowie die gewünschte Beschäftigungsstelle in 10 Jahren wurden erfasst. Weiter wurde eine Befragung nach der derzeitigen operativen Tätigkeit und dem Operationsspektrum durchgeführt.

Statistische Analysen

Absolute und relative Häufigkeiten der Beschäftigungsstelle wurden für die Stichprobe, sowie stratifiziert für Geschlecht, Weiterbildungsassistent und Facharzt (seit 0 bis 5 Jahren, 6 bis 10 Jahren, >10 Jahren) berechnet. Die derzeitige berufliche Position der Fachärzte und der Berufswunsch in 10 Jahren wurden mittels Kreuztabellen gegenübergestellt wie auch die Tätigkeitsfelder. Ein möglicher statistischer signifikanter Unterschied der Antworten zwischen der ersten und zweiten Befragung wurde mittels des Pearson-Chi-Quadrat-Tests auf Unabhängigkeit ermittelt. Ein signifikanter Unterschied wurde bei einem p-Wert von $< 0{,}05$ angenommen. Alle Analysen wurden mit dem Softwarepaket R (R version 4.1.3 [2022-03-10], [8]) durchgeführt.

Zusammenfassung

Fragestellung: Der Versorgungsbedarf in der Augenheilkunde steigt durch eine Zunahme an Augenerkrankungen infolge des demografischen Wandels stetig an. Im Rahmen dieser Studie werden die derzeitige berufliche Situation und die Zukunftsperspektive von Augenärzten unter 49 Jahren analysiert und mit einer Erhebung vor 6 Jahren verglichen.
Methoden: Im Jahr 2022 wurde eine Umfrage unter Mitgliedern des Berufsverbandes der Augenärzte Deutschlands und der Deutschen Ophthalmologischen Gesellschaft durchgeführt. Alle Mitglieder unter 49 Jahren erhielten einen Online-Fragebogen zur aktuellen beruflichen Situation sowie der Zukunftsperspektive (gewünschte Arbeitszeit, Organisationsform). Verglichen werden die Ergebnisse mit einer Umfrage von 2016 des Berufsverbandes der Augenärzte Deutschlands.
Ergebnisse: Es nahmen insgesamt 1014 Personen an der Umfrage teil (62,7 % Frauen, mittleres Alter 39,3 ± 8 Jahre, 75,6 % Fachärzte). Die Rücklaufquote der Befragung lag bei 25 %. Bei einer Facharzttätigkeit von 0 bis 5 Jahren zeigte sich eine höhere Anzahl der angestellten Augenärzte (21 % selbstständig vs. 32 % angestellt), im Zeitverlauf nahm die Anzahl der selbstständigen Augenärzte zu (6 bis 10 Jahre: 40 %, > 10 Jahre: 59,3 %). Von den selbstständigen Fachärzten gaben 95,9 % an, in 10 Jahren in der gleichen Beschäftigungsform wie derzeit arbeiten zu wollen. Bezüglich der beruflichen Zukunft der Augenärzte zeigte sich bei den anderen Beschäftigungsformen der Wunsch, in eine selbstständige Praxis zu wechseln. Im Gegensatz zu der Umfrage von 2016 zeigten sich geschlechterspezifische Unterschiede bezogen auf die derzeitige Beschäftigungsform. Die Anzahl der selbstständigen Frauen sank von 43 % auf 26 %, die der selbstständigen Männer von 63 % auf 39 %, die Anzahl der Augenärzte in Medizinischen Versorgungszentren (MVZ) hat sich im Vergleich zum Jahr 2016 mehr als verdoppelt. Die Zukunftsperspektive wies ähnliche Vorstellungen und Wünsche zu beiden Befragungszeitpunkten auf.
Schlussfolgerung: Die Ergebnisse der Befragung der Augenärzte unter 49 Jahren in Deutschland zeigten ähnliche berufliche Vorstellungen wie im Jahr 2016 auf. Es wurde deutlich, dass der Wunsch nach einer selbstständigen Tätigkeit in 10 Jahren sehr hoch ist. Erwartet wird von den Augenärzten jedoch eine weitere Ausweitung von Großpraxen oder medizinischen Versorgungszentren, die diesem Wunsch entgegensteht. Die Zahl der selbstständigen Ärzte nimmt derzeit ab, und der Wunsch nach Selbstständigkeit ist nur schwer umsetzbar.

Schlüsselwörter
Augenheilkunde · Selbstständigkeit · Arbeitszeit · Geschlecht · Operationen

Ergebnisse

Es nahmen 1014 Personen (Frauen: 62,7 %, Männer: 37,1 %, diverse Personen: 0,2 %) an dieser Umfrage teil. Die Rücklaufquote der Befragung lag bei 25 %. Das mittlere Alter betrug 39,3 ± 8 Jahre; 767 (75,6 %) der Befragten waren Facharzt für Augenheilkunde, im Mittel seit 8,3 ± 5,0 Jahren. Die häufigste Beschäftigungsform der Augenärzte war die Selbstständigkeit oder die Beschäftigungsform als angestellter Augenarzt in einer Praxis. Mit Zunahme der Tätigkeitsdauer nahm die Anzahl der selbstständigen Augenärzte zu (6 bis 10 Jahre: 40 %, >10 Jahre: 59,3 %) und der Anteil der angestellten Augenärzte schrittweise ab. Dies war auch im Jahr 2016 der Fall. Jedoch waren in der Umfrage des Jahres 2016 mehr Ärzte in der Selbstständigkeit tätig als im Jahr 2022 (gesamt: 39,1 % [2022] vs. 60,6 % [2016]). Die Anzahl der angestellten Ärzte im MVZ hat sich im Vergleich zum Jahr 2016 mehr als verdoppelt (8,3 % zu 18,9 %) (**Tab. 1**).

Personen in der Facharztweiterbildung waren zu 35 % an einer Universitätsaugenklinik angestellt, zu 29 % in einer nicht-universitären Augenklinik, zu 13 % in einem medizinischen Versorgungszentrum und zu 20 % in einer Praxis angestellt, lediglich 3 % gaben andere Tätigkeiten an. Im Jahr 2016 zeigte sich ein sehr ähnliches Bild der derzeitigen Beschäftigungsform der Weiterbildungsassistenten.

Unterschiedliche Ergebnisse zeigten sich hinsichtlich der derzeitigen beruflichen Situation zwischen den Geschlechtern. Frauen sind häufiger in einer Anstellung tätig als Männer (46 % vs. 33 %), während Frauen seltener in einer selbstständigen Praxis arbeiten (26 % vs. 39 %). Vergleichsweise zu 2016 ist die Anzahl der selbstständigen Frauen gesunken. Im Jahr 2016 waren 43 % der Frauen selbstständig, und auch die Anzahl der selbstständig tätigen Männer sank von 63 % auf 39 %. Es zeigte sich zwischen den Geschlechtern ein signifikanter Unterschied der aktuellen Beschäftigungsform zwischen den beiden Umfragezeitpunkten (Chi-Quadrat-Test: $p < 0{,}05$).

Von den selbstständigen Fachärzten gaben 95,9 % an, in 10 Jahren in der gleichen Beschäftigungsform wie derzeit ar-

Tab. 1 Derzeitige berufliche Tätigkeit der an dieser Umfrage teilnehmenden Augenärzte und der teilnehmenden Augenärzte im Jahre 2016

	Alle Fachärzte		0 bis 5 Jahre Facharzt		6 bis 10 Jahre Facharzt		> 10 Jahre Facharzt	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
2022								
Arzt in Universitätsaugenklinik	58	7,9	34	11,9	13	6,4	11	4,4
Arzt in anderer Augenklinik	57	7,7	25	8,8	19	9,3	13	5,2
Selbstständiger Arzt in Praxis	288	39,1	59	20,7	82	40,2	147	59,3
Angestellter Arzt in Praxis	173	23,5	92	32,3	51	25	30	12,1
Angestellter Arzt in MVZ	139	18,9	65	22,8	35	17,2	39	15,7
In anderer ärztlicher Tätigkeit	12	1,6	3	1,05	3	1,5	6	2,4
Nicht ärztlich berufstätig	10	1,4	7	2,5	1	0,5	2	0,8
2016								
Arzt in Universitätsaugenklinik	32	7,4	14	10,6	10	8,0	8	4,6
Arzt in anderer Augenklinik	14	3,2	8	6,1	4	3,2	2	1,1
Selbstständiger Arzt in Praxis	262	60,6	44	33,3	88	70,4	130	74,3
Angestellter Arzt in Praxis	80	18,5	42	31,8	14	11,2	24	13,7
Angestellter Arzt in MVZ	36	8,3	20	15,2	8	6,4	8	4,6
In anderer ärztlicher Tätigkeit	4	0,9	2	1,5	1	0,8	1	0,6
Nicht ärztlich berufstätig	4	0,9	2	1,5	0	0	2	1,1

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Tab. 2 Derzeitige Tätigkeit der Augenfachärzte und Berufswunsch (Angaben in absoluten Zahlen)

Fachaugenärzte		Wo wollen Sie in 10 Jahren arbeiten?		
		Arzt in Universitätsaugenklinik/Arzt in anderer Augenklinik	Angestellter Arzt in Praxis/angestellter Arzt in MVZ	Selbstständiger Arzt in Praxis
2022				
Wo arbeiten Sie derzeit?	Arzt in Universitätsaugenklinik/Arzt in anderer Augenklinik	58	16	36
	Angestellter Arzt in Praxis/angestellter Arzt in MVZ	7	129	160
	Selbstständiger Arzt in Praxis	1	10	256
2016				
Wo arbeiten Sie derzeit?	Arzt in Universitätsaugenklinik/Arzt in anderer Augenklinik	22	5	16
	Angestellter Arzt in Praxis/angestellter Arzt in MVZ	2	41	63
	Selbstständiger Arzt in Praxis	1	7	241

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beiten zu wollen. Der häufigste Wunsch der Fachärzte im Angestelltenverhältnis ist es, in Zukunft als selbstständige Augenärzte tätig zu sein (54,1 %). Bei den Ärzten in Kliniken war der häufigste Wunsch, in dieser Berufsform zu bleiben (52,7 %), und mit 32,7 % zeigte sich der Wunsch, in die Selbstständigkeit zu wechseln, als deutlich größer als in eine Anstellung in Praxis oder MVZ. Verglichen mit der Befragung von 2016 zeigten sich sehr ähnliche Ergebnisse für die zukünftig gewünschte Berufsform. Der Änderungswunsch, in 10 Jahren als selbstständige Ärzte zu arbeiten, ist wie im Jahr 2016 stark vertreten (**Tab. 2**).

Von den Weiterbildungsassistenten möchten sowohl die im Vertragsarztbereich angestellten Ärzte als auch die Ärzte in Kliniken in 10 Jahren am häufigsten in einer selbstständigen Praxis arbeiten. Auch im Jahr 2016 wünschte die Mehrzahl der Weiterbildungsassistenten, in 10 Jahren selbstständig tätig zu sein (**Tab. 3**). Von den Weiterbildungsassistenten möchten 39 % später in einer selbstständigen Praxis arbeiten. Im Jahr 2016 lag der Wunsch bei 44 %. Der Wunsch nach der Selbstständigkeit ist bei den Fachärzten höher als bei den Weiterbildungsassistenten, auch mit zunehmender Facharzttätigkeit ist der Wunsch nach der Selbstständigkeit gleichbleibend hoch (0 bis 5 Jahre: 66 %, > 5 Jahre: 63 %).

Bezüglich einer beruflichen Veränderung äußerten mehr Frauen den Wunsch zur Veränderung im Vergleich zu den Männern (49 % vs. 40 %). Der häufigste Wunsch einer beruflichen Veränderung zeigt sich bei beiden Geschlechtern in einem Wechsel als selbstständiger Arzt in eine Praxis in 10 Jahren, diese Tätigkeit wird von beiden Geschlechtern zu jeweils 32 % gewünscht.

