Association Between Medication-Taking and Refractive Error in a Large General Population-Based Cohort

Karina Patasova,[1,2] Anthony P. Khawaja,[3] Bani Tamraz,[4] Katie M. Williams,[1–3,5,6] Omar A. Mahroo,[1–3,5,6] Maxim Freidin,[2] Ameenat L. Solebo,[7] Jelle Vehof,[1,2,8] Mario Falchi,[2] Jugnoo S. Rahi,[6,9] Chris J. Hammond,[1,2] and Pirro G. Hysi[1,2,7]

[1]Section of Ophthalmology, School of Life Course Sciences, King's College London, United Kingdom
[2]Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, United Kingdom
[3]NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and the UCL Institute of Ophthalmology, London, United Kingdom
[4]Department of Clinical Pharmacy, University of California San Francisco, San Francisco, California, United States
[5]Department of Ophthalmology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[6]Institute of Ophthalmology, University College London, London, United Kingdom
[7]UCL Great Ormond Street Hospital Institute of Child Health, London, United Kingdom
[8]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[9]Ulverscroft Vision Research Group, University College London, London, United Kingdom

Correspondence: Pirro G. Hysi, Section of Ophthalmology, School of Life Course Sciences, St Thomas' Hospital, King's College London, Westminster Bridge Road, London SE1 7EH, UK; pirro.hysi@kcl.ac.uk.

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Purpose. Refractive errors, particularly myopia, are common and a leading cause of blindness. This study aimed to explore associations between medications and refractive error in an aging adult cohort and to determine whether childhood-onset refractive errors predict future medication use to provide novel insights into disease mechanisms.

Methods. The study compared the spherical equivalent values measured in 102,318 UK Biobank participants taking the 960 most commonly used medications. The strengths of associations were evaluated against the self-reported age of spectacle wear. The causality of refractive error changes was inferred using sensitivity and Mendelian randomization analyses.

Results. Anti-glaucoma drugs were associated with 1 to 2 diopters greater myopic refraction, particularly in subjects who started wearing correction in the first two decades of life, potentially due to the association of higher intraocular pressure since early years with both myopia and, later in life, glaucoma. All classes of pain-control medications, including paracetamol, opiates, non-steroidal antiinflammatory drugs, and gabapentinoids, were associated with greater hyperopia (+0.68–1.15 diopters), after correction for deprivation, education, and polypharmacy and sensitivity analyses for common diagnoses. Oral hypoglycemics (metformin, gliburonide) were associated with myopia, as was allopurinol, and participants using bronchodilators (ipratropium and salbutamol) were more hyperopic.

Conclusions. This study finds for the first time, to our knowledge, that medication use is associated with refractive error in adults. The novel finding that analgesics are associated with hyperopic refraction, and the possibility that multisite chronic pain predisposes to hyperopia, deserves further research. Some drugs, such as antihyperglycemic or bronchodilators, may directly alter refractive error. Intraocular pressure appears causative for myopia.

Keywords: myopia, medications, intraocular pressure, chronic pain, refractive error

Refractive errors arise from mismatches between the light-converging power of the cornea and lens and the axial length of the eye. They are common[1] and increasingly a cause of visual impairment in many communities.[2] Of the different forms of refractive error, myopia is by far the most prevalent. The prevalence of myopia is rising worldwide, especially in Asia,[3] but also in Europe[4] and the rest of the world.[5] At the current pace of growth, half of the world population is expected to develop myopia by 2050.[6]

Factors affecting myopia prevalence are wide ranging from perinatal to early developmental.[7] Educational attainment[8] and behavioral factors, such as time spent outdoors,[9,10] are important drivers of generational shifts in the prevalence of myopia.[11] Nevertheless, cultural and socioeconomic changes are often intercorrelated spatially and temporally. Disentangling effects of each social and cultural factor from others is challenging. For example, the extra time spent indoors coincides with an environment that

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is changing its dioptric structure[12] and ambient light intensity, as well as concurrent cultural changes, such as diet, also associated with myopia in children.[13] Several other environmental and cultural factors also vary across generations and may contribute to myopia risk.[14] Morbidity structure and patterns of medication use are also likely to have altered through generations, potentially affecting the eye and its optical properties.[15]

Documented drug-induced refractive errors are mostly described in relation to transient myopia or other idiosyncratic ocular manifestations in the eye.[15,16] It is currently unknown whether subtler, chronic changes in the spherical equivalent (SpE) are associated with commonly prescribed medications in the broader community. The investigation of systemic medication use in relation to spherical equivalent might help identify potentially modifiable risk factors. This study aims to investigate potential associations between commonly used medications and refractive error. It explores the hypotheses that medication taken in adulthood is associated with altered SpE measurements and whether refraction status in earlier ages is associated with morbidity and medication-taking patterns in later life. This would give us insights into the etiology of these conditions and provide opportunities for their early detection and prevention.

Methods

Study Population

The UK Biobank cohort includes 502,682 participants, all UK residents selected from the UK National Health Service register.[17] Participants provided extensive reports on their lifestyle and environmental exposures, either by filling in touch-screen questionnaires or through face-to-face interviews.[17] All UK Biobank data were acquired cross-sectionally, although previous medical histories were also reported and coded according to the International Classification of Diseases, 10th Revision (ICD10; standard UK Biobank field number 41270)[17] or retrospectively recorded as answers to questionnaires.

