A genome-wide analysis of 340,318 participants identifies four novel loci associated with the age of first spectacle wear

Karina Patasova [1,2], Anthony P Khawaja [3], Robert Wojciechowski [4], Omar A Mahroo [1-3,5], Mario Falchi [2], Jugnoo S Rahi [6,7,8], Chris J Hammond [1,2], Pirro G Hysi [1,2,7,*] and the UK Biobank Eye & Vision Consortium

1 Section of Ophthalmology, School of Life Course Sciences, King's College London, UK.

2 Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, UK

3 NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and the UCL Institute of Ophthalmology, UK.

4 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

5 Department of Ophthalmology, St Thomas' Hospital, Guys and St 'Thomas' NHS Foundation Trust, London, UK.

6 Institute of Ophthalmology, University College London

7 UCL Great Ormond Street Hospital Institute of Child Health, London, UK

8 Ulverscroft Vision Research Group, University College London, London, UK.

* Corresponding author. Address: St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH, UK. Email: pirro.hysi@kcl.ac.uk ; Telephone: +44(0)2071888545 FAX: +44 (0)2071886761

Abstract

Refractive errors, particularly myopia, are the most common eye conditions, often leading to serious visual impairment. The age of onset is correlated with the severity of refractive error in adulthood observed in epidemiological and genetic studies and can be used as a proxy in refractive error genetic studies. To further elucidate genetic factors that influence refractive error, we analysed self-reported age of refractive error correction data from the UK Biobank European and perform genome-wide time-to-event analyses on the age of first spectacle wear. Genome-wide proportional hazards-ratios analyses were conducted in 340,318 European subjects. We subsequently assessed the similarities and differences in the genetic architectures of refractive error correction from different causes. All-cause age of first spectacle wear (AFSW) was genetically strongly correlated (r_g=-0.68) with spherical equivalent (the measured strength of spectacle lens required to correct the refractive error) and was used as a proxy for refractive error. Time-to-event analyses found genome-wide significant associations at 44 independent genomic loci, many of which (*GJD2, LAMA2*, etc.) were previously associated with refractive error. We also identified six novel regions associated with AFSW, the most significant of which was on chromosome 17q (p = 3.06 x 10^{-09} for rs55882072), replicating in an independent dataset. We found that genes associated with AFSW were significantly enriched for expression in central nervous system tissues, were involved in neurogenesis. This work demonstrates the merits of time-to-event study design in the genetic investigation of refractive error and contributes additional knowledge on its genetic risk factors in the general population.

Introduction

Refractive errors, particularly myopia, are the most common eye conditions, often leading to serious visual impairment (1). The prevalence of myopia has increased over the past decades, reaching the highest rates in East Asia (2), but also in Europe (3) and the United States (4). Refractive errors arise from a mismatch between the cornea's refractive power and the crystalline lens on one side and the eye's axial length on the other. The physiological process that normally balances them, called emmetropisation, consists of a gradual elongation of the sagittal diameter of the eye to match the eyes' refractive power(5). Refractive error results when light converges in front of the retina (myopia), behind the retina (hypermetropia) or follows other non-optimal patterns of light convergence. The strength of spectacles or contact lenses to correct refractive errors and focus light on the retina in these adult volunteers is summarised by the spherical equivalent, with a minus number denoting a concave lens for myopia correction or a plus number for a convex lens correcting hyperopia or long-sightedness. Refractive errors are often underdiagnosed, and delays in correcting them can result in productivity loss. They may also lead to complications causing visual impairment and potentially blindness. High myopia is associated with later-life posterior staphylomas, retinal detachment, cataract, and other complications (6–8). The likelihood of high and pathological myopia increases proportionally with the gravity of refractive error, which is correlated with the age at which myopia first developed.