Bezüglich einer gewünschten Wochenarbeitszeit in 10 Jahren gaben die Weiterbildungsassistenten zu 52 % an, dann 31 bis 39 h arbeiten zu wollen, 39,7 % der Fachärzte streben in 10 Jahren eine Wochenarbeitszeit von 31 bis 39 h an und 39 % eine Arbeitszeit von 21 bis 30 h (**Tab. 4**). Auch im Jahr 2016 wünschte die Mehrheit der Weiterbildungsassistenten eine Stundenanzahl von 31–39 h in 10 Jahren (54,8 %). Unabhängig von der Facharztdauer wurde von den Fachärzten im Jahr 2016 mehrheitlich eine Stundenanzahl von 31–39 h gewünscht. Bei der diesjährigen Befragung wurde nur in der Gruppe der Fachärzte mit einer Facharztdauer zwischen 6 und 10 Jahren diese Stundenanzahl am häufigsten gewünscht. Personen mit geringerer Facharztdauer (0 bis 5 Jahre Facharzt) oder längerer Facharztdauer (> 10 Jahre Facharzt) wünschten am häufigsten eine Stundenanzahl von 21–30 h.

Frauen wünschen sich mit 47 % eine Wochenarbeitszeit von 21–30 h, wohingegen Männer am häufigsten 31–39 h arbeiten möchten (48 %). Eine Arbeitszeit von 20 h und weniger wird kaum gewünscht (Frauen: 6 %, Männer: 6 %). Von den weiblichen Fachärzten, welche als selbstständige Ärzte in einer Praxis arbeiten oder in einem

Tab. 3 Derzeitige Tätigkeit der Augenfachärzte und Berufswunsch (Angaben in absoluten Zahlen)

Weiterbildungsassistenten		Wo wollen Sie in 10 Jahren arbeiten?		
		Arzt in Universitätsaugenklinik/Arzt in anderer Augenklinik	Angestellter Arzt in Praxis/ angestellter Arzt in MVZ	Selbstständiger Arzt in Praxis
2022				
Wo arbeiten Sie derzeit?	Arzt in Universitätsaugenklinik/ Arzt in anderer Augenklinik	41	44	49
	Angestellter Arzt in Praxis/ angestellter Arzt in MVZ	11	27	31
2016				
Wo arbeiten Sie derzeit?	Arzt in Universitätsaugenklinik/ Arzt in anderer Augenklinik	11	8	16
	Angestellter Arzt in Praxis/ angestellter Arzt in MVZ	2	14	11

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Tab. 4 Erwünschte Wochenarbeitszeit der Weiterbildungsassistenten und Fachärzte in 10 Jahren

	Weiterbildungsassistenten		Alle Fachärzte		0 bis 5 Jahre Facharzt		6 bis 10 Jahre Facharzt		> 10 Jahre Facharzt	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
20 und weniger Stunden	7	3,2	53	7,5	14	5,1	12	6,3	27	11,3
21–30 h	66	30,1	275	39	110	40	70	36,6	95	39,7
31–39 h	114	52,1	280	39,7	108	39,3	80	41,9	92	38,5
40 und mehr Stunden	32	16,6	97	13,8	43	15,6	29	15,2	25	10,5

Tab. 5 Erwünschte Wochenarbeitszeit der weiblichen Fachärzte im Jahr 2022 und im Jahr 2016

Facharzt, weiblich	Arzt in Universitätsaugenklinik/Arzt in anderer Augenklinik		Angestellter Arzt in Praxis/angestellter Arzt in MVZ		Selbstständiger Arzt in Praxis	
	n	%	*n*	%	*n*	%
Im Jahr 2022						
20 und weniger Stunden	4	2,6	16	6	15	10,3
21–30 h	51	32,5	157	58,8	62	42,8
31–39 h	86	54,8	85	31,8	55	37,9
40 und mehr Stunden	16	10,2	9	3,4	13	9
Im Jahr 2016						
20 und weniger Stunden	2	3,2	10	10,8	8	6,8
21–30 h	18	29,5	45	48,4	37	31,6
31–39 h	36	59	35	37,6	63	53,9
40 und mehr Stunden	5	8,2	3	3,2	9	7,7

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Angestelltenverhältnis (Praxis oder MVZ) beschäftigt sind, wird eine Arbeitszeit von 21–30 h am häufigsten gewünscht. Weibliche Fachärzte in Kliniken (Augenklinik/Universitätsklinik) wünschen sich eine Arbeitszeit von 31–39 h. Im Jahr 2016 wurde innerhalb der einzelnen Beschäftigungsgruppen der weiblichen Fachärzte zum Teil eine höhere Stundenanzahl gewünscht. So wollten die selbstständigen Ärzte und Ärzte in Kliniken bevorzugt zwischen 31 und 39 h arbeiten. Personen im Angestelltenverhältnis wünschten auch hier eine Arbeitszeit von 21–30 h. Vergleichsweise zu den weiblichen Fachärzten wünschen die männlichen Fachärzte eine höhere Stundenanzahl in den einzelnen Beschäftigungsgruppen. Die selbstständig tätigen männlichen Fachärzte und die angestellten Fachärzte wünschten im Jahr 2022 insbesondere eine Stundenzahl von 31–39 h, während die weiblichen Fachärzte in diesen Berufsgruppen eine Stundenzahl von 21–30 h bevorzugten. Im Jahr 2016 wurden bei den männlichen Fachärzten ähnliche Ergebnisse aufgezeigt. In der Berufsgruppe der Personen in Kliniken lag die gewünschte Arbeitszeit hier vergleichsweise zur diesjährigen Befragung etwas höher bei über 40 h und mehr (**Tab. 5 und 6**).

Von den befragten Augenärzten sind derzeit 47,9 % operativ tätig. In 10 Jahren wünschen sich 62,3 % eine operative augenärztliche Tätigkeit. Die am meisten gewünschten Operationsarten sind: intravitreale operative Medikamentenapplikationen (IVOM: 49 %), Kataraktoperationen (43 %) und Lidoperationen (35 %). Diese Operationsformen werden sowohl von bisher nicht operativ tätigen Personen als auch von bereits operativ tätigen Personen gewünscht (**Tab. 7 und 8**). Es konnte ein Zusammenhang mit der gewünschten Wochenarbeitszeit aufgezeigt werden. Personen mit der gewünschten Wochenarbeitszeit von bis zu 20 h wünschen sich zu 40 % eine operative Tätigkeit, 62 % mit 21–30 h, 70 % der Personen mit einer gewünschten Arbeitszeit von 31–39 h und 83 % mit einer gewünschten Arbeitszeit von 40 und mehr Stunden wünschen sich eine operative Tätigkeit.

Insgesamt bewerten 8 % der Umfrageteilnehmer die Zukunft der Einzelpraxis als gut, und 19 % sehen eher eine positive

Tab. 6 Erwünschte Wochenarbeitszeit der männlichen Fachärzte im Jahr 2022 und im Jahr 2016						
Facharzt, männlich	**Arzt in Universitäts-augenklinik/Arzt in anderer Augenklinik**		**Angestellter Arzt in Praxis/angestellter Arzt in MVZ**		**Selbstständiger Arzt in Praxis**	
	n	*%*	*n*	*%*	*n*	*%*
Im Jahr 2022						
20 und weniger Stunden	3	3,4	5	4,6	12	9,4
21–30 h	7	7,9	23	21,1	30	23,6
31–39 h	46	51,7	55	50,5	57	44,9
40 und mehr Stunden	33	37,1	26	23,8	28	22,1
Im Jahr 2016						
20 und weniger Stunden	0	0	1	1,9	7	5
21–30 h	2	7,1	8	15,4	32	22,7
31–39 h	12	42,9	25	48,1	65	46,1
40 und mehr Stunden	14	50	18	34,6	37	26,2

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Tab. 7 Beschreibung des gewünschten operativen Spektrums in 10 Jahren (bereits operativ tätige Augenärzte)		
N **= 1014**	**Zukünftige gewünschte operative augenärztliche Tätigkeit**	
	n	*%*
Operationen (gesamt)	449	44,28
Lidoperationen	251	24,75
Schieloperationen	39	3,85
Hornhaut-/Bindehautoperationen	141	13,91
Glaukomoperationen	143	14,10
Kataraktoperationen	313	30,87
Netzhautoperationen	110	10,85
IVOM	360	35,50
Refraktive Chirurgie	138	13,61

IVOM intravitreale operative Medikamentenapplikationen

Tab. 8 Beschreibung des gewünschten operativen Spektrums in 10 Jahren (bisher nicht operativ tätige Augenärzte)		
N **= 1014**	**Zukünftige gewünschte operative augenärztliche Tätigkeit**	
	n	*%*
Operationen (gesamt)	179	17,65
Lidoperationen	104	10,25
Schieloperationen	14	1,38
Hornhaut-/Bindehautoperationen	47	4,63
Glaukomoperationen	32	3,16
Kataraktoperationen	127	12,52
Netzhautoperationen	22	2,17
IVOM	139	13,71
Refraktive Chirurgie	55	5,42

IVOM intravitreale operative Medikamentenapplikationen

Zukunft für die Einzelpraxis. Die Zukunftsperspektive der Gemeinschaftspraxis wird von 36 % als gut und von 56 % als eher positiv bewertet. Im Vergleich wird die Zukunft von großen Praxen und MVZ besonders positiv eingeschätzt. Von 51 % der Umfrageteilnehmer wird die Zukunftsperspektive als gut und von 35 % als eher positiv bewertet (**Tab. 9**).

Diskussion

In dieser Umfrage wurden die berufliche Situation der Augenärzte (Fachärzte und Weiterbildungsassistenten) und deren berufliche Vorstellungen/Wünsche für die Arbeitssituation in 10 Jahren erhoben. Im Jahr 2016 wurde diese Umfrage bereits mit ähnlichem Fragenkatalog durchgeführt, und es zeigte sich ein ähnliches Stimmungsbild der Augenärzte in Bezug auf die Form der Tätigkeit und den Tätigkeitsumfang. Zu beiden Befragungszeitpunkten wurde erfasst, dass ein zukünftiger beruflicher Wechsel am häufigsten hin zu einer selbstständigen Tätigkeit angestrebt wird.