Approximately 23% (N = 117,279) of all participants underwent a comprehensive ophthalmological examination.[18] Noncycloplegic autorefraction was performed cross-sectionally at the time of recruitment, using a Tomey RC 5000 device (Tomey Corp., Nagoya, Japan), and for each participant the spherical equivalent was calculated as SpE = sphere + $\frac{1}{2}$ cylinder power (UK Biobank field numbers 5084-5085, 5086-5087) for each eye separately. The spherical equivalent measure that we have used in this study represents the average SpE of the left and right eyes. Measurements from one eye were used if data from the fellow eye were unavailable. Following previously published recommendations,[19] we excluded participants with a previous history of eye surgery, self-reported cataract with mild myopia, or bilateral or unilateral eye injury resulting in vision loss (SpE measurements in the intact, healthy eye were included). To minimize confounding arising from the population genetic structure, we limited the study sample to individuals of European ancestry, as ascertained by using genetic information.

In addition, the UK Biobank participants retrospectively reported the age at first refractive correction (hereafter referred to as the age of spectacle wear, AOSW). The information about AOSW was collected during the imaging visit, which included refractive error assessment. Information on medication use was also collected retrospectively, using touch-screen questionnaires and face-to-face interviews.[20] The names of the treatments, but not the dosage or the duration of treatment, were recorded. Participants were asked to answer the question "Do you regularly take any prescription medications?" and were prompted to specify what they were taking.[20] The interviewer recorded the name of both prescription and over-the-counter medications.[20] The regular prescription medications were defined as regular treatments taken daily, weekly, monthly, or quarterly, for drugs such as depot injections.[20] Drugs taken transiently (for example, a single-week course of antibiotics or analgesics taken 2 days before the interview) and recently discontinued treatments were not recorded.[20] Names of medications were selected from listed options that included both generic and trade names.

For our analyses, we matched available generic and trade names to the active ingredients. Active ingredients of brand names were retrieved using information from the electronic medicine compendium (available at https://www.medicines.org.uk/emc/). We selected pharmaceutical drugs that had at least 10 users of European ancestry in our dataset and excluded topical dermatological treatments, as well as herbal and homoeopathic remedies. We specifically included medication taken systemically (orally and parenterally), inhalers, and eye drops. When more than one active ingredient was present in one medication, each was counted as if separately prescribed and added to the count of medications containing the same specific active ingredient alone. Polypharmacy was defined as the reported intake of 5 or more medications during the reporting period,[21] even though these medications were not necessarily taken at the exact same time. In the subsequent paragraphs, we will use the term "medication" interchangeably for "active ingredient."

We included polypharmacy, physical activity, social and economic conditions, and other potential confounders as relevant covariates in our analyses. Physical activity of the study participants was ascertained through touch-screen questionnaires asking about all other forms of exertion, whether occupational or leisure. The length, intensity, and typical duration of daily walking and of moderate or vigorous physical activity (UK Biobank field numbers 864, 874, 894), the 24-recall of those activities (UK Biobank field numbers 104920, 104910, 104900), and the frequency of physical activity that lasted for at least 10 minutes (field numbers 864, 884, 904) were documented.

Years of education were calculated from self-reported data on academic and professional qualifications (field number 6138) according to the International Standard Classification of Education categories.[22] The Townsend deprivation index (field number 189) was calculated by aggregating data from the national census, based on previously described methods.[23] The Townsend deprivation index was used as a proxy for a participant's socioeconomic status.[24] The index is based on four components of material deprivation: (1) unemployment, (2) car non-ownership, (3) home non-ownership, and (4) household overcrowding.[24]

The study received the approval of the institutional and/or national research committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all study participants at recruitment.

Statistical Analyses

Descriptive analyses were performed using the epiDisplay package in R (R Foundation for Statistical

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Computing, Vienna, Austria). We calculated means, standard errors, medians, and interquartile ranges for normally and non-normally distributed continuous variables. Categorical data were described by computing frequencies. Results were considered statistically significant if they passed the threshold of 0.05.

The associations between refractive error and medications were tested in linear mixed models (LMMs). We used lme4[25] and lmertest[26] packages to generate the models. SpE was not fully normally distributed; however, following convention, we used untransformed refractive error as the outcome in our model, with the self-reported intake of each of the pharmaceutically active ingredients as predictors. Additionally, the models were adjusted for recruitment age and age squared, sex, number of years spent in formal education, Townsend deprivation index, and polypharmacy. The birth cohort was defined as the participant's birth decade and was used as a random-effect grouping factor in our mixed models to account for potential nonlinear intergenerational effects.[4] The LMM coefficients for each treatment represent adjusted the difference in SpE between medication users and non-users. Associations were considered significant if their probabilities were below the Bonferroni multiple testing correction adjustment level (alpha/number of medications, alpha = 0.05). We performed three main analyses in our study, including all participants with available data (n = 481 medications), subjects who started wearing spectacles before the age of 35 (n = 228 medications), and those who started after the age of 35 (n = 241 medications). The Bonferroni corrected P values were generated using the p.adjust function in R and were 0.0001, 0.000219, and 0.000207, respectively.