Environmental factors, such as educational attainment (9) and time spent outdoors, vastly influence the development and progression of myopia. Their effects depend on lifestyles and cultural trends, but they typically affect whole cohorts across countries and societies (3) sharing similar living environments. Within a society at any given time, the environmental exposures are stable and relatively homogenously distributed, and heritable factors explain over half of the spherical equivalent and risk to refractive error (10). Several genetic studies conducted in the general population have identified DNA variations associated with the risk of refractive error (11,12) and age of first lens or spectacle correction for myopia (13). Genes associated with the age at first correction for myopia usually overlap with those associated with spherical equivalent (14), and both predispose to pathological myopia (15). Yet, the timing of the individual genes' effects is not evenly distributed throughout the childhood years or lifetime. Different genes have varying strength of effect and association throughout the

years and among the genetic factors associated with spherical equivalent, some genes predispose to earlier refractive correction than others (16). Additionally, there is considerable genetic pleiotropy in the eye and the same genetic factors may be independently be associated with several endophenotypes (17) each a potential to alter the age in which correction of refractive errors is needed.

This study aims to explore the genetic factors that contribute to the risk of early onset of refractive error, using as a proxy the self-reported age of first spectacle wear in a sample of 340,318 UK Biobank participants. This study also further explores the genetic relationship between age of refractive correction and mean spherical equivalent.

Results

The final study sample included 340,318 UK Biobank participants of European ancestry who reported the AFSW in the electronic questionnaire; of them, 46% (N = 156,388) were men and 54% (N = 183,930) were women with a mean age of 58 years (± 7.5 years). The age of the first spectacle wear followed bimodal distribution with the first mode between 1-35 years, peaking at the age of thirteen, and the second mode between the ages of 36-72 years with a peak at the age of 43 (Supplementary Figure 1). Participants that started wearing glasses/contact lenses before the age of 35 tended to be more myopic, while subjects with AFSW over 35 years were more likely to have hyperopia (Supplementary Figure 2). For the vast majority of the study participants the cause of spectacle wearing was not known. For the subset of participants who specified the reason for wearing glasses/contact lenses (N = 93,067), 41% (N = 37,762) reported myopia. Presbyopia (33%; N = 31,137) and hypermetropia (21%; N = 19,178) were the second and the third most commonly self-reported reasons for refractive correction (18).

The large study sample size (N = 340,318) resulted in relatively high genomic inflation factor (λ = 1.23) in our analyses of time to the first spectacle correction, but the low intercept of the linkage disequilibrium score regression 0.93, and (intercept-1)/(mean (X2) − 1) ratio (-0.19, SE = 0.02), reassuringly indicate a conservative control for potential confounding in our study.

We first assessed the degree of similarity between the genomic architectures of the spherical equivalent, self-reported age of first lens or spectacle correction for myopia, first self-reported correction for hyperopia and self-reported first correction for any reason. Consistent with previous reports, we found a strong genetic correlation between age of first myopia correction and spherical equivalent (r_g=-0.97). We also noted that the age of first correction in participants with myopia alone is also strongly genetically correlated with the age of the first correction of any refractive error (r_g= 0.89, Table 1) and less so with the age of the first correction among hyperopic subjects (r_g= -0.65). Spherical equivalent and all causes AFSW shared most of their heritability and were significantly correlated (r_g= -0.68, p = 9.6 x 10^{-171}). Because of the strong correlation and the phenotypic information was available for considerably more individuals with all-cause AFSW information than any other phenotypic definition, we focused this work on the analysis of the all-causes AFSW, because of our expectation of superior statistical power.

Our genome-wide association study for time to the first lens or spectacle wear, found a significant association with 44 independent genomic regions (Figure 1), many of which previously reported in relation to refractive errors (12). The statistically strongest association was observed between AFSW and *TSPAN10* gene (rs7405453, HR = 1.03, p = 1.71 x 10^{-35}). The second strongest association was found at another locus previously associated with spherical equivalent (rs4736886, near the *ZMAT4* gene, p = 3.36 x 10^{-27}). Interestingly both genes that show the most significant associations with AFSW, although known for associations with refractive error, have relatively low effects sizes over the spherical equivalent. Only further down the list of our genome-wide associations with AFSW do we find the genes usually considered as the strongest risk factors to refractive error, such as *GJD2*, *LAMA2* and *PRSS56* (p = 1.63 x 10^{-12}, p = 6.27 x 10^{-24} and p = 1.31 x 10^{-18}), respectively).