Der Wunsch nach der Selbstständigkeit ist somit auch in der diesjährigen Befragung vergleichbar hoch wie im Jahr 2016. Auch hier war der häufigste berufliche Änderungswunsch, in die Selbstständigkeit zu wechseln. Der Wunsch nach Selbstständigkeit, steht im Widerspruch zu den Zahlen der Ärztestatistik. Während im Jahr 2017 22 % der ambulant tätigen Augenärzte in einer Anstellung waren, ist die Zahl im Bericht der Ärztestatistik im Jahr 2021 bereits auf 30 % gestiegen [2]. Diese Steigerung zeigt sich auch bei den Ergebnissen der durchgeführten Befragung. Die Zahl der angestellten Ärzte im MVZ hat sich mehr als verdoppelt (8,3 % zu 18,9 %). Es stellt sich also die Frage, ob dieser Wunsch nach Selbstständigkeit sich auch in der Realität wiederfindet und umgesetzt werden kann oder ob es strukturelle Probleme geben könnte, welche den Weg in die Selbstständigkeit zunehmend erschweren. Hier spielt sicher die Verfügbarkeit von frei werdenden Augenarztsitzen eine Rolle, erschwerend kommt hinzu, dass die Anzahl der Augenarztsitze, welche durch internationale Firmen (Private-Equity-Gesellschaften) gekauft werden, steigt. So wurden allein im Jahr 2017 70 solche Über-

Tab. 9 Einschätzung der Zukunftsperspektive für eine Einzelpraxis, große Praxen/MVZ und eine Gemeinschaftspraxis mit 2 bis 4 Augenärzten, stratifiziert nach Ausbildungsstatus und Beschäftigungsform

	Stimmt (in %)	Eher ja (in %)	Eher nein (in %)	Falsch (in %)
Alle				
Ich sehe eine gute Zukunft für die Einzelpraxis	8	19	54	19
Ich sehe eine gute Zukunft für die Gemeinschaftspraxis mit 2 bis 4 Augenärzten	36	56	7	1
Ich sehe eine gute Zukunft für große Praxen und MVZ	51	35	10	3
Weiterbildungsassistent				
Ich sehe eine gute Zukunft für die Einzelpraxis	7	26	54	12
Ich sehe eine gute Zukunft für die Gemeinschaftspraxis mit 2 bis 4 Augenärzten	35	56	8	2
Ich sehe eine gute Zukunft für große Praxen und MVZ	58	31	9	1
Facharzt: Klinik				
Ich sehe eine gute Zukunft für die Einzelpraxis	*6*	*13*	*53*	*28*
Ich sehe eine gute Zukunft für die Gemeinschaftspraxis mit 2 bis 4 Augenärzten	*36*	*54*	*10*	*1*
Ich sehe eine gute Zukunft für große Praxen und MVZ	*51*	*37*	*7*	*6*
Facharzt: angestellt (Praxis oder MVZ)				
Ich sehe eine gute Zukunft für die Einzelpraxis	*2*	*15*	*61*	*22*
Ich sehe eine gute Zukunft für die Gemeinschaftspraxis mit 2 bis 4 Augenärzten	33	60	6	1
Ich sehe eine gute Zukunft für große Praxen und MVZ	52	36	10	3
Facharzt: selbstständig				
Ich sehe eine gute Zukunft für die Einzelpraxis	14	22	45	19
Ich sehe eine gute Zukunft für die Gemeinschaftspraxis mit 2 bis 4 Augenärzten	40	52	7	2
Ich sehe eine gute Zukunft für große Praxen und MVZ	46	37	13	4

MVZ medizinisches Versorgungszentrum

nahmen eines Augenarztsitzes festgestellt [7], und diese werden in absehbarer Zeit nicht erneut über die Kassenärztliche Vereinigung (KV) ausgeschrieben. Durch die Befragung zeigte sich anhand der gesteigerten Anzahl an angestellten Augenärzten und des zeitgleich hohen Wunsches nach Selbstständigkeit eine deutliche Diskrepanz zwischen den Wünschen und den möglichen Arbeitsbedingungen in der Augenheilkunde. In der Umfrage wurde als häufigster Grund, welcher einen Wechsel in die Selbstständigkeit erschwert, angegeben, dass die zeitliche Belastung als Selbstständiger zu groß sein würde (36%). Als zweithäufigster Grund gaben die Umfrageteilnehmer an, dass ein Kassensitz in Wohnortnähe nicht verfügbar ist (30%). Der Weg in die Selbstständigkeit wird zudem erschwert durch persönliche Sorgen, wie z. B. den hohen Zeitaufwand und die gegebenen Ressourcen im Markt (Verfügbarkeit von Augenarztsitzen), und daher scheint der Wunsch nach Selbstständigkeit schwierig umsetzbar zu sein.

Die Ergebnisse zur gewünschten Stundenanzahl lassen vermuten, dass eine geringere Stundenanzahl (von ca. 5–7 h pro Tag) oder eine Beschäftigung an einzelnen Tagen (3- oder 4-Tage-Woche) das gewünschte Maß wäre. Deutlich wurde bei der Befragung auch, dass die derzeitige Stundenanzahl von der gewünschten abweicht und tendenziell die Befragten in Zukunft eine Reduktion der Arbeitszeit anstreben, dies war auch im Jahr 2016 der Fall. Vergleichsweise zur Umfrage von 2016 ist die gewünschte Stundenanzahl noch etwas weiter gesunken. Das *Ärzteblatt* gab im Jahr 2017 eine Wochenarbeitszeit für Augenärzte von durchschnittlich 47 h pro Woche an [4]. Eine Erhöhung der Teilzeittätigkeit in der Augenheilkunde würde die beschriebene Problematik der bedarfsgerechten Versorgung in der Augenheilkunde weiter verschärfen. Der Wunsch nach einer Teilzeittätigkeit kann außerdem im Widerspruch zu den Wünschen nach einer selbstständigen Tätigkeit stehen, denn eine Teilzeittätigkeit in Selbstständigkeit ist unter den derzeitig gegebenen gesetzlichen Voraussetzungen (es gibt lediglich hälftige oder volle selbstständige KV-Sitze, während es bei MVZ auch geviertelte Kassensitze gibt) nur eingeschränkt umsetzbar. Allerdings ist in Gemeinschaftspraxen auch als Selbstständiger eine Teilzeittätigkeit gut möglich. Schlussendlich könnte der Zeitaufwand aber dazu führen, dass trotz des Wunsches nach Selbstständigkeit eine Tätigkeit als angestellter Augenarzt bevorzugt wird.

Die Zukunft der Einzelpraxis in der Augenheilkunde wird auch in der aktuellen Befragung deutlich negativer bewertet als die Zukunftsperspektive für große Praxen/MVZ oder Gemeinschaftspraxen mit 2 bis 4 Augenärzten. Insbesondere angestellte Fachärzte (Praxis oder MVZ) und Fachärzte in Kliniken bewerten die Zukunft der Einzelpraxis negativer, und es zeigt sich ein ähnlich negatives Bild auf wie im Jahr 2016 ($p = 0{,}22$). Dies weist auf ein mögliches weiteres Problem hin auf dem Weg in die Selbstständigkeit. Vertragssitze sind häufig nur als selbstständige Einzelpraxen verfügbar, dies ist jedoch, wie aufgezeigt, kaum gewünscht von den Augenärzten unter 49 Jahren.

Die durchgeführte Umfrage ist durch einige Limitationen gekennzeichnet, welche im Folgenden diskutiert werden. Ein möglicher Selektionseffekt ist nicht auszuschließen, da die Befragung unter Mitgliedern des Berufsverbands der Augenärzte Deutschlands e. V. (BVA) und der Deutschen Ophthalmologischen Gesellschaft durchgeführt wurde. Auch besteht die Möglichkeit, dass Weiterbildungsassistenten und Augenärzte mit einem berufspolitischen Interesse an der Befragung teilgenommen haben. Eine weitere Limitation ist durch einige vorgegebene Antwortmöglichkeiten in der Umfrage gegeben, welche potenziell als suggestiv gewertet werden könnten. Vor Durchführung der Umfrage wurde über den Fragenkatalog diskutiert und entschieden, die bereits bestehende Form zu verwenden, um die größtmögliche Vergleichbarkeit zur Umfrage von 2016 zu gewährleisten.

Schlussfolgernd lässt sich sagen, dass die Ergebnisse der Befragung der Augenärzte unter 49 Jahren in Deutschland ähnliche Vorstellungen zeigten wie im Jahr 2016. Auch heute ist der Wunsch nach der Selbstständigkeit am größten, spiegelt sich dennoch bisher nicht in der derzeitigen Situation der Augenärzte in Deutschland wider und steht im Kontrast zur gesteigerten Anzahl von angestellten Augenärzten. Die Zukunft von großen Praxen, MVZ oder Gemeinschaftspraxen mit 2 bis 4 Augenärzten wird positiver eingeschätzt als die Zukunft von Einzelpraxen. Die negativ eingeschätzte Zukunft von Einzelpraxen zeigt auch auf, dass der Wunsch nach der Selbstständigkeit vielfach nur schwer umsetzbar ist, wenn freiwerdende Sitze in Gemeinschaftspraxen teilweise lieber in einen Angestelltensitz umgewandelt werden, als die freiwerdenden Sitze an einen neuen freiberuflichen Partner weiterzugeben. Am häufigsten wünschen die Weiterbildungsassistenten eine Wochenarbeitszeit von 31–39 h pro Woche und die Fachärzte gleichermaßen eine wöchentliche Arbeitszeit von 21–30 h und 31–39 h pro Woche.

Abstract

Career prospects for ophthalmologists under 49 years old. A survey in Germany from 2022

Objective: The need for care in ophthalmology is constantly increasing due to demographic changes. The study analyzed the current professional situation and future prospects of ophthalmologists under 49 years old.
Methods: The survey of members of the German Association of Ophthalmologists (Berufsverband der Augenärzte Deutschlands) and the German Ophthalmologic Society (Deutsche Ophthalmologische Gesellschaft) was conducted in 2022. All members under the age of 49 years received an online questionnaire on the current professional situation as well as future perspectives (desired working hours, form of organization). The results of the survey were additionally compared with the 2016 survey of the German Association of Ophthalmologists. A similar questionnaire was used at that time.
Results: A total of 1014 people participated in the survey (62.7% women, mean age 39.3 ± 8 years, 75.6% specialists). The response rate to the survey was 25%. Specialist practice from 0 to 5 years showed a higher number of employed ophthalmologists (21% self-employed vs. 32% employed); over time the number of self-employed ophthalmologists increased (6–10 years: 40%, > 10 years: 59.3%). Overall, 46% of women were employed in a practice compared with 33% of men. Of the self-employed specialists, 95.9% said they planned to work in the same type of employment in 10 years as currently. Regarding ophthalmologists' career future, the other employment types showed a desire to move to independent practice. Compared to the 2016 survey, gender differences related to the current type of employment were evident. The number of self-employed women decreased from 43% to 26% and self-employed men decreased from 63% to 39%. The number of ophthalmologists in ambulatory healthcare centers was doubled compared to 2016. Ophthalmologists reported similar future perspectives at both survey times.
Conclusion: The results of the survey of ophthalmologists under 49 years in Germany showed similar perceptions as in 2016. It became clear that the desire to be self-employed in 10 years is very high; however, ophthalmologists expected large practices or medical care centers to prevail in the market. The number of self-employed doctors is decreasing and the desire for self-employment is difficult to realize.

Keywords
Ophthalmology · Self-employment · Working hours · Gender · Surgery

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Einhaltung ethischer Richtlinien

Interessenkonflikt. A.K. Schuster hat die Stiftungsprofessur für ophthalmologische Versorgungsforschung der Stiftung Auge inne. Er erhält Forschungsgelder und -unterstützung von Abbvie, Apellis, Bayer Vital, Heidelberg Engineering, Santen und Novartis. B. Bertram war bis November 2021 2. Vorsitzender des Berufsverbandes der Augenärzte Deutschlands e. V. und ist Mitglied des Gesamtpräsidiums der Deutschen Ophthalmologischen Gesellschaft. Finanzielle Interessen: keine im Zusammenhang mit diesem Manuskript. S. Siebelmann erhält Beratungsgebühren von Bausch & Lomb, Zeiss und Haag-Streit. M. Böhm, H. Faber, A. Zhour und A. Hartmann geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autor/-innen keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien.