Mendelian Randomization

Association between any two variables does not necessarily imply that one causes the other. Exploration of causation in many cases is difficult, as it may require observations spanning over a long period of time and may be subject to bias due to the co-occurrence of confounding factors. An established bias-reducing procedure is randomized clinical trials (RCTs). The key in RCTs is to randomly assign participants to each of the study arms, regardless of the confounding.

Mendelian randomization (Supplementary Fig. S1) is an alternative randomization technique, conceptually similar to RCTs. We know from Mendel's laws of heredity that alleles segregate randomly after each meiosis and that they are assorted to offspring independently of the traits for which they code. If several polymorphisms are associated with a hypothetical trait (trait 1), they will be randomly be reshuffled as they are transmitted from one generation to the next, assigning each child at the moment of conception with an almost unique combination of risk alleles. The net sum of the risk that these alleles confer with respect to trait 1 is referred to as a polygenic risk score. Because the alleles are reassigned after each different conception, the PRS predicts only the hypothetical trait 1 and no other trait, unless strongly correlated with trait 1.

If trait 1 predisposes to another phenotype, such as spherical equivalent in our study, the individuals who randomly received a higher dose of genetic risk will be exposed at birth to higher levels of trait 1 (which in this context is referred to as "exposure"), and in response to this exposure these individuals will have, on average, higher levels of a second phenotype (trait 2, or the "outcome"), which should not be observationally correlated with the exposure. When the exposure causally influences the outcome, each individual genetic factor (in this context referred to as "instrumental variables") selected to increase the exposure will also proportionally increase the likelihood of the outcome. With increasing polygenic risk toward the exposure, the likelihood of its outcome also changes proportionally. Mendelian randomization (MR) statistically tests the linearity of the correlation of effect sizes of the genetic associations of the same instruments with the exposure and outcome phenotypes. As an example, we can use as instrumental variables the genetic variants significantly associated with intraocular pressure (IOP, the exposure) to examine if the association of IOP with the outcome (SpE) is causal or vice versa.

To further explore relationships between refractive error and medication intake, we built MR models to test for potential causal relationships between SpE and 12 different phenotypes. MR instrumental variables included independent genome-wide significant genetic variants ($P < 5 \times 10^{-8}$, $r^2 < 0.1$) associated with the specific selected traits. For every medication significantly associated with refractive error, we aimed to perform two experiments. The first assessed the relationship between refractive error and underlying disease potentially confounding the association with the treatments. The second tested causality between SpE and medication classes that included drugs associated with refraction. The analyses were performed using the R MendelianRandomization package. Given that the outcomes were tested on refractive error data that were partially obtained from the UK Biobank (about 25% of the effective sample size), whenever the instrument variables were identified through prior UK Biobank analyses we also corrected for overlap of samples between analyses by setting the parameter psi to the observational correlation between exposure and outcome phenotypes. This correction effectively treats analyses as one-sample MRs and may be overly conservative, given the partial potential sample overlap. These results are provided as sensitivity analyses in relevant cases. Common and independent genetic variants associated with selected phenotypes (instrumental variables) were extracted from publicly available genome-wide association study (GWAS) summary statistics (https://www.ebi.ac.uk/gwas/). Three separate, yet complementary, MR tests were used (MR-Egger, simple median, and inverse-variance weighted). These tests are usually applied together to jointly estimate causality; that is, they are not independent tests requiring multiple testing correction. In special circumstances (significant sample overlap) a maximum likelihood test is added to test whether causality remains significant even after adjustment.

Secondary Analyses

Secondary analyses were conducted to address the potential confounding effect of comorbidities and involved removing individuals with a previous medical history of the most prevalent diagnoses among the category receiving a specific medication. Sequentially, and for each ICD10 entry, individuals reporting the same codes were dropped from the models, and associations were also tested in the subsample of the study participants who did not report any ICD10 codes.

Secondary associations also assessed the potential confounding effect of other factors. We generated nine models to test relationships between SpE and selected treatments, adjusted for age, age squared, sex, and socioeco-