Although the effects of association with spherical equivalent were usually linearly correlated with their effect over the AFSW for the same alleles, there were notable exceptions. For example, the SNP alleles at the known *BMP3, ZMAT4* and *TSPAN10* loci predispose to much earlier correction compared to the final spherical equivalent status in adulthood than most other loci. Conversely, alleles in the *SOX2-OT* gene seem to confer a low risk towards myopia, but at a much later age than the general regression line across all loci (Figure 2). Interestingly, there were some examples (e.g. BMP3), where the association with age of first spectacle wear was

different in individuals with myopia only compared to the entire sample that included corrections for all sources of refractive error. This maybe attributable to the particularities of the effects of these genes on the AFSW among myopes. However, most of the effects observed showed similar patterns of relationship between AFSW and spherical equivalent in subgroup analyses, such as time to event analyses conducted on a sample of 45,404 UK Biobank participants that excluded causes of refractive error other than myopia (Supplementary Figure 3).

We observe a genome-wide association with six additional loci that, to our knowledge, were not described in any previous GWAS for refractive error (12). We discovered new associations with polymorphisms within the genomic sequence of the *NEGR1* gene (rs1204700722, HR = 1.013, p = 3.72 x 10^{-08}), a member of an immunoglobulin superfamily cell adhesion molecule supergroup, implicated in neuronal growth and connectivity (12), where previous studies have identified association with depression and affective disorders (19). Novel significant association was also found at a chromosome 2 intergenic region between the *TRIB2* and *LOC1005064* gene sequences (rs10164589, HR = 1.013, p= 3.96 x 10^{-08}). The *TRIB2* gene is a pseudokinase family member that regulates intracellular cell signalling through ubiquitination and scaffolding (20). Additionally, we found an association for a locus on chromosome 3 (rs6577621, HR = 1.014, p = 8.15 x 10^{-09}) in a region located between the *TBC1D5* gene, a regulator of GTPase-activating proteins (21) and the *SATB1* gene, which participates in chromatin remodeling (22). Finally, we found an association for polymorphisms located within the *ADAM11* gene (rs55882072, HR = 1.015, p = 3.06 x 10^{-09}) a metalloprotease that regulates cell and matrix communications (23) and markers within *BRWD1* gene (rs8131965, HR = 0.98, p = 5.41 x 10^{-09}).

Four out of six novel regions replicated in a slightly smaller, but independent cohort (13) (Table 2), at a Bonferroni multiple testing correction level (p-value < 0.05/6 = 0.01, Table 2). Specifically, *NEGR1*, *TRIB2*, *TBC1D5*, *LOC100287944*, *ADAM11* risk alleles were associated with earlier-age myopia, while *BRWD1* showed significant association with later-age refractive error correction (Table 2). Most SNPs were associated, at various levels of statistical significance, with spherical equivalent in the refracted subgroup of European UK Biobank participants (Supplementary Table 1).

The Cox proportional hazards model assumes that the effects of the tested SNPs have a constant, linear relationship with age. Proportionality of the hazards analyses showed that this assumption held true for many

loci, for example, *BMP4, TMEM161B, XPO6* (Supplementary Table 2). By contrast, many loci exhibited non-linear effects with age, including *TSPAN10*, *OCA2* loci and interestingly *PAX6*, a gene known to harbour variants that cause microphthalmia and severe eye malformation (24) (Supplementary Table 2), with effects peaking around adolescence. For example, the *LAMA2* variant had a stronger effect over AFSW hazard at an early age, peaking around 16 and a more subdued effect after the age of 40, similar to the effects of other well-known refractive error genes such as *GJD2*, *ZMAT4*, *RDH5* and interestingly *PRSS56*, a gene also known to be associated with eye structural malformations (25) (Supplementary Figure 4). Among novel loci, *TBC1D5* exerted its influence at an early age, whereas *NEGR1* and *TRIB2* and *ADAM11* were expressed over the entire lifespan with the strongest effects over AFSW observed in adolescence (Supplementary Figure 5).