Literatur

1. Borchert Y (2021) Anzahl und Statistik der Praxen für Augenärzte in Deutschland. https://www.gesundheitsmarkt.de/anzahl-und-statistik-praxen-augenaerzte-deutschland/#:~:text=Im%20station%C3%A4ren%20Bereich%20sind%20102.652,das%20entspricht%2083%2C25%20%25. Zugegriffen: 15. Sept. 2022
2. Bundesärztekammer (2021) Ärztestatistik. https://www.bundesaerztekammer.de/baek/ueber-uns/aerztestatistik/aerztestatistik-2021. Zugegriffen: 15. Sept. 2022
3. Bundesärztekammer (2021) Wenn ein leichter Zuwachs in den Mangel führt. https://www.bundesaerztekammer.de/presse/aktuelles/detail/aerztestatistik-wenn-ein-leichter-zuwachs-in-den-mangel-fuehrt. Zugegriffen: 15. Sept. 2022
4. Deutsches Ärzteblatt (2017) Niedergelassene Ärzte arbeiten durchschnittlich 50 Stunden in der Woche. https://www.aerzteblatt.de/nachrichten/76988/Niedergelassene-Aerzte-arbeiten-durchschnittlich-50-Stunden-in-der%20Woche#:

~:text=Berlin%20%E2%80%93%20Praxisinhaber%20kommen%20pro%20Woche,%C3%BCber%204.360%20Praxen%20beteiligt%20haben. Zugegriffen: 15. Sept. 2022
5. Deutsche Ophthalmologische Gesellschaft (2020) DOG Roadmap. https://www.dog.org/wp-content/uploads/2016/02/DOG-Roadmap2020_web.pdf. Zugegriffen: 15. Sept. 2022
6. Kis A, Augustin J, Lischka T (2021) Parameters for measuring the regional healthcare situation: a comparison of different healthcare parameters by the example of ophthalmologic care in the metropolitan region Hamburg. Ophthalmologe 118:933–939
7. Korzilius H (2018) Ambulante Versorgung: Investoren auf Einkaufstou. Dtsch Arztebl 115(39)
8. R Core Team (2022) A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/. Zugegriffen: 11. Okt. 2022
9. Schuster AK, Harris J, Nickels S et al (2019) Berufliche Zukunftsperspektive von Augenärzten unter 49 Jahren. Ophthalmologe 116:951–956
10. Schuster AK, Wolfram C, Pfeiffer N et al (2019) Augenheilkunde 2019 – Wo stehen wir? Ophthalmologe 116:829–837

In eigener Sache

Leitthemenübersicht von *Die Ophthalmologie*

***Die Ophthalmologie* bietet Ihnen jeden Monat umfassende und aktuelle Beiträge zu interessanten Themenschwerpunkten aus allen Bereichen der Augenheilkunde.**

Rückblick – 2022

01/22 Originalien
02/22 Smartphone basierte Fundusfotografie
03/22 UV-Schäden und UV-Schutz
04/22 Update korneales Crosslinking
05/22 Kindliche Hornhauttrübungen
06/22 Ökologische Nachhaltigkeit in der Augenheilkunde
07/22 Lymphome am und im Auge
08/22 Komplikationen nach vitreomakulärer und vitreoretinaler Chirurgie
09/22 Regenerative Medizin in der Augenheilkunde
10/22 Trabekulektomie
11/22 Retinale Gefäßverschlüsse
12/22 Das erworbene Jaensch-Brown-Syndrom

Rückblick & Vorschau – 2023

01/23 Originalien
02/23 Aktuelle Aspekte der augenprothetischen Versorgung
03/23 Lidtumore
04/23 Neue und alte Verfahren der Glaukomchirurgie im Vergleich
05/23 Das okuläre Pemphigoid
06/23 Augenveränderungen bei Erwachsenen mit Frühgeborenenanamnese
07/23 Akutschmerztherapie nach Augeneingriffen
08/23 Benigne Erkrankungen des vorderen Augenabschnitts im Kindes- und Jugendalter aus ophthalmopathologischer Sicht
09/23 Führung in der Augenheilkunde
10/23 Chronische Schmerzen in der Augenheilkunde
11/23 Vitrektomie/Glaskörper und AMD
12/23 Versorgungsforschung im Bereich Glaukomerkrankungen
(Änderungen vorbehalten)

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5 Zusätzliche Daten

Das in diesem Kapitel präsentierte Material stellt ergänzende Daten aus den zuvor gezeigten Publikationen dar, die für die Diskussion der Ergebnisse in dieser Dissertation relevant sind.

Publikation I

Bi-Gaussian analysis reveals distinct education-related alterations in spherical equivalent and axial length—results from the Gutenberg Health Study

Suppl. Table 1. Univariable regression models stratified by sex, adjusted for age and genetic risk score of myopia (using generalized estimation equations). Data from the Gutenberg Health Study (2012-2017).

Female participants:	**Year of Education**		
	Estimate	95%-CI	p
Spherical Equivalent	-0.10	[-0.13- -0.06]	<0.001
Axial Length	0.06	[0.04-0.08]	<0.001
Corneal Curvature	0.01	[-0.00-0.01]	0.01
Anterior chamber depth	0.01	[-0.00-0.01]	0.01
Lens thickness	-0.0002	[-0.01-0.00]	0.08
Male participants:			
Spherical Equivalent	-0.11	[-0.14- -0.08]	<0.001
Axial Length	0.06	[0.04-0.07]	<0.001
Corneal Curvature	-0.00001	[-0.00-0.00]	0.96
Anterior chamber depth	0.009	[-0.00-0.00]	0.001
Lens thickness	-0.003	[-0.01-0.00]	0.10

Publikation IV

Change in systemic medication and its influence on intraocular pressure – results from the Gutenberg Health Study

Suppl. Table 6: Association between systemically acting drugs and a change in intraocular pressure over 5 years stratified for sex. Data from the German population-based Gutenberg Health Study (2007-2017, N=9,633 individuals). Linear GEE models were calculated, controlling for comedication, age, baseline body mass index, body mass index difference over 5 years, systolic blood pressure difference and diabetes.

		Male participants				**Female participants**		
		New intake	Discontinued	Continuous intake		New intake	Discontinued	Continuous intake
β-Adrenoceptor antagonists, selective	B (95%-CI)	-0.21 (-0.47, 0.04)	0.35 (-0.01, 0.71)	-0.06 (-0.25, 0.14)		**-0.33** **(-0.55,-0.10)**	0.32 (-0.01, 0.64)	-0.13 (-0.31, 0.06)
	p	0.10	0.06	0.55		**0.01**	0.06	0.18
Thiazide diuretics	B (95%-CI)	0.24 (-0.02, 0.49)	-0.12 (-0.50, 0.25)	0.08 (-0.16, 0.32)		0.004 (-0.23, 0.24)	-0.15 (-0.57, 0.26)	-0.04 (-0.32, 0.24)
	p	0.08	0.51	0.50		0.97	0.46	0.78
Loop diuretics	B (95%-CI)	-0.14 (-0.65, 0.36)	-0.23 (-1.24, 0.78)	0.24 (-0.19, 0.67)		-0.16 (-0.61, 0.29)	-0.05 (-0.98, 0.88)	-0.40 (-0.94, 0.15)
	p	0.57	0.65	0.28		0.49	0.91	0.16
ACE inhibitors	B (95%-CI)	-0.02 (-0.24, 0.20)	-0.02 (-0.35, 0.30)	**-0.29** **(-0.52,-0.06)**		-0.004 (-0.25, 0.25)	-0.15 (-0.52, 0.21)	0.02 (-0.22, 0.27)
	p	0.86	0.89	**0.01**		0.97	0.42	0.86
Angiotensin II receptor blockers	B (95%-CI)	0.05 (-0.21, 0.30)	0.14 (-0.42, 0.70)	-0.04 (-0.30, 0.21)		-0.16 (-0.38, 0.07)	-0.27 (-0.80, 0.25)	0.01 (-0.27, 0.29)
	p	0.72	0.63	0.73		0.17	0.31	0.93
Calcium channel blocker	B (95%-CI)	-0.36 (-0.59, -0.13)	0.16 (-0.31, 0.64)	0.04 (-0.21, 0.29)		-0.08 (-0.31, 0.16)	0.22 (-0.31, 0.74)	0.03 (-0.33, 0.38)
	p	**0.002**	0.50	0.74		0.53	0.42	0.88
Statins	B (95%-CI)	-0.23 (-0.47, 0.01)	-0.01 (-0.35, 0.34)	0.03 (-0.17, 0.24)		-0.04 (-0.31, 0.23)	0.05 (-0.35, 0.44)	0.002 (-0.26, 0.26)
	p	0.06	0.97	0.75		0.78	0.81	0.99
Non-selective monoamine reuptake inhibitors	B (95%-CI)	0.31 (-0.17, 0.80)	0.38 (-0.15, 0.90)	**1.30** (**0.30, 2.29**)		0.18 (-0.17, 0.53)	0.07 (-0.45, 0.58)	0.16 (-0.28, 0.60)

		Male participants				Female participants		
		New intake	Discontinued	Continuous intake		New intake	Discontinued	Continuous intake
	p	0.21	0.16	**0.01**		0.31	0.80	0.48
Selective serotonin reuptake inhibitors	B (95%-CI)	0.01 (-0.48, 0.50)	0.47 (-0.02, 0.96)	0.42 (-0.42, 1.25)		-0.31 (-0.74, 0.11)	0.27 (-0.16, 0.69)	0.12 (-0.31, 0.54)
	p	0.97	0.06	0.33		0.15	0.22	0.59
Other antidepressants	B (95%-CI)	-0.44 (-1.17, 0.28)	-0.49 (-1.14, 0.17)	-0.42 (-1.07, 0.23)		**0.39 (0.04, 0.74)**	**0.99 (0.24, 1.75**)	0.05 (-0.50, 0.59)
	p	0.23	0.14	0.20		**0.03**	**0.01**	0.87

*p-values less than or equal to 0.05 are marked

6 Diskussion

In der Dissertation wurden mögliche Geschlechterunterschiede in drei Bereichen der Ophthalmologie untersucht. Im folgenden Kapitel werden die Ergebnisse zusammengefasst und diskutiert.

Mit Blick auf die okuläre Anatomie von Frauen und Männern zeigten sich geschlechtsspezifische Unterschiede. Grundsätzlich wiesen Männer etwas größere beziehungsweise längere biometrische Augenparameter auf. Dies betrifft die Achsenlänge des Auges, die Linsendicke, die Hornhautverkrümmung und den White-to-White Abstand. Bei der Untersuchung der Biometrie zeigte sich zusätzlich ein Zusammenhang zwischen der Hornhautkrümmung mit der Bildungsdauer, diese Assoziation war nur bei Frauen vorhanden (Publikation I, Suppl. Table 1) [46]. Bei der Analyse der augenbiometrischen Unterschiede bei Frühgeborenen zwischen den Geschlechtern zeigte sich, dass sowohl bei Frauen als auch bei Männern eine Korrelation zwischen einer dickeren zentralen Foveadicke mit niedrigerem Gestationsalter besteht, wobei Männer stärker betroffen waren [47]. Eine erhöhte zentrale Foveadicke könnte im Erwachsenenalter von Frühgeborenen möglicherweise Auswirkungen auf die Sehschärfe und die Entwicklung einer AMD haben [48], wobei dieser Einfluss bei männlichen Personen stärker ausgeprägt zu sein scheint. Auf andere okulare Parameter in Bezug auf Gestationsalter oder Geburtsgewichtsperzentile hatte das Geschlecht keinen Einfluss.

Bei der Untersuchung des Augeninnendrucks wurde ein signifikant höherer Augeninnendruck bei Männern im Vergleich zu Frauen gezeigt [49]. Auch war ein Unterschied in der Auswirkung verschiedener systemischer Medikationen zwischen den Geschlechtern erkennbar. Während bei Männern eine Verbindung zwischen der Veränderung des Augeninnendrucks über 5 Jahre und der kontinuierlichen Einnahme von nicht-selektiven Monoamin-Wiederaufnahmehemmern festgestellt wurde, zeigte sich bei Frauen eine Assoziation mit der Anwendung von Antidepressiva vom ATC-Subtyp N06AX (Publikation IV, Suppl. Tabelle 6) [50]. Auch die Veränderung des Augeninnendrucks über 5 Jahre war bei Männern höher (0,77 ± 2,11 mmHg) als bei Frauen (0,69 ± 1,96 mmHg; $p<0,05$) [51]. Zudem stellten wir fest, dass der Augeninnendruck saisonalen Schwankungen unterliegt, mit niedrigeren Werten im Sommer und höheren im Winter. Diese Beobachtung wurde teilweise durch den systolischen Blutdruck beeinflusst und zeigte sich bei beiden Geschlechtern [49]. Die Untersuchung der visuellen Lebensqualität über 5 Jahre zeigte, dass Männer grundsätzlich eine minimal höhere „Visual functioning scale (VFS)“ aufweisen als Frauen zum Baseline Zeitpunkt (Frauen: 89,56, Männer: 89,59). Bei beiden Geschlechtern zeigte sich ein Zusammenhang zwischen der Verschlechterung der Sehschärfe und der Reduktion der visuellen Lebensqualität über 5 Jahre, wobei dieser Rückgang bei Frauen signifikant stärker ausgeprägt war.