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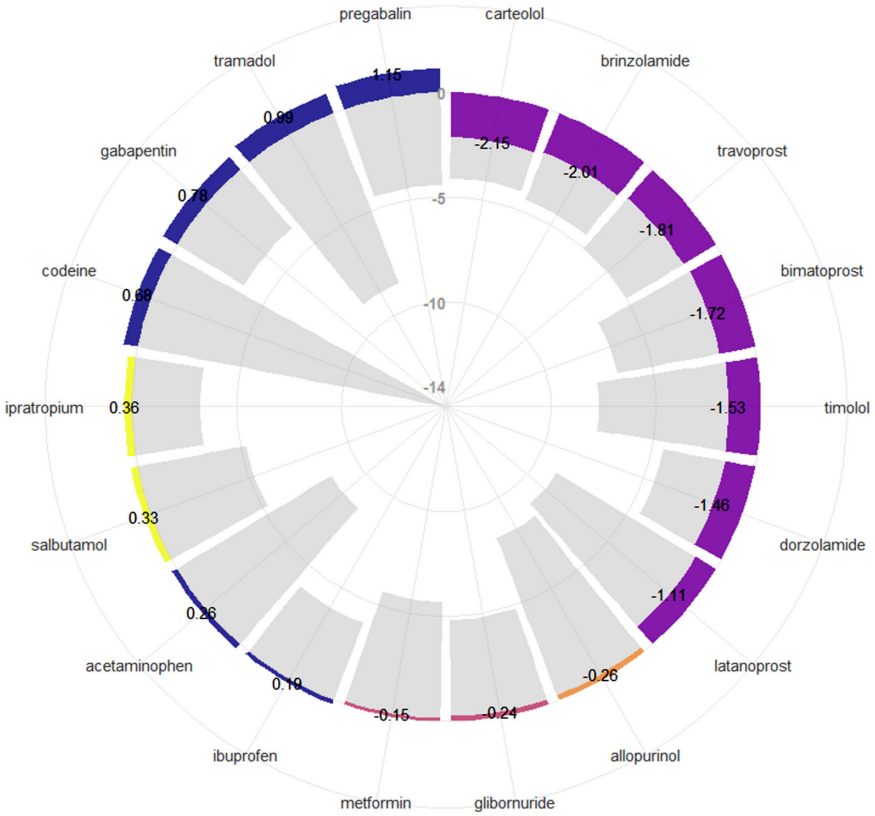

Figure 1. Circular bar plot showing the associations between refractive error and 18 different medications. *Colored bars* represent the LMM betas, and *gray bars* show the *P* values of the associations. The values refer to the difference in spherical equivalent between the group of subjects under the specific medication and the control group (rest of the cohort that does not report taking that same medication).

nomic factors, as well as nine different measures of physical activity.

Results

The study sample included 102,318 UK Biobank participants of homogeneous European ancestry; 47% (47,874) were men, and median age was 59 years (interquartile range [IQR], 51–64). A more detailed description of the sample's demographic characteristics can be found in Supplementary Table S1. SpE followed a characteristic distribution where most individual observations are seen both closer to the mean value and to the extremes, giving it a characteristic shape of a sharper peak with heavy and wider tails compared to the normal distribution (also called leptokurtic distribution; Supplementary Fig. S2) also seen in other populations.[14] The AOSW among the subset of participants for whom this information was available followed a bimodal distribution (Supplementary Fig. S3), with the first mode occurring between 1 and 35 years, peaking around the age of 13, and the second mode peaking around 47 years, when the average spherical equivalent is hyperopic (Supplementary Fig. S4).

We focused on the subsample of the UK Biobank participants (N = 102,318) of European ancestry for whom SpE was directly measured. In this sample, 481 active ingredients were taken orally, parenterally, or through nasal sprays or eye drops by a minimum of 10 participants. The most commonly reported medications used during the surveyed period were paracetamol (also known as acetaminophen, 17%), followed by simvastatin (13%) and acetylsalicylic acid (aspirin, 13%) (Supplementary Fig. S5). The median number of reported medications per participant was two (IQR, 0–4), but 18% (18,558) of the subjects were taking more than five medications. The number of medications taken was significantly associated with demographic and socioeconomic factors. Age and Townsend deprivation index had a statistically strong positive relationship with polypharmacy, whereas education was negatively associated with the concurrent use of multiple medications (Supplementary Table S2).

Eighteen different medications showed statistically significant associations with refractive error after adjustment for multiple testing (Table, Fig. 1). The seven strongest associations were from medications of different classes commonly used to control IOP and glaucoma. In particular, three prostaglandin agonists (latanoprost, $P = 2.98 \times 10^{-20}$; bimatoprost, $P = 1.47 \times 10^{-11}$; travoprost, $P = 2.45 \times 10^{-8}$), two carbonic anhydrase inhibitors (dorzolamide, $P = 1.58 \times 10^{-11}$; brinzolamide, $P = 2.68 \times 10^{-9}$), and two beta blockers (timolol, $P = 9.57 \times 10^{-12}$; carteololl $P = 7.95 \times 10^{-5}$) were associated with a lower (i.e., more myopic) SpE (Table). Subjects taking these medications had, on average, SpE values that were 1 to 2 diopters lower than those of the other participants. We stratified analyses by AOSW in a subset of 90,550 participants for whom this information was available. The associations between IOP-lowering medication and SpE were driven by participants who reported spectacle correction earlier in life (AOSW < 35 years) (Table), particularly in the first two decades (Fig. 2), well before the

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Table. Results of LMMs Testing the Association Between Refractive Error and Medication Intake