Our associations with AFSW showed significant enrichment in different body tissues, particularly in the nervous system and retina (Supplementary Table 3-5), particularly the brain prefrontal cortex, especially in late infancy. Consistent with a higher than expected expression in cerebral tissues, AFSW genes showed strong genetic correlations with neurological traits such as cognitive ability (r_g=-0.43, p = 2.69 x 10^{-05}), neuroticism (r_g= -0.49, p= 0.0039), insomnia (r_g=-0.29, p=0.01), and measures of educational attainment (years of schooling, r_g= -0.39, p = 1.95 x 10^{-08}, Supplementary Table 6) and several socio-economically influenced traits.

Gene-set enrichment analyses showed that, similarly to the findings of other published refractive error GWAS (12), genes associated with AFSW were involved in nervous system development (Supplementary Table 7) and other processes, such as cell signalling and intracellular communications that were other biological processes highlighted in our analyses (Supplementary Table 7). Gene Ontology enrichment analysis results also supported previous conclusions that genes involved in refractive error influence RNA polymerase transcription and gene expression (12).

Discussion

AFSW is a heterogeneous phenotype that is contributed to by the presence and age of onset of several different forms of refractive error. Observationally and genetically, this phenotype is strongly correlated with presence

and age of developing myopia, the most common form of refractive error in the general population, although other forms of refractive error are also correlated with it. Our study demonstrated that AFSW survival analysis is a powerful statistical method that could be used to augment the existing information available from directly measured refractive error. We found evidence that refractive error and AFSW were strongly correlated and shared most of their heritability and genetic risk loci. Additionally, we have identified six novel regions associated with the age of refractive correction and replicated four of them. One of the new genes, *TRIB2*, was previously reported for several different ocular traits and disorders. Similar to previous observed genetic associations, polymorphisms within and around the *TRIB2* gene are associated with, among others, optic cup disc area (26) and primary open-angle glaucoma (27), which are consistent with previous observations of genetic pleiotropy between refractive error and optic nerve changes described previously (12). In addition, three other AFSW-associated genes were linked to neurological and neurodevelopmental traits, for which genetic correlation with the refractive error was previously reported: polymorphisms within or near the *TBC1D5/SATB1* genes are associated, among others, with cortical thickness (28), Parkinson's disease (29), schizophrenia (30), general cognitive function (30) and educational attainment (31). Interestingly, the *ADAM11* gene is implicated in familial epilepsy (32,33), while the *BRWD1* gene polymorphisms are associated with general cognitive function (34). Both cognitive ability and educational attainment correlated with the genetic risk of refractive disorders (12). Similarly, another newly associated gene, *NEGR1,* influences neurite outgrowth (35), a process where extracellular cues attach to transmembrane receptors, initiating signalling cascade and reorganising neuronal structure (36). Neurite outgrowth was essential for functional wiring and building connectivity in the developing brain. *NEGR1* was linked to several neurodevelopmental disorders – intellectual disability, dyslexia (37) and autism (38) due to its function in brain connectivity.

We independently replicated four out of six novel loci associated with AFSW at robust multiple testing correction levels. Alleles of the *TRIB2*, *TBC1D5* and *ADAM11* genes that were associated with myopia were significantly associated with correction at an earlier age, while those at the *BRWD1* locus showed association with myopia correction at older ages. Although *NEGR1* and *LOC100287944* were not significantly associated with the age of first spectacle wear to correct for myopia in the replication dataset, the estimated effects had the

same direction of the effects as in the discovery GWAS, and it is possible that a lack of statistical significance in replication analyses could be due to sample size and power limitations.

The strongest genetic association in our study was identified with a variant located within *TSPAN10*. This gene showed a moderate association with refractive error (12), but was strongly associated with corneal astigmatism (17) as well as with strabismus and amblyopia (39), which manifest early in childhood. Notably, the association between *TSPAN10* strabismus was independent of refractive error (39). Because our study sample wasn't limited to individuals with myopia and hyperopia, the observed association between early AFSW and *TSPAN10* may have reflected contributions from other ocular disorders such as astigmatism, strabismus or amblyopia.