Bei der Untersuchung der psychosozialen Unterschiede der Einstellungen von Augenärzten unter 49 Jahren in Deutschland zeigte sich, dass Frauen häufiger als Männer den Wunsch nach einer beruflichen Veränderung äußerten (49% vs. 40%). Von den Frauen wurde mit 21-30 h/Woche eine geringere Wochenarbeitszeit gewünscht im Vergleich zu dem Wunsch der Männer, welche am ehesten 31-39 h/Woche arbeiten wollten [18].

Augenbiometrie und physiologische Unterschiede

Die Kenntnis der Augenbiometrie ist für die Diagnostik und Therapie von Augenerkrankungen von hoher Relevanz [52]. Unserer Ergebnisse zeigten physiologische Unterschiede zwischen den Geschlechtern auf, wobei Männer längere beziehungsweise größere Augenparametern aufwiesen. Geschlechterunterschiede bezüglich der Augenbiometrie wurden bisher hauptsächlich im asiatischen Raum berichtet [53-55], während entsprechende Untersuchungen bei kaukasischen Populationen seltener sind. Logan et al. untersuchten das rechte Auge von 373 Studenten im Vereinigten Königreich. Die Autoren berichteten, dass die Achsenlänge bei Frauen signifikant kürzer war als bei Männern [56].

Die biometrischen Unterschiede werden auch bereits deutlich bei der Verwendung von „deep learning“ Algorithmen. Allein anhand des Augenbildhintergrundes kann mithilfe der künstlichen Intelligenz bereits identifiziert werden, ob es sich um ein männliches oder weibliches Auge handelt [57].

Zudem sind die biometrischen Unterschiede von Relevanz für die Bewertung von Refraktionsfehlern sowie der Berechnung der Stärke von Intraokularlinsen. Zhang et al. untersuchten 5519 Patienten nach einer Kataraktoperation. Eine optische Biometrie wurde gemessen, die Brechkraft der implantierten Intraokularlinse (IOL) und die IOL-Formel für die Refraktionsvorhersage wurde erfasst. Die Autoren berichteten, dass sich das Geschlecht bei allen 5 untersuchten Formeln als unabhängiger Prädiktor für den Refraktionsvorhersagefehler zeigte. Eine geschlechterspezifische Optimierung der Linsenkonstanten könnte den Refraktionsfehler verringern [58].

Bezüglich des Augeninnendrucks fanden wir einen höheren Augeninnendruck bei Männern [49]. In einigen anderen Studien findet sich kein Geschlechterunterschied bezogen auf den Augeninnendruck [59-61]. Grund dafür könnten der Einbezug verschiedener Altersgruppen sein. Beim Vergleich zwischen Frauen und Männern unter 60 Jahren zeigen sich höhere Werte bei Männern, während die Augeninnendruckwerte bei über 60 Jahren gleich sind [62]. Da das Alter in unserer Studie zwischen 35 bis 74 Jahren liegt wurden viele junge Männer einbezogen und das Ergebnis von einem höheren Augeninnendruck bei Männern stützt die genannte These.

Ein möglicher Geschlechterunterschied beim Augeninnendruck in verschiedenen Studien könnte grundsätzlich auch durch eine unterschiedliche hormonelle Regulation zustande kommen [62]. Der Augeninnendruck vor der Menopause ist im Mittel geringer im Vergleich zu nach der Menopause (15,24 mmHg vs. 18,48 mmHg), da Progesteron und Östrogen protektiv wirken [63]. Eine Hormontherapie nach der Postmenopause kann den Augeninnendruck um 1-5 mmHg reduzieren [64-66]. Die Anzahl der Frauen, welche eine Hormontherapie während oder nach den Wechseljahren erhalten haben ist in Deutschland stark gesunken. Laut der Techniker Krankenkasse erhielt nur etwa jede 16. erwerbstätige Frau im Alter zwischen 45 und 65 Jahren ein entsprechendes Hormonpräparat verschrieben [67].

Des Weiteren zeigten sich bei Frauen ein Zusammenhang mit der Einnahme von Antidepressiva vom ATC-Subtyp N06AX mit einer Veränderung des Augeninnendrucks über 5 Jahre. Dieser Unterschied, kann wie in unserer Publikation erläutert [50], auf verschiedene Wirkweisen der Medikation zwischen den Geschlechtern zurückgeführt werden. Verschiedene Studien haben beobachtet, dass Frauen tendenziell besser auf serotonerge Antidepressiva ansprechen als Männer [68-70]. Es ist jedoch wichtig zu beachten, dass es auch Studien gibt, die diesen Beobachtungen widersprechen [71-74]. Das Verständnis der geschlechtsspezifischen Reaktion auf die Einnahme von Antidepressiva ist komplex, insbesondere angesichts widersprüchlicher Studienergebnisse. Dieser Aspekt spiegelt sich möglicherweise auch in der Verbindung zwischen der Einnahme von Antidepressiva und den Veränderungen des Augeninnendrucks wider.

Visuelle Lebensqualität

Im Rahmen unserer Studie fanden wir relevante Geschlechterunterschiede bei der visuellen Lebensqualität [75]. Andere Studien zeigten im Querschnitt eine niedrigere visuelle Lebensqualität bei Frauen im Vergleich zu Männern [76, 77]. Sturrock et al. untersuchte über einen Zeitraum von 6 Monaten die visuelle Lebensqualität im Längsschnitt und berichtete von einem Zusammenhang zwischen einer Verschlechterung des sehbedingten emotionalen Wohlbefindens und dem weiblichen Geschlecht [78].

Ein Grund hierfür könnte zum Beispiel sein, dass ein deutlich höherer Anteil an Frauen von Sehminderung und Blindheit betroffen sind [79]. Die höhere Prävalenz von Blindheit bei Frauen ist weltweit in allen Altersgruppen ab 40 Jahren zu beobachten [80]. Die Gründe hierfür könnten vielfältig sein. In den höheren Altersgruppen könnte es durch eine längere Lebenserwartung der Frauen bedingt sein, da die meisten Augenerkrankungen vorrangig im höheren Alter auftreten wie die AMD und die Katarakt [81, 82]. Die Katarakterkrankung ist in Entwicklungsländern die Hauptursache einer Erblindung. Frauen weisen eine deutliche höhere Prävalenz dieser Erkrankung auf [83]. Dies liegt zum einen an der höheren Lebenserwartung und zum anderen an einem Unterschied beim sozioökonomischen Status [84]. Männer werden im Schnitt häufiger an einer Katarakt operiert [83]. Zusätzlich zu den genannten Gründen für eine höhere Prävalenz der Erblindung bei Frauen, zeigte eine Studie mit Daten aus Spanien, dass Frauen durchschnittlich länger auf medizinische Behandlungen in der Primärversorgung warteten als Männer [85]. Zudem ergab eine Studie aus Deutschland zur Inanspruchnahme von Augenarztbesuchen, dass in der Altersgruppe ab 85 Jahren Männer häufiger mindestens einmal einen Augenarzt aufgesucht hatten [86]. Dies zeigt ein potenzielles geschlechterspezifisches Ungleichgewicht bei der Versorgung in der Augenheilkunde auf. Ein weiterer Grund für die stärkere Verschlechterung der visuellen Lebensqualität bei Frauen über 5 Jahre könnte dadurch begründet sein, dass Frauen möglicherweise ein höheres Risiko aufweisen auf Grund von einer Sehbehinderung mentale Probleme zu entwickeln [87, 88]. In der Allgemeinbevölkerung gibt es beispielsweise eine höhere Rate von psychischen Erkrankungen wie z. B. Depressionen bei Frauen [89], diese höhere Rate könnte aus hormonellen Unterschieden, einer unterschiedlichen Symptomwahrnehmung oder einer genetischen Veranlagung resultieren [90-93]. Es ist wichtig zu beachten, dass in der Gesellschaft Depressionen oft als stereotypisch weibliche Erkrankung betrachtet werden, was zu einer möglichen Überdiagnose bei Frauen führen könnte, während Depressionen bei Männern möglicherweise übersehen werden [89, 94]. Beide Geschlechtern zeigen eine unterschiedliche Symptomatik bei einer Depression. Frauen berichten grundsätzlich häufiger von Symptomen als Männer [95-97]. Einige Studien stellen die These auf, dass Frauen häufig aufmerksamer gegenüber ihrem Körper sind und somit körperliche Symptome eher wahrnehmen [98, 99]. Ein weiterer Grund sind stereotypische Geschlechterbilder in der Gesellschaft. Männern wurde lange Zeit das Bild von einem „starken Mann“ suggeriert, welche nicht weinen und keine Schwäche zeigen dürfen. Das könnte dazu führen, dass Symptome eher ignoriert werden und Männer daher erst später zum Arzt gehen [100-102]. Diese grundlegende Problematik verdeutlicht sich am Beispiel der Depression. Die Prävalenz der Depression ist bei Frauen deutlich höher im Vergleich zu Männern [89], doch die Suizidrate ist wiederum deutlich höher bei den Männern (vier-Mal häufiger) [103]. Dies spricht für eine hohe Dunkelziffer der Depression bei Männern, da diese später oder nicht zum Arzt gehen [104]. Die geringere Reduktion der visuellen Lebensqualität bei Männern könnte somit auch durch eine andere Symptomwahrnehmung beziehungsweise ein anderes Symptomreporting gekennzeichnet sein.

Psychosoziale Einstellungen der Augenärzte

In unserer Befragung zeigten mehr Frauen den Wunsch nach einer beruflichen Veränderung. Die Gründe hierfür können vielfältig sein. Der Anteil der weiblichen Augenärzte ist in den letzten Jahrzehnten angestiegen. Derzeit sind etwa 25-30% der Augenärzte weltweit Frauen und 35-45% der Ärzte in Weiterbildung [19]. Vor allem in Führungspositionen und auch in chirurgischen Subspezialisierungen der Ophthalmologie sind Frauen unterrepräsentiert. Grundsätzlich werden Frauen auch heute noch mit Vorurteilen und Diskriminierung konfrontiert, dies zeigt sich auch am geschlechtsspezifischen Lohngefälle [19, 105]. Im Jahr 2018 wurde ein Ranking der einflussreichsten Personen in der Augenheilkunde veröffentlicht („The Ophthalmologist’s 2018 Top

100 most influential people“). Lediglich 13 Frauen waren hierunter [106]. Die aktuelle Geschlechterungleichheit könnte somit auch zu einer höheren Unzufriedenheit bei den weiblichen Augenärzten führen. Der Grund für die geringere gewünschte Arbeitsdauer bei Frauen könnte zusätzlich damit zusammenhängen, dass Frauen auch heutzutage in der Mehrheit mehr Verantwortung für familiäre Aufgaben wie etwa die Versorgung der Kinder tragen [107-109]. Bei einer Befragung von 297 Augenärzten in Indien gaben 68% (202/297) der Augenärzte an, dass es herausfordernder ist eine weibliche Augenärztin zu sein. Als Grund hierfür wurde die höhere familiäre Verantwortung angegeben [107]. In der Zukunft sollten Ziele zur Integration und Diversität noch stärker verfolgt werden, um Frauen und auch ethnische Minderheiten im Berufsweg der Augenheilkunde zu unterstützen [110].