Medications Tested	Medication Action/Class	All Study Participants ($N = 102,318$)				Participants with AOSW Between 5 and 35 Years ($n = 38,960$)				Participants with AOSW Over 35 Years ($n = 48,240$)			
		β*	SE*	*P*-value*	Bonferroni-Corrected *P*-value*	β*	SE*	*P*-value*	Bonferroni-Corrected *P*-value*	β*	SE*	*P*-value*	Bonferroni-Corrected *P*-value*
Latanoprost	IOP-lowering (prostaglandin analogue)	−0.99	0.11	2.99×10^{-20}	1.44×10^{-17}	−1.11	0.18	1.38×10^{-9}	3.1×10^{-7}	−0.2	0.07	0.007	1
Timolol	IOP-lowering (β blocker)	−1.05	0.15	9.57×10^{-12}	4.60×10^{-9}	−1.53	0.27	1.92×10^{-8}	4.3×10^{-6}	−0.13	0.1	0.19	1
Bimatoprost	IOP-lowering (prostaglandin analog)	−1.27	0.19	1.48×10^{-11}	7.10×10^{-9}	−1.72	0.33	1.94×10^{-7}	4.4×10^{-5}	−0.07	0.12	0.57	1
Dorzolamide	IOP-lowering (carbonic anhydrase inhibitor)	−1.4	0.21	1.58×10^{-11}	7.58×10^{-9}	−1.46	0.35	3.40×10^{-5}	7.7×10^{-3}	−0.36	0.15	0.02	1
Brinzolamide	IOP-lowering (carbonic anhydrase inhibitor)	−1.61	0.27	2.68×10^{-9}	1.29×10^{-6}	−2.01	0.49	3.75×10^{-5}	8.5×10^{-3}	−0.32	0.18	0.07	1
Travoprost	IOP-lowering (prostaglandin analog)	−1.3	0.23	2.45×10^{-8}	1.18×10^{-5}	−1.81	0.41	1.07×10^{-5}	0.02	−0.18	0.15	0.25	1
Carteolol	IOP-lowering (β blocker)	−2.15	0.55	7.95×10^{-5}	0.04	−3.8	1.02	0.0002	0.05	−0.98	0.33	0.002	0.61
Codeine	Analgesic (opiate)	0.26	0.04	2.65×10^{-9}	1.27×10^{-6}	0.68	0.09	1.32×10^{-15}	3.0×10^{-13}	0.02	0.03	0.58	1
Pregabalin	Analgesic and anticonvulsant (gabapentinoid)	0.59	0.14	1.63×10^{-5}	0.008	1.15	0.28	3.88×10^{-5}	0.09	0.12	0.09	0.16	1
Tramadol	Analgesic (opiate)	0.35	0.08	2.41×10^{-5}	0.012	0.99	0.17	1.98×10^{-9}	4.5×10^{-7}	−0.05	0.05	0.4	1
Acetaminophen	Analgesic (aniline analgesic)	0.09	0.02	0.0001	0.07	0.26	0.04	2.59×10^{-9}	5.9×10^{-7}	0.02	0.01	0.3	1
Gabapentin	Analgesic and anticonvulsant (GABA analog)	0.25	0.11	0.03	1	0.78	0.21	0.0001	0.41	−0.04	0.07	0.63	1
Ibuprofen	Analgesic (NSAID)	0.05	0.03	0.04	1	0.19	0.05	0.0001	0.25	0	0.02	0.95	1
Metformin	Oral hypoglycemic (biguanide)	−0.17	0.05	0.0008	0.37	−0.05	0.1	0.6	1	−0.15	0.03	2.14×10^{-6}	0.0005
Glibornuride	Oral hypoglycemic (sulfonylurea)	−0.26	0.09	0.003	1	−0.08	0.16	0.6	1	−0.24	0.05	1.50×10^{-5}	0.004
Allopurinol	Gout (xanthine oxidase inhibitor)	−0.22	0.08	0.003	1	−0.32	0.15	0.036	1	−0.26	0.04	5.14×10^{-9}	1.23×10^{-6}
Salbutamol	Bronchodilator (β2 adrenergic receptor agonist)	0.1	0.04	0.006	1	0.33	0.07	5.42×10^{-6}	0.012	0.01	0.02	0.80	1
Ipratropium	Bronchodilator (anticholinergic bronchodilator)	0.45	0.16	0.006	1	0.6	0.31	0.06	1	0.36	0.1	0.0005	0.1

Models were adjusted for sex, age, age squared, years of education, Townsend deprivation index, and number of medications taken concomitantly. The results are shown for medications that passed Bonferroni correction in at least one of the groups.

* Average difference in spherical equivalent between participants under the medication and those not reporting taking the same medication (the LMM coefficient).