Our study also found strong associations with markers located near or within *ZMAT4*, *LAMA2* and *GJD2* genes. Similarly to previously published results, we found that *LAMA2* and *GJD2* had an early effect that increased with age (16). In particular, these genes were observed to have the strongest effect on myopia in 10 – 25 year-olds but were also expressed during the entire age span of myopia development (16).

The results of this study confirm the strong correlation between AFSW and myopia. These results also demonstrate that AFSW is a complex phenotype that is likely to capture pleiotropic genetic effects that influence phenotypic traits other than myopia. SNP loci associated with AFSW appear to exert their effects at different time, although it is not clear whether the effect size changes over time of these loci are due in part to that pleiotropy or can simply be explained by their effects over myopia.

A potential limitation of our study is that the phenotype used in our study was based on self-reported data and not on clinical evaluations. Although self-reported data is occasionally prone to recall bias that could affect the results, its wider availability compared to directly measured refractive error may lead to statistical power gains. Other potential limitation includes the generalisability of these results. The effect sizes we report were largely consistent in the two large European population cohorts in which they were initially estimated and replicated. However, both cohorts are likely to be enriched for myopic participants. Findings in these cohorts may not be generalisable to other general population cohorts, and particularly they may not apply to more diverse populations.

Our study identified genome-significant associations with 44 independent loci, most of which were documented in refractive error and myopia GWAS. We demonstrate that the effects of many of these regions strongly correlate with myopic refraction but vary with age, which to date was reported for a handful of spherical equivalent genes. Additionally, we find associations with six novel regions and successfully replicate four of them in an independent cohort. Our results support the role of neural development and signalling in the pathogenesis of myopia. The findings of our study further our knowledge on the genetic basis of refractive disorders and demonstrate the value of large-scale population-based genetic studies.

Materials and Methods

Study population and phenotyping. The UK Biobank cohort is a large population-based longitudinal study that includes 502,682 volunteers from across the United Kingdom, aged between 40 and 69 years at the time of recruitment (40). The study participants were recruited via the UK National Health Service register based on their living proximity to the twenty-two assessment centers (40). At the baseline assessment, the data on socio-economic, lifestyle and health-related factors was collected via touch-screen questionnaires and face-to-face interviews (40). The electronic questionnaire contained several eyesight-related inquires, including the questions about the age of first spectacle wear (The UK Biobank field number: 2217) and reasons for refractive correction (Field number: 6147) (40). About 23% of all UK Biobank participants (N = 117,279) undertook ophthalmic examination (41), including non-cycloplegic autorefraction carried out using Tomey RC 5000 device (Tomey Corp., Nagoya, Japan). For each participant, the spherical equivalent was calculated (SPHE= sphere + ½ cylinder power) (UK Biobank field numbers: 5084-5085; 5086 – 5087), and subsequently, the average measurement of the two eyes was estimated. The UK Biobank enrollees who had ocular surgery or eye infection four weeks before the assessment did not participate in the ophthalmic examination. The spherical equivalent readings of participants who had eye surgery, infection, bilateral eye injury before the assessment, or self-reported cataract with mild myopia, as described before (41) were excluded from the analyses. To minimise confounding arising from population genetic structure, we limited the study sample to individuals of European

ancestry, as ascertained by using genetic information. Ancestry was defined based on Principal Component Analyses of the participants' genotypes, pre-computed and calculated by the UK Biobank working group.

Genetic data. Genotyping was performed on 488,377 subjects from the UK Biobank cohort as described before (40) using two similar and mutually-compatible genotyping platforms (Applied Biosystems UK BiLEVE Axiom Array and the UK Biobank Axiom Array), which although not fully identical, shared approximately 95% of genetic markers. However, our analyses used a subset of Biobank participants, for whom information about the refractive error was available. Specifically, our spherical equivalent analyses were conducted in N = 102,117 subjects, the all-causes age of spectacle wear in N = 340,318 subjects, age of spectacle wear in individuals with myopia in N = 24,363 and in individuals with hypermetropia in N = 24,711 subjects. To avoid bias arising from genetic stratification and admixture, all subjects were of European ancestry.