7 Schlussfolgerung und Ausblick

Die Gendermedizin ist eine junge, aber wachsende Disziplin, welche sich zum Ziel gesetzt hat alle Bereiche der klinischen und forschenden Medizin geschlechtersensibel zu gestalten. Die Nichtbeachtung von Geschlechterunterschieden in der Medizin kann die Gesundheit aller Personen gefährden. In der Augenheilkunde wurden Geschlechterunterschiede bisher kaum untersucht. Gefundene Geschlechterunterschiede fließen bisher nicht in die klinische Praxis ein und teils gibt es widersprüchliche Ergebnisse zu möglichen Geschlechterunterschieden oder dem Einfluss von Hormonen.

Bei der Untersuchung der gesetzten Schwerpunkte in der Dissertation finden sich im biologischen Bereich und psychosozialen Bereich nur einige wenige Unterschiede zwischen den Geschlechtern.

In unserer Studie wurde festgestellt, dass der Augeninnendruck sowie dessen Steigerung tendenziell bei Frauen höher ausfällt als bei Männern. Diese Ergebnisse unterstreichen die Bedeutung einer regelmäßigen Überwachung des Augeninnendrucks zur frühzeitigen Erkennung potenzieller Risiken. Eine aufmerksame Überwachung bei beiden Geschlechtern ist essenziell, um die Gesundheit der Augen optimal zu schützen. Die Analyse der Augenbiometrie ergab, dass Männer im Vergleich zu Frauen generell größere beziehungsweise längere Augenparameter aufwiesen. Zudem wurden Hinweise auf geschlechtsspezifische Entwicklungsunterschiede bei Frühgeborenen gefunden, wobei bei beiden Geschlechtern eine dickere zentrale Foveadicke mit einem niedrigeren Gestationsalter einherging, diese Auswirkung jedoch bei Männern stärker ausgeprägt war. Des Weiteren wurde aufgezeigt, dass die visuelle Lebensqualität bei Frauen im Querschnitt schlechter ist und auch im Zeitverlauf stärker abfällt. Wichtig ist es hierbei nicht außer Acht zu lassen, dass Männer häufiger Symptome weniger kommunizieren oder weniger schwerwiegend einschätzen.

Schlussfolgernd lässt sich sagen, dass die Gendermedizin in der Augenheilkunde noch am Anfang steht und es weiterer Forschung bedarf, um eine patientenindividuelle Versorgung sicherzustellen. Die vorliegende Dissertation gibt erste Hinweise darauf, dass wenige geschlechterspezifische Unterschiede bezüglich der Physiologie und Augenanatomie, der visuellen Lebensqualität und den psychosozialen Einstellungen der Augenärzte bestehen. Für die Zukunft ist es von Bedeutung weitere Bereiche der Augenheilkunde geschlechterspezifisch zu erforschen, um eine patientenindividuelle Diagnostik und Therapie sicherzustellen.

Literaturverzeichnis

1. Lippi, D., R. Bianucci, and S. Donell, *Gender medicine: its historical roots.* Postgraduate Medical Journal, 2020. **96**(1138): p. 480-486. https://doi.org/10.1136/postgradmedj-2019-137452.
2. Pflegezeitschrift, *GenderMedizin in fünf Minuten*, in *Pflegezeitschrift*. 2020. *Pflegez* **73**, 36–37 (2020). https://doi.org/10.1007/s41906-019-0229-6.
3. Rieder, A. and B. Lohff, *Gender Medizin. Geschlechtsspezifische Aspekte für die klinische Praxis*. 2008. https://doi.org/10.1007/978-3-211-68290-6.
4. Haider, A., et al., *Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome.* European Heart Journal, 2019. **41**(13): p. 1328-1336. https://doi.org/10.1093/eurheartj/ehz898.
5. Townsend, N., et al., *Cardiovascular disease in Europe: epidemiological update 2016.* Eur Heart J, 2016. **37**(42): p. 3232-3245. https://doi.org/10.1093/eurheartj/ehw334.
6. Cleland, J.G., et al., *The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis.* Eur Heart J, 2003. **24**(5): p. 442-63. https://doi.org/10.1016/S0195-668X(02)00823-0.
7. Regitz-Zagrosek, V., *Geschlecht und Herz-Kreislauf-Erkrankungen.* Der Internist, 2017. **58**(4): p. 336-343. https://doi.org/10.1007/s00108-017-0214-3.
8. Blomkalns, A.L., et al., *Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative.* J Am Coll Cardiol, 2005. **45**(6): p. 832-7. https://doi.org/10.1016/j.jacc.2004.11.055.
9. Hvelplund, A., et al., *Women with acute coronary syndrome are less invasively examined and subsequently less treated than men.* Eur Heart J, 2010. **31**(6): p. 684-90. https://doi.org/10.1093/eurheartj/ehp493.
10. Deutsches Ärzteblatt, *Warum Herzinfarkte bei Frauen anders verlaufen.* 2016. Verfügbar unter: https://www.aerzteblatt.de/nachrichten/65522/Warum-Herzinfarkte-bei-Frauen-anders-verlaufen. Zuletzt aufgerufen am: 08.10.2023.
11. Coventry, L.L., J. Finn, and A.P. Bremner, *Sex differences in symptom presentation in acute myocardial infarction: a systematic review and meta-analysis.* Heart Lung, 2011. **40**(6): p. 477-91. https://doi.org/10.1016/j.hrtlng.2011.05.001.
12. Remfry, E., et al., *Sex-based differences in risk factors for incident myocardial infarction and stroke in the UK Biobank.* Eur Heart J Qual Care Clin Outcomes, 2024. **10**(2): p. 132-142. https://doi.org/10.1093/ehjqcco/qcad029.
13. Sasaki, M., et al., *Gender-specific association of early age-related macular degeneration with systemic and genetic factors in a Japanese population.* Scientific Reports, 2018. **8**(1): p. 785. https://doi.org/10.1038/s41598-017-18487-4.
14. Zhou, M., et al., *Geographic distributions of age-related macular degeneration incidence: a systematic review and meta-analysis.* British Journal of Ophthalmology, 2021. **105**(10): p. 1427-1434. https://doi.org/10.1136/bjophthalmol-2020-316820.
15. Vajaranant, T.S., et al., *Gender and glaucoma: what we know and what we need to know.* Curr Opin Ophthalmol, 2010. **21**(2): p. 91-9. https://doi.org/10.1097/ICU.0b013e3283360b7e.
16. Tehrani, S., *Gender Difference in the Pathophysiology and Treatment of Glaucoma.* Current Eye Research, 2015. **40**(2): p. 191-200. https://doi.org/10.3109/02713683.2014.968935.
17. Gamulescu, M.A., *[Gender medicine in ophthalmology : The "small difference" between women and men].* Ophthalmologe, 2020. **117**(8): p. 831-842. https://doi.org/10.1007/s00347-020-01174-7.
18. Hartmann, A., et al., *Berufliche Zukunftsperspektive von Augenärzten unter 49 Jahren.* Die Ophthalmologie, 2023. **120**(7): p. 726-733. https://doi.org/10.1007/s00347-022-01806-0.

19. Gill, H.K., et al., *An Eye on Gender Equality: A Review of the Evolving Role and Representation of Women in Ophthalmology.* American Journal of Ophthalmology, 2022. **236**: p. 232-240. https://doi.org/10.1016/j.ajo.2021.07.006.
20. Rudnicka, E., et al., *The World Health Organization (WHO) approach to healthy ageing.* Maturitas, 2020. **139**: p. 6-11. https://doi.org/10.1016/j.maturitas.2020.05.018.
21. Gemmati, D., et al., *“Bridging the Gap” Everything that Could Have Been Avoided If We Had Applied Gender Medicine, Pharmacogenetics and Personalized Medicine in the Gender-Omics and Sex-Omics Era.* International Journal of Molecular Sciences, 2020. **21**(1): p. 296. https://doi.org/10.3390/ijms21010296
22. Johnson P.A., F.T., Glynn A., Salganicoff A., Wood S.F., Goldstein J.M. , *Precision Medicine: How Sex and Gender Drive Innovation.* 2016. DOI: http://www.tbf.org/~/media/TBFOrg/Files/Reports/ConnorsCenterBrochure-2016.pdf2016. Zuletzt aufgerufen am 16.01.2025.
23. De Loof, A., *Only two sex forms but multiple gender variants: How to explain?* Commun Integr Biol, 2018. **11**(1): p. e1427399. https://doi.org/10.1080/19420889.2018.1427399.
24. Joel, D., *Genetic-gonadal-genitals sex (3G-sex) and the misconception of brain and gender, or, why 3G-males and 3G-females have intersex brain and intersex gender.* Biol Sex Differ, 2012. **3**(1): p. 27. https://doi.org/10.1186/2042-6410-3-27.
25. Bhargava, A., et al., *Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement.* Endocr Rev, 2021. **42**(3): p. 219-258. https://doi.org/10.1210/endrev/bnaa034.
26. Kautzky-Willer, A., *Gendermedizin.* Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz, 2014. **57**(9): p. 1022-1030. https://doi.org/10.1007/s00103-014-2011-7.
27. Borna, S. and G. White, *"Sex" and "Gender": Two Confused and Confusing Concepts in the "Women in Corporate Management" Literature.* Journal of Business Ethics, 2003. **47**(2): p. 89-99. https://doi.org/10.1023/A:1026082400801.
28. Heise, L., et al., *Gender inequality and restrictive gender norms: framing the challenges to health.* The Lancet, 2019. **393**(10189): p. 2440-2454. https://doi.org/10.1016/S0140-6736(19)30652-X.
29. Basu, S., et al., *Learning to Be Gendered: Gender Socialization in Early Adolescence Among Urban Poor in Delhi, India, and Shanghai, China.* J Adolesc Health, 2017. **61**(4s): p. S24-s29. https://doi.org/10.1016/j.jadohealth.2017.03.012.
30. Shai, A., S. Koffler, and Y. Hashiloni-Dolev, *Feminism, gender medicine and beyond: a feminist analysis of "gender medicine".* International Journal for Equity in Health, 2021. **20**(1): p. 177. https://doi.org/10.1186/s12939-021-01511-5.
31. Oertelt-Prigione, S. and S. Hiltner, *Medizin: Gendermedizin im Spannungsfeld zwischen Zukunft und Tradition*, in *Handbuch Interdisziplinäre Geschlechterforschung*, B. Kortendiek, B. Riegraf, and K. Sabisch, Editors. 2018, Springer Fachmedien Wiesbaden: Wiesbaden. p. 1-10 https://doi.org/10.1007/978-3-658-12500-4_139-1.
32. Bohon, C.J. and W.A. Sadler, *Women's Health Equity Act.* Women's Health Issues, 1991. **1**(4): p. 193-194. https://doi.org/10.1016/S1049-3867(05)80217-8.
33. Rescigno, F., *Gender medicine as a tool for implementing the right to health.* International Journal of Risk & Safety in Medicine, 2022. **33**: p. 185-192. https://doi.org/10.3233/JRS-227009.
34. Institute of Medicine Committee on Understanding the Biology of, S. and D. Gender, *The National Academies Collection: Reports funded by National Institutes of Health*, in *Exploring the Biological Contributions to Human Health: Does Sex Matter?*, T.M. Wizemann and M.L. Pardue, Editors. 2001, National Academies Press (US) Copyright 2001 by the National Academy of Sciences. All rights reserved.: Washington (DC). https://doi.org/10.17226/10028.
35. Merone, L., et al., *Sex Inequalities in Medical Research: A Systematic Scoping Review of the Literature.* Womens Health Rep (New Rochelle), 2022. **3**(1): p. 49-59. https://doi.org/10.1089/whr.2021.0083.
36. Daitch, V., et al., *Underrepresentation of women in randomized controlled trials: a systematic review and meta-analysis.* Trials, 2022. **23**(1): p. 1038. https://doi.org/10.1186/s13063-022-07004-2.
37. Cottingham, M.D. and J.A. Fisher, *Gendered Logics of Biomedical Research: Women in U.S. Phase I Clinical Trials.* Social Problems, 2020. **69**(2): p. 492-509. https://doi.org/10.1093/socpro/spaa035.