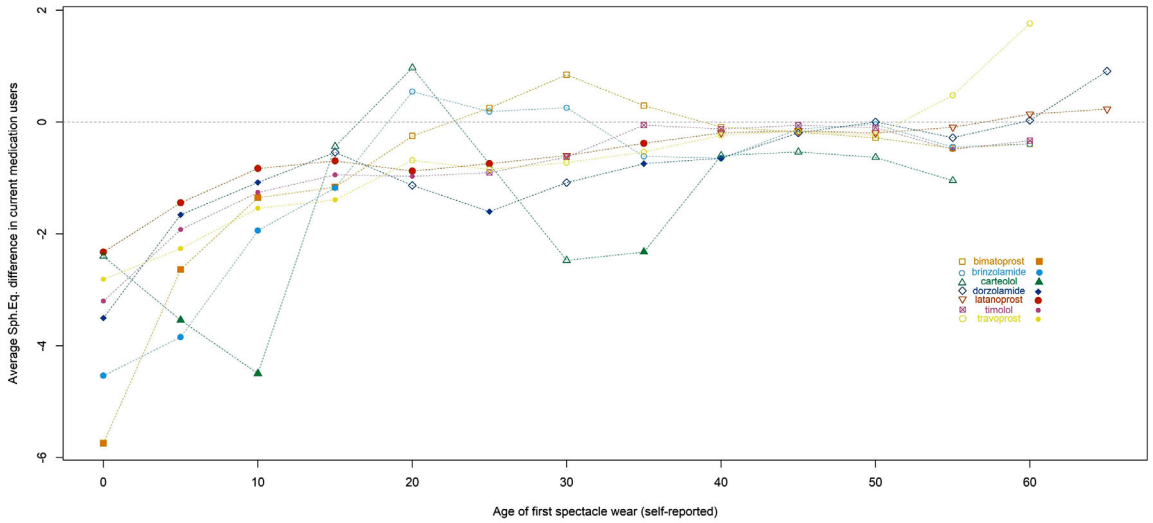

Figure 2. The differences in spherical equivalent between subjects receiving IOP-lowering medication and subjects who were not receiving them, by age of first spectacle wear. The AOSW shown on the *x*-axis is the first year of each of the 5-year periods in which the individuals started correcting their refractive error (e.g., 0–5, 5–10), and the *y*-axis denotes the adjusted difference in spherical equivalent observed in each group. The medications are specified in the figure legend, where a *symbol* to the left of a medication name denotes results that are not statistically significant (see Methods), and a *solid symbol* to the right indicates a statistically significant difference.

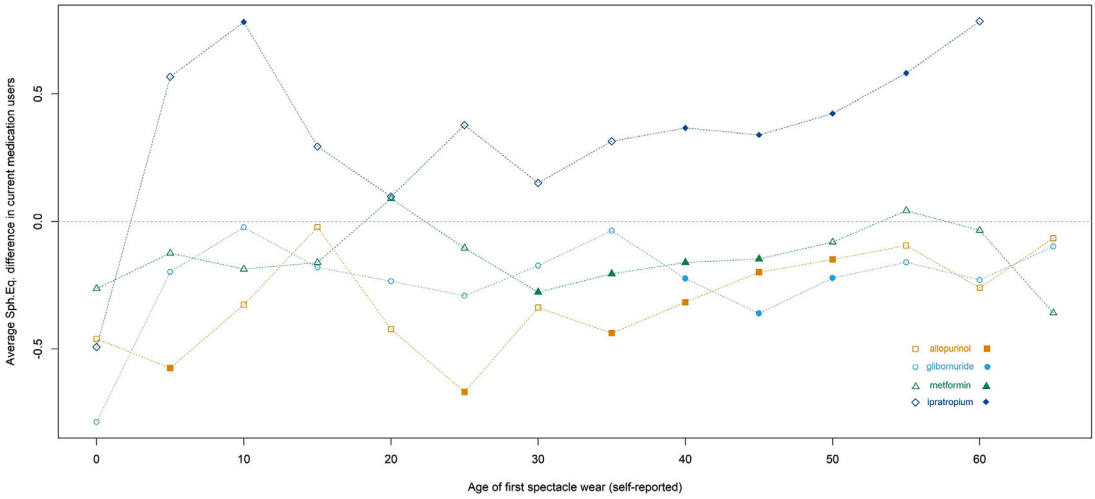

Figure 3. The differences in spherical equivalent between subjects receiving antihyperglycemic, anti-uricemic or ipratropium medication and subjects who were not receiving them, by age of first spectacle wear. The AOSW shown on the *x*-axis is the first year of each of the 5-year periods in which the individuals started correcting their refractive error (e.g., 0–5, 5–10), and the *y*-axis denotes the adjusted difference in spherical equivalent observed in each group. The medications are specified in the figure legend, where a *symbol* to the left of a medication name denotes results that are not statistically significant (see Methods), and a *solid symbol* to the right indicates a statistically significant difference.

age in which these medications are typically prescribed. For the group that started wearing glasses or contact lenses at a later age (AOSW > 35 years), there was no statistically significant difference in SpE between individuals prescribed IOP-lowering medication and those not.

Two other groups of drugs showed associations with SpE and AOSW. First, three drugs usually prescribed for metabolic disturbances showed a statistically significant association with lower (i.e., more myopic) SpE among participants who started wearing corrective lenses or glasses later in life (Table). Two of them were oral antihyperglycemic agents, metformin (β = –0.15, SE = 0.03, $P = 2.14 \times 10^{-6}$) and glibornuride (β = –0.24, SE = 0.05, $P = 1.5 \times 10^{-5}$). Allopurinol was also significantly associated with myopia (β = –0.26, SE = 0.04, $P = 5.14 \times 10^{-9}$) among individuals whose refraction was corrected at or after the fourth decade (Table). Ipratropium was associated with a positive SpE (hyperopia), particularly among participants with late AOSW (β = 0.36, SE = 0.1, P = 0.0005), becoming progressively stronger with increasing AOSW. These associations were particularly significant among individuals who started refractive correction after the fourth decade of life (Fig. 3), but because we lacked suitable instrumental variables (single nucleotide polymorphisms [SNPs] significantly

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associated with their intake in addition to the diseases they are indicated for) we were unable to draw firm conclusions about the direction of causality. We also found a positive and significant association with salbutamol ($\beta = 0.33$, SE = 0.07, $P = 5.42 \times 10^{-6}$), another bronchoactive medication (Table), but only in the group with early AOSW.