38. Liu, K.A. and N.A. Mager, *Women's involvement in clinical trials: historical perspective and future implications.* Pharm Pract (Granada), 2016. **14**(1): p. 708. https://doi.org/10.18549/PharmPract.2016.01.708.
39. Waltz, M., A.D. Lyerly, and J.A. Fisher, *Exclusion of Women from Phase I Trials: Perspectives from Investigators and Research Oversight Officials.* Ethics Hum Res, 2023. **45**(6): p. 19-30. https://doi.org/10.1002/eahr.500170.
40. Cain, J., et al., *Contraceptive requirements for clinical research.* Obstetrics & Gynecology, 2000. **95**(6, Part 1): p. 861-866. https://doi.org/10.1016/S0029-7844(00)00824-3.
41. Doyal, L., *Sex and gender: the challenges for epidemiologists.* Int J Health Serv, 2003. **33**(3): p. 569-79. https://doi.org/10.2190/cwk2-u7r6-vce0-e47p.
42. Garofalo, E.M. and H.M. Garvin, *Chapter 4 - The confusion between biological sex and gender and potential implications of misinterpretations*, in *Sex Estimation of the Human Skeleton*, A.R. Klales, Editor. 2020, Academic Press. p. 35-52. https://doi.org/10.1016/B978-0-12-815767-1.00004-3.
43. Simon, V., *Wanted: women in clinical trials.* Science, 2005. **308**(5728): p. 1517. https://doi.org/10.1126/science.1115616.
44. Nolan, M.R. and T.L. Nguyen, *Analysis and reporting of sex differences in phase III medical device clinical trials-how are we doing?* J Womens Health (Larchmt), 2013. **22**(5): p. 399-401. https://doi.org/10.1089/jwh.2013.4400.
45. Harkin, T.S., et al. *Drug Safety : Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women*. 2001. Verfügbar unter: https://www.gao.gov/products/gao-01-286r. Zuletzt aufgerufen am: 16.01.2025
46. Hartmann, A., et al., *Bi-Gaussian analysis reveals distinct education-related alterations in spherical equivalent and axial length-results from the Gutenberg Health Study.* Graefes Arch Clin Exp Ophthalmol, 2024. **262**(6): p. 1819-1828. https://doi.org/10.1007/s00417-024-06395-z.
47. Fieß, A., et al., *Sex-Specific Differences in the Relationship Between Prematurity and Ocular Geometry.* Investigative Ophthalmology & Visual Science, 2024. **65**(6): p. 23-23. https://doi.org/10.1167/iovs.65.6.23.
48. Fieß, A., et al., *Low Birth Weight Is Linked to Age-Related Macular Degeneration: Results From the Population-Based Gutenberg Health Study (GHS).* Investigative ophthalmology & visual science, 2019. **60**(14): p. 4943-4950. https://doi.org/10.1167/iovs.19-27964.
49. Hartmann, A., et al., *Intraocular Pressure and Its Relation to Climate Parameters—Results From the Gutenberg Health Study.* Investigative Ophthalmology & Visual Science, 2023. **64**(7): p. 15-15. https://doi.org/10.1167/iovs.64.7.15.
50. Laspas, P., et al., *Change in Systemic Medication and its Influence on Intraocular Pressure - Results From the Gutenberg Health Study.* Invest Ophthalmol Vis Sci, 2024. **65**(14): p. 4. https://doi.org/10.1167/iovs.65.14.4.
51. Hartmann, A., et al., *Change of Intraocular Pressure Over 5 Years and its Relationship to Cardiovascular Parameters: Results From the Gutenberg Health Study.* Investigative Ophthalmology & Visual Science, 2024. **65**(1): p. 12-12. https://doi.org/10.1167/iovs.65.1.12.
52. Kolačko, Š., et al., *Do Gender, Age, Body Mass and Height Influence Eye Biometrical Properties in Young Adults? A Pilot Study.* Int J Environ Res Public Health, 2021. **18**(21). https://doi.org/10.3390/ijerph182111719.
53. Sun, Y., et al., *Distribution of ocular biometry in young Chinese eyes: The Anyang University Students Eye Study.* Acta Ophthalmologica, 2021. **99**(6): p. 621-627. https://doi.org/10.1111/aos.14710.
54. Zhao, M.H., et al., *Investigation of ocular biometry in 4- to 9-year-old Chinese children.* BMC Ophthalmol, 2023. **23**(1): p. 225. https://doi.org/10.1186/s12886-023-02975-5.
55. Lim, L.S., et al., *Distribution and Determinants of Ocular Biometric Parameters in an Asian Population: The Singapore Malay Eye Study.* Investigative Ophthalmology & Visual Science, 2010. **51**(1): p. 103-109. https://doi.org/10.1167/iovs.09-3553.
56. Logan, N.S., et al., *Ametropia and ocular biometry in a U.K. university student population.* Optom Vis Sci, 2005. **82**(4): p. 261-6. https://doi.org/10.1097/01.opx.0000159358.71125.95.

57. Poplin, R., et al., *Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning.* Nat Biomed Eng, 2018. **2**(3): p. 158-164. https://doi.org/10.1038/s41551-018-0195-0.
58. Zhang, Y., et al., *Gender differences in refraction prediction error of five formulas for cataract surgery.* BMC Ophthalmol, 2021. **21**(1): p. 183. https://doi.org/10.1186/s12886-021-01950-2.
59. Yassin, S.A. and E.R. Al-Tamimi, *Age, gender and refractive error association with intraocular pressure in healthy Saudi participants: A cross-sectional study.* Saudi J Ophthalmol, 2016. **30**(1): p. 44-8. https://doi.org/10.1016/j.sjopt.2015.11.007.
60. Hohberger, B., et al., *Germany: Longitudinal analysis of intraocular pressure in healthy eyes.* Cogent Medicine, 2020. **7**(1): p. 1750862. https://doi.org/10.1080/2331205X.2020.1750862.
61. Klein, B.E., R. Klein, and K.L. Linton, *Intraocular pressure in an American community. The Beaver Dam Eye Study.* Invest Ophthalmol Vis Sci, 1992. **33**(7): p. 2224-8.
62. Liu, X., et al., *Variation in intraocular pressure by sex, age, and geographic location in China: A nationwide study of 284,937 adults.* Front Endocrinol (Lausanne), 2022. **13**: p. 949827. https://doi.org/10.3389/fendo.2022.949827.
63. Panchami, et al., *Postmenopausal intraocular pressure changes in South Indian females.* J Clin Diagn Res, 2013. **7**(7): p. 1322-4. https://doi.org/10.7860/jcdr/2013/5325.3145.
64. Vajaranant, T.S., et al., *Effects of Hormone Therapy on Intraocular Pressure: The Women's Health Initiative-Sight Exam Study.* Am J Ophthalmol, 2016. **165**: p. 115-24. https://doi.org/10.1016/j.ajo.2016.02.025.
65. Sator, M.O., et al., *Hormone replacement therapy and intraocular pressure.* Maturitas, 1997. **28**(1): p. 55-8. https://doi.org/10.1016/s0378-5122(97)00060-1.
66. Altıntaş, Ö., et al., *The Effects of Menopause and Hormone Replacement Therapy on Quality and Quantity of Tear, Intraocular Pressure and Ocular Blood Flow.* Ophthalmologica, 2004. **218**: p. 120 - 129. https://doi.org/10.1159/000076148.
67. Deutsches Ärztesblatt, *Immer weniger Frauen nehmen in Wechseljahren Hormonpräparate.* 2021. Verfügbar unter: https://www.aerzteblatt.de/nachrichten/125916/Immer-weniger-Frauen-nehmen-in-Wechseljahren-Hormonpraeparate#:~:text=Dienstag%2C%2027.%20Juli%202021&text=Hamburg%20%E2%80%93%20Immer%20weniger%20Frauen%20nehmen,Krankenkasse%20heute%20in%20Hamburg%20mitteilte. Zuletzt aufgerufen am: 12.11.2023.
68. Keers, R. and K.J. Aitchison, *Gender differences in antidepressant drug response.* International Review of Psychiatry, 2010. **22**(5): p. 485-500. https://doi.org/10.3109/09540261.2010.496448.
69. Khan, A., et al., *Sex differences in antidepressant response in recent antidepressant clinical trials.* J Clin Psychopharmacol, 2005. **25**(4): p. 318-24. https://doi.org/10.1097/01.jcp.0000168879.03169.ce.
70. Yang, S.J., et al., *Gender differences in 12-week antidepressant treatment outcomes for a naturalistic secondary care cohort: the CRESCEND study.* Psychiatry Res, 2011. **189**(1): p. 82-90. https://doi.org/10.1016/j.psychres.2010.12.027.
71. Entsuah, A.R., H. Huang, and M.E. Thase, *Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo.* J Clin Psychiatry, 2001. **62**(11): p. 869-77. https://doi.org/10.4088/jcp.v62n1106.
72. Thiels, C., et al., *Gender differences in routine treatment of depressed outpatients with the selective serotonin reuptake inhibitor sertraline.* Int Clin Psychopharmacol, 2005. **20**(1): p. 1-7. https://doi.org/10.1097/00004850-200501000-00001.
73. Gougoulaki, M., et al., *Sex differences in depressive symptoms and tolerability after treatment with selective serotonin reuptake inhibitor antidepressants: Secondary analyses of the GENPOD trial.* Journal of Psychopharmacology, 2021. **35**(8): p. 919-927. https://doi.org/10.1177/0269881120986417.
74. Sramek, J.J., M.F. Murphy, and N.R. Cutler, *Sex differences in the psychopharmacological treatment of depression.* Dialogues Clin Neurosci, 2016. **18**(4): p. 447-457. https://doi.org/10.31887/DCNS.2016.18.4/ncutler.

75. Hartmann, A., et al., *Gender-specific changes in vision-related quality of life over time – results from the population-based Gutenberg Health Study.* Graefe's Archive for Clinical and Experimental Ophthalmology, 2025. https://doi.org/10.1007/s00417-025-06741-9.
76. Rausch-Koster, P.T., et al., *Predictors of vision-related quality of life in patients with macular oedema receiving intra-vitreal anti-VEGF treatment.* Ophthalmic and Physiological Optics, 2022. **42**(4): p. 849-857. https://doi.org/10.1111/opo.12984.
77. Nickels, S., et al., *Vision-related quality of life considering both eyes: results from the German population-based Gutenberg Health Study (GHS).* Health Qual Life Outcomes, 2019. **17**(1): p. 98. https://doi.org/10.1186/s12955-019-1158-1.
78. Sturrock, B.A., et al., *The Influence of Coping on Vision-Related Quality of Life in Patients With Low Vision: A Prospective Longitudinal Study.* Investigative Ophthalmology & Visual Science, 2015. **56**(4): p. 2416-2422. https://doi.org/10.1167/iovs.14-16223.
79. Courtright, P., *Gender and blindness: Taking a global and a local perspective.* Oman J Ophthalmol, 2009. **2**(2): p. 55-6. https://doi.org/10.4103/0974-620x.53032.
80. Abou-Gareeb, I., et al., *Gender and blindness: a meta-analysis of population-based prevalence surveys.* Ophthalmic Epidemiology, 2001. **8**(1): p. 39-56. https://doi.org/10.1076/opep.8.1.39.1540.
81. Nowak, M.S. and J. Smigielski, *The Prevalence of Age-Related Eye Diseases and Cataract Surgery among Older Adults in the City of Lodz, Poland.* J Ophthalmol, 2015. **2015**: p. 605814. https://doi.org/10.1155/2015/605814.
82. Tan, A.G., et al., *Comparison of age-specific cataract prevalence in two population-based surveys 6 years apart.* BMC Ophthalmology, 2006. **6**(1): p. 17. https://doi.org/10.1186/1471-2415-6-17.
83. Prasad, M., et al., *Gender differences in blindness, cataract blindness and cataract surgical coverage in India: a systematic review and meta-analysis.* Br J Ophthalmol, 2020. **104**(2): p. 220-224. https://doi.org/10.1136/bjophthalmol-2018-313562.
84. Fang, R., et al., *Global, regional, national burden and gender disparity of cataract: findings from the global burden of disease study 2019.* BMC Public Health, 2022. **22**(1): p. 2068. https://doi.org/10.1186/s12889-022-14491-0.
85. García-Corchero, J.D. and D. Jiménez-Rubio, *Waiting times in healthcare: equal treatment for equal need?* International Journal for Equity in Health, 2022. **21**(1): p. 184. https://doi.org/10.1186/s12939-022-01799-x.
86. Schuster, A.K., et al., *Inanspruchnahme von augenärztlichen Leistungen bei Versicherten mit Pflegebedarf.* Der Ophthalmologe, 2018. **115**(10): p. 832-841. https://doi.org/10.1007/s00347-018-0694-0.
87. Demmin, D.L. and S.M. Silverstein, *Visual Impairment and Mental Health: Unmet Needs and Treatment Options.* Clin Ophthalmol, 2020. **14**: p. 4229-4251. https://doi.org/10.2147/opth.S258783.
88. van der Aa, H.P., et al., *Validated Prediction Model of Depression in Visually Impaired Older Adults.* Ophthalmology, 2016. **123**(5): p. 1164-6. https://doi.org/10.1016/j.ophtha.2015.11.028.
89. Salk, R.H., J.S. Hyde, and L.Y. Abramson, *Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms.* Psychol Bull, 2017. **143**(8): p. 783-822. https://doi.org/10.1037/bul0000102.
90. Albert, P.R., *Why is depression more prevalent in women?* J Psychiatry Neurosci, 2015. **40**(4): p. 219-21. https://doi.org/10.1503/jpn.150205.
91. Freeman, E.W., et al., *Associations of Hormones and Menopausal Status With Depressed Mood in Women With No History of Depression.* Archives of General Psychiatry, 2006. **63**(4): p. 375-382. https://doi.org/10.1001/archpsyc.63.4.375.
92. Angst, J., et al., *Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies.* Eur Arch Psychiatry Clin Neurosci, 2002. **252**(5): p. 201-9. https://doi.org/10.1007/s00406-002-0381-6.
93. Kang, H.-J., et al., *Sex differences in the genetic architecture of depression.* Scientific Reports, 2020. **10**(1): p. 9927. https://doi.org/10.1038/s41598-020-66672-9.
94. Bacigalupe, A., et al., *Is the diagnosis and treatment of depression gender-biased? Evidence from a population-based aging cohort in Sweden.* Int J Equity Health, 2024. **23**(1): p. 252. https://doi.org/10.1186/s12939-024-02320-2.

95. Barsky, A.J., H.M. Peekna, and J.F. Borus, *Somatic symptom reporting in women and men.* J Gen Intern Med, 2001. **16**(4): p. 266-75. https://doi.org/10.1046/j.1525-1497.2001.00229.x.
96. Kroenke, K. and R.L. Spitzer, *Gender differences in the reporting of physical and somatoform symptoms.* Psychosom Med, 1998. **60**(2): p. 150-5. https://doi.org/10.1097/00006842-199803000-00006.
97. Ladwig, K.H., et al., *Gender differences of symptom reporting and medical health care utilization in the German population.* Eur J Epidemiol, 2000. **16**(6): p. 511-8. https://doi.org/10.1023/a:1007629920752.
98. Ballering, A.V., et al., *Gender and sex independently associate with common somatic symptoms and lifetime prevalence of chronic disease.* Social Science & Medicine, 2020. **253**: p. 112968. https://doi.org/10.1016/j.socscimed.2020.112968.
99. Bekker, M.H.J., M.A. Croon, and S. Vermaas, *Inner body and outward appearance—the relationship between orientation toward outward appearance, body awareness and symptom perception.* Personality and Individual Differences, 2002. **33**(2): p. 213-225. https://doi.org/10.1016/S0191-8869(01)00146-5.
100. Mahalik, J.R., S.M. Burns, and M. Syzdek, *Masculinity and perceived normative health behaviors as predictors of men's health behaviors.* Soc Sci Med, 2007. **64**(11): p. 2201-9. https://doi.org/10.1016/j.socscimed.2007.02.035.
101. Hammond, W.P., D. Matthews, and G. Corbie-Smith, *Psychosocial factors associated with routine health examination scheduling and receipt among African American men.* J Natl Med Assoc, 2010. **102**(4): p. 276-89. https://doi.org/10.1016/s0027-9684(15)30600-3.
102. Novak, J.R., et al., *Associations Between Masculine Norms and Health-Care Utilization in Highly Religious, Heterosexual Men.* Am J Mens Health, 2019. **13**(3): p. 1557988319856739. https://doi.org/10.1177/1557988319856739.
103. Hedegaard, H., S.C. Curtin, and M. Warner, *Suicide Mortality in the United States, 1999-2019.* NCHS Data Brief, 2021(398): p. 1-8. Verfügbar unter: https://www.cdc.gov/nchs/products/databriefs/db398.htm. Zuletzt aufgerufen am: 17.01.2025.
104. Call, J.B. and K. Shafer, *Gendered Manifestations of Depression and Help Seeking Among Men.* Am J Mens Health, 2018. **12**(1): p. 41-51. https://doi.org/10.1177/1557988315623993.
105. Lo, T.C.S., et al., *Differences in practice of ophthalmology by gender in Australia.* Clin Exp Ophthalmol, 2019. **47**(7): p. 840-846. https://doi.org/10.1111/ceo.13523.
106. Khan, H. and M. Moosajee, *Facing up to gender inequality in ophthalmology and vision science.* Eye (Lond), 2018. **32**(9): p. 1421-1422. https://doi.org/10.1038/s41433-018-0147-7.
107. Nair, A.G., et al., *Work satisfaction, burnout and gender-based inequalities among ophthalmologists in India: A survey.* Work, 2017. **56**(2): p. 221-228. https://doi.org/10.3233/wor-172488.
108. Jolly, S., et al., *Gender differences in time spent on parenting and domestic responsibilities by high-achieving young physician-researchers.* Ann Intern Med, 2014. **160**(5): p. 344-53. https://doi.org/10.7326/m13-0974.
109. Ly, D.P. and A.B. Jena, *Sex Differences in Time Spent on Household Activities and Care of Children Among US Physicians, 2003-2016.* Mayo Clin Proc, 2018. **93**(10): p. 1484-1487. https://doi.org/10.1016/j.mayocp.2018.02.018.
110. Yashadhana, A., et al., *Gender and ethnic diversity in global ophthalmology and optometry association leadership: a time for change.* Ophthalmic Physiol Opt, 2021. **41**(3): p. 623-629. https://doi.org/10.1111/opo.12793.

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Publikationen

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1. Fieß A*, **Hartmann A***, Mildenberger E, Urschitz MS, Laspas P, Schultheis A, Stoffelns B, Pfeiffer N, Gißler S#, Schuster AK#. Sex-Specific Differences in the Relationship Between Prematurity and Ocular Geometry. Investigative Ophthalmology & Visual Science (IOVS): https://doi.org/10.1167/iovs.65.6.23

2. **Hartmann A**, Grabitz SD, Hoffmann E, Wild PS, Schmidtmann I, Lackner KJ, Beutel ME, Münzel T, Tüscher O, Schattenberg JM, Pfeiffer N, and Schuster AK. Intraocular Pressure and Its Relation to Climate Parameters—Results From the Gutenberg Health Study. Investigative Ophthalmology & Visual Science (IOVS): https://doi.org/10.1167/iovs.64.7.15

3. **Hartmann A,** Scholz I, Hoffmann EM, Strzalkowska A, Lackner KJ, Münzel T, Wicke F, Schmidtmann I, Tüscher O, Schattenberg JM, Konstantinides S, Wild PS, Pfeiffer N, Schuster AK. Change of intraocular pressure over 5 years and its relationship to cardiovascular parameters – results from the Gutenberg Health Study. Investigative Ophthalmology & Visual Science: https://doi.org/10.1167/iovs.65.1.12

4. **Hartmann A**, Bertram B, Siebelmann S, Böhm M, Faber H, Zhour A, Schuster AK. Berufliche Zukunftsperspektive von Augenärzten unter 49 Jahren. Die Ophthalmologie 2023: https://doi.org/10.1007/s00347-022-01806-0

5. **Hartmann A**, Grabitz SD, Wagner FM, Wild PS, Müller-Nurasyid M, Lackner KJ, Beutel ME, Münzel T, Tüscher O, Jörn Markus Schattenberg, Norbert Pfeiffer & Alexander Karl-Georg Schuster**.** Bi-Gaussian analysis reveals distinct education-related alterations in spherical equivalent and axial length—results from the Gutenberg Health Study. Graefes Arch Clin Exp Ophthal-mol (2024): https://doi.org/10.1007/s00417-024-06395-z

6. Fieß A*, Gißler S*, Mildenberger E, Hoffmann E, Laspas P, Stoffelns B, Pfeiffer N, **Hartmann A#**, Schuster A#. Fetal growth restriction leads to an enlarged cup-to-disc ratio in adults born at full term. American Journal of Ophthalmology: https://doi.org/10.1016/j.ajo.2024.02.008

7. Fieß A*, Gißler S*, Mildenberger E, Urschitz MS, Laspas P, Stoffelns B, Pfeiffer N, **Hartmann A#**, Schuster AK#. Macular morphology is not affected by low or high birth weight in individuals born at term – Results from the Gutenberg Prematurity Eye Study. Acta Ophthalmol, 102: e657-e658: https://doi.org/10.1111/aos.16666

8. Fieß A*, **Hartmann A***, Hoffmann EM, Mildenberger E, Stingl J, Pfeiffer N, Gißler S, Schuster AK. The impact of different types of prenatal growth restriction on retinal nerve fibre layer thickness. Acta ophthalmologica. https://doi.org/10.1111/aos.17426

9. Laspas, P*, **Hartmann A*,** Scholz I, Hoffmann EM, Khawaja AP, Lackner KJ, Münzel T, Kerahrodi JG, Schmidtmann I, Tüscher O, Schattenberg JM, Pfeiffer N, Konstantinidis S, Wild PS, Schuster AK. Change in Systemic Medication and its Influence on Intraocular Pressure – Results From the Gutenberg Health Study. Investigative Ophthalmology & Visual Science (IOVS): https://doi.org/10.1167/iovs.65.14.4

10. **Hartmann A**, Grabitz SD, Wild PS, Lackner KJ, Münzel T, Ghaemi Kerahrodi J, Singer S, Geschke K, Schattenberg JM, Konstantinides S, Pfeiffer N & Schuster AK. Gender-specific changes in vision-related quality of life over time – results from the population-based Gutenberg Health Study. Graefes Arch Clin Exp Ophthalmol (2025). https://doi.org/10.1007/s00417-025-06741-9

PRÄSENTATIONEN

„Intraocular pressure and its relation to climate parameters – results from the Gutenberg Health Study“. Konferenz der Association for Research in Vision and Ophthalmology (ARVO) im April. 2023 in New Orleans, USA.

„Frequency of COVID-19 symptoms in the general population: an analysis of the Gutenberg COVID-19 Study“. Deutsche Ophthalmologische Gesellschaft (DOG) Konferenz im September 2022 in Berlin, Deutschland.

„Changes in intraocular pressure over 5 years and its relationship with cardiovascular parameters - results of the Gutenberg Health Study". Deutsche Ophthalmologische Gesellschaft (DOG) Konferenz im September 2023 in Berlin, Deutschland.

ZERTIFIKAT

Coursera – Data Analysis with R
(URL: https://www.coursera.org/account/accomplishments/specialization/certificate/F5AW3J3H7JJU)