Unexpectedly, our analyses revealed several significant associations between refractive error and a pharmacologically heterogeneous group of drugs for which the main clinical indication is pain management and analgesia. They were all associated with higher mean SpE (i.e., hyperopia). Participants receiving codeine ($\beta = 0.68$, SE = 0.09, $P = 1.32 \times 10^{-15}$) and tramadol ($\beta = 0.99$, SE = 0.17, $P = 1.97 \times 10^{-9}$), either alone or in combination with other non-opioid analgesics, were significantly more hyperopic than participants with no known history of opiate use (Table). Other analgesics, such as tramadol ($P = 1.97 \times 10^{-9}$), codeine ($P = 1.32 \times 10^{-15}$), paracetamol ($P = 2.58 \times 10^{-9}$), ibuprofen ($P = 0.0001$), pregabalin ($P = 3.88 \times 10^{-5}$), and gabapentin ($P = 0.0002$), were also associated with hyperopia in the group who wore spectacles early in life (AOSW between 5 and 35 years) (Table, Supplementary Fig. S6), before the typical age of presbyopia.

Other analgesic medications were nominally associated but below our strict multiple testing correction significance threshold. Typically, analgesics were used in combination with other medications, and the strength of their association was blunted by our correction for the total number of medications taken. For example, two additional nonsteroidal antiinflammatory medications (naproxen and diclofenac) were significantly associated with SpE when the number of total medications was removed from the model (Bonferroni-corrected $P = 0.02$ and $P = 0.04$, respectively).

There was no statistically significant relationship between the strength of these associations and comorbidity (Supplementary Figs. S7, S8, S9, S10, S11, S12) or physical activity (Supplementary Table S3), and associations with analgesic drugs remained significant.

Mendelian Randomization Models of Causality

The likelihood of taking any particular medication is correlated with pre-existing disease.[20] Any observed SpE differences among the users of certain medications may be driven by the presence of underlying conditions or the primary effect of the medication on eye structures. To explore causality, we used MR techniques to assess the relationship between the primary disease for which these medications were indicated and SpE (Supplementary Table S4). In addition, because the same medication is often prescribed to treat several different diseases, we used MR to assess the relationship between different medication classes and refractive error (Supplementary Table S4). We used SNPs significantly associated with the primary diseases or medication taking as instruments and their effect over SpE[27] for the outcome.

MR analyses results supported previously published suggestions that higher IOP caused lower (more myopic) SpE[27] (MR–Egger $P = 0.02$), with no significant directional pleiotropy (intercept $P = 0.256$). This remained statistically significant after correcting for overlap of study samples (maximum likelihood method adjusted for sample overlap $P = 0.001$). MR also suggested that this relationship is not mediated by IOP-lowering medications.[20]

MR analyses using instruments from previous GWASs[28] revealed strong evidence of pleiotropy, and not causation, between type 2 diabetes and SpE (MR–Egger $P < 0.001$, intercept $P = 0.001$). However, we found statistical evidence suggesting that oral antidiabetic medications[20] may directly and causally contribute to refractive error (MR–Egger $P = 0.003$, intercept $P = 0.166$).

We found no evidence for a causal relationship between chronic obstructive pulmonary disease[29] (the main therapeutic indication for ipratropium) and SpE (MR–Egger $P = 0.23$). Neither gout[30] nor uric acid levels[31] had any statistically significant causal influence on refractive error, although the instruments selected for these analyses were weak and potentially unreliable (only nine and one instruments available for these two traits, respectively).

Our analyses found a causative relationship between multisite chronic pain[32] and myopia (Supplementary Table S4). Although phenotypically the traits are not correlated (Pearson's $r = 0.05$) and SNPs that are associated with multisite chronic pain are generally not associated with SpE at statistically significant levels (Supplementary Table S5), individuals with progressively higher centiles of multisite chronic pain PRS distribution have increasingly higher average measurements of SpE (Supplementary Fig. S13). MR models find that this relationship is statistically significant and that multisite chronic pain directly contributed to hyperopia (MR–Egger $P = 0.02$, intercept $P = 0.15$). This relationship remained significant even after correcting for overlap of samples in which exposure and outcome effects were measured (maximum-likelihood method $P < 0.001$) (Supplementary Table S4, Supplementary Fig. S14). These findings suggest that there is a causal link between sensitivity to pain and refractive error and not specific diseases that causally influence SpE. We found no significant causal relationship between nonsteroid antiinflammatory drugs and SpE (MR–Egger $P = 0.18$). Likewise, salicylic acid and its derivatives were not causally associated with SpE (MR–Egger $P = 0.849$), and rheumatoid arthritis[33] was not causal to SpE (MR–Egger $P = 0.13$).

Discussion

Here we analyzed associations between medication and spherical equivalent in a large general population-based cohort. Previous large studies have found significant correlations cross-sectionally between IOP and negative spherical equivalent in children,[34,35] but not with the speed of myopia progression.[35] Our work suggests that IOP-lowering medications are associated with lower SpE (more myopic refraction) and the use of analgesics with higher SpE (more hyperopic refraction). These associations are particularly strong among individuals who develop refractive errors early in life. Previous studies have linked glaucoma and myopia, particularly high myopia, which is usually of very early onset (before the age of 10 years).[36] Lower (more myopic) SpE is associated with higher IOP in observational studies.[34,35] Only some recent studies suggest that IOP may be one of the contributing causes of myopia.[27] The association between IOP-lowering treatment and SpE could, therefore, be a consequence of elevated IOP.

The link between pain medication and hyperopia (longsightedness) is interesting, as it was unexpected. These associations remained statistically significant even after addressing potential sources of confounding and regardless of the subjects' comorbidities or current activity levels. The

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mechanism behind these associations is not entirely clear. However, given the heterogeneity of opiates, nonsteroidal antiinflammatory drugs, paracetamol, and gabapentin and their very different modes of action, it is most likely that any direct effects on the eye do not cause associations.

Our MR analyses suggest a causal effect of multisite and chronic pain over hyperopic refractive error. Chronic pain is a complex trait that is not fully understood. Among the potential causes of hyperalgesia is a lower threshold for excitation of sensory neurons, possibly linked to genetic variants affecting gated and ungated cation channels.[37] Interestingly, refractive error is associated with genetic polymorphisms in the ungated cation channels and, more generally, with possible changes in the efficiency of visual sensory signal transduction.[38] In addition, pain induces activation of autonomic responses, including efferent sympathetic activity, leading to pupil dilation[39] and accommodation relaxation. This may possibly affect mechanisms driving the development of refractive error including, for example, dynamic changes in the choroid, or the magnitude and direction of blurring of the retinal image. However, the evidence provided here is purely probabilistic, and more work is needed to investigate possible mechanisms behind these novel findings.

Medications aimed at metabolic diseases such as diabetes (metformin and glibornuride) and hyperuricemia (allopurinol) were associated with a more negative spherical equivalent. These associations were particularly significant among individuals who started refractive correction after the fourth decade of life (Fig. 3), but, because we lacked suitable instrumental variables (SNPs significantly associated with their intake in addition to the diseases they are indicated for), we were unable to draw firm conclusions about the direction of causality.

We found evidence suggesting that oral antihyperglycemics may have some direct effects on lowering the spherical equivalent and potentially cause late-onset myopia. Given that the effects were more pronounced in the later decades in life when diabetes and antidiabetic therapies are started, myopia is unlikely to be due to axial length changes. Hyperglycemia thickens the crystalline lens[40] and increases its refractive index.[41] Autonomic dysfunction of sympathetic and parasympathetic activity in diabetes and changes in pupil size and lens power might also be relevant.[42] This evidence is probabilistic and does not refute other alternatives that we may have lacked sufficient power to test in full. For example, both diabetes and poor metabolic control of glucose have been associated with myopia development,[43] so we cannot fully exclude earlier life interactions between glucose and emmetropization.

Similarly, we hypothesize that the mechanisms through which allopurinol is associated with lower SpE may involve growing lens opacity as opposed to changes in axial length. Exposure to higher levels of uric acid may cause osmolar changes that, over time, alter the refraction index of the lens through mechanisms similar to those described before for diabetes.[44] Gout[45] (but not allopurinol[44]) may be associated with age-related cataract, which can cause SpE changes,[46] but our MR analyses were underpowered for this condition and could not detect any relationship between hyperuricemia and SpE. Also, the relationship between SpE and ipratropium, a drug commonly prescribed against chronic obstructive pulmonary disease, remains unexplained. Ipratropium is an anticholinergic drug,[47] similar to atropine, mild mydriatic effects of which may add to the likelihood of hyperopic correction later in life, especially in individuals with a degree of pre-existing hyperopia and presbyopia. A similar argument can also be made for salbutamol,[48] an adrenergic agonist with similar effects on the lens and pupil.

Strong statistical evidence for one mechanism cannot conclusively exclude the importance of concomitant mechanisms. For example, several medications significantly associated with lower SpE are sulfonamides (dorzolamide, brinzolamide, and glibornuride). Drugs in the sulfonamide class,[49] particularly dorzolamide,[50] have been linked to episodes of transient myopia, and the relative overrepresentation of these drugs in our results raises the possibility of the presence of a small direct myopia-inducing effect of these drugs.

The results of this study should be interpreted within the context and limitations of the design of the study from which they were obtained. Generalizing them to other populations should therefore warrant caution. For example, our sample included volunteers of European descent and had a higher percentage of university/college graduates and less deprivation than the population average. This study also did not have any information on medication dosage and length of the treatment. Incorporation of this information would have improved the power of the models. Our MR models had uneven power due to the differing number and quality of available instrumental variables. Finally, although previous research demonstrated good validity of self-reported medication intake,[51,52] recall bias and misclassification are potential issues, especially among older participants. False-positive results could arise from residual confounding, despite our attempts to minimize this.

To our knowledge, our work is the largest cohort-based epidemiological study exploring associations of commonly used medications with refractive error in the general population. We identified several classes of medications associated with spherical equivalent changes, some of which may be attributable to the medication and not merely the underlying conditions. More research is needed to replicate the novel associations between analgesic use and hyperopic refractive error and to clarify the mechanisms connecting them to spherical equivalent.

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