Phasing and further genomic imputation were conducted as described before (40). Briefly, imputation was carried out using Haplotype Reference Consortium (HRC) data as a primary reference panel, but also merged 1000 Genomes phase 3 and UK10K reference panels. Only markers shared between HRC and 1000 genomes/UK10K datasets were selected for imputation; therefore, a final dataset covered 93,095,623 autosomal SNPs in conjunction with large structural variants indels (40)

Statistical analyses. Descriptive analyses were carried out using *epiDisplay* package in R. We calculated frequencies and percentages and means and standard errors for categorical and continuous variables. For our time-to-event genetic association analyses, we build Cox proportional hazards regression model adjusted for age and sex. Likelihood ratio test was used to compute p-values for each SNP in the model. We used two R packages, *gwasurvivr* (42) and *SPACox* (43), to calculate hazard ratios (HR) and their corresponding p-values. The genetic variants with p-values below the customary genome-wide significance level of 5×10^{-08} were considered statistically significant. The proportionality of the hazards for significant associations was assessed using the *survival* package in R (https://cran.r-project.org/web/packages/survival/). Subgroup sensitivity analyses were conducted in samples that only included participants with available spherical equivalent measurements that were consistent with myopia (N=24,363).

We sought replication of the novel genetic associations using time-to-event results previously published by Kiefer et al.(12). Replication was considered significant if the association probabilities were below the Bonferroni multiple testing correction level (observed p-value multiplied by the number of tests no higher than 0.05). The genomic inflation arising from sample stratification and uncontrolled admixture was tested ld score regression (44).

Data from 45,771 research volunteers recruited among the customer base of the *23andMe* genomics company (Sunnyvale, CA, USA) were used for replication. More detailed information can be found in the original publication (13), but briefly, the phenotypic status was ascertained through an online medical history questionnaire or an eyesight questionnaire. Participants were genotyped and additional SNP genotypes were imputed against the 1000 genomes data and the imputed genotypes from individuals of European ancestry were used for Cox proportional hazards models. Although the analyses conducted in this replication set are in many ways comparable to those in the discovery UK Biobank cohort, there is one difference in the study designs. The 23andMe cohort analyzed exclusively individuals who self-reported correction for myopia and not other forms of refractive error.

Genetic correlations between identified loci and other phenotypic traits were assessed using ld-score regression (45) and the summary statistics from GWAS Catalog (46).

The shared functionality of associated genes was further explored through gene-set enrichment analyses, as implemented in MAGENTA software (47). The relationship between genotypes and gene expression was modelled using Mendelian Randomisation tests implemented in the SMR program (48), using expression data from GTEx release v8 (https://gtexportal.org/home/datasets), the Atlas of the Developing Human Brain (49) (BrainSpan 11) and retinal cis-eQTL data from healthy donors (50).

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Data availability. The UK Biobank data is available to all bona fide researchers through a dedicated electronic Access Management System (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). Full GWAS summary statistics for the *23andMe* discovery data set will be made available through *23andMe* to qualified researchers under an agreement with *23andMe* that protects the privacy of the *23andMe* participants. Please visit https://research.23andme.com/collaborate/#dataset-access/ for more information and to apply to access the data.

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Legend to figures:

Figure 1. Manhattan plot displaying 44 genome-significant associations with the age of first spectacle wear in UK Biobank cohort (N = 340,318). The plot shows log10 transformed p-values for each marker plotted against the chromosomal location. The red dashed line indicates the genome-wide significance threshold (p-value < 5×10^{-08}). Regions are named with symbols of the transcript-coding genes nearest to the most strongly associated variant in the region.

Figure 2. Scatterplot displaying the correlation between the age of first spectacle wear hazards ratios and spherical equivalent beta coefficients. Hazard ratios shown here as (ln (HR)) represent the multiplicative change in the rate of first spectacle wear per copy of the myopia risk allele calculated in the full sample of 340,318 UK Biobank participants, which was taken as reference. The results are shown for the most strongly associated SNPs in their respective loci. The purple labels depict names of some of the gene loci exhibiting stronger effects over the age of first spectacle wear, SNPs in blue are associated with spherical equivalent but not AFSW, and SNPs in turquoise are associated with AFSW but not spherical equivalent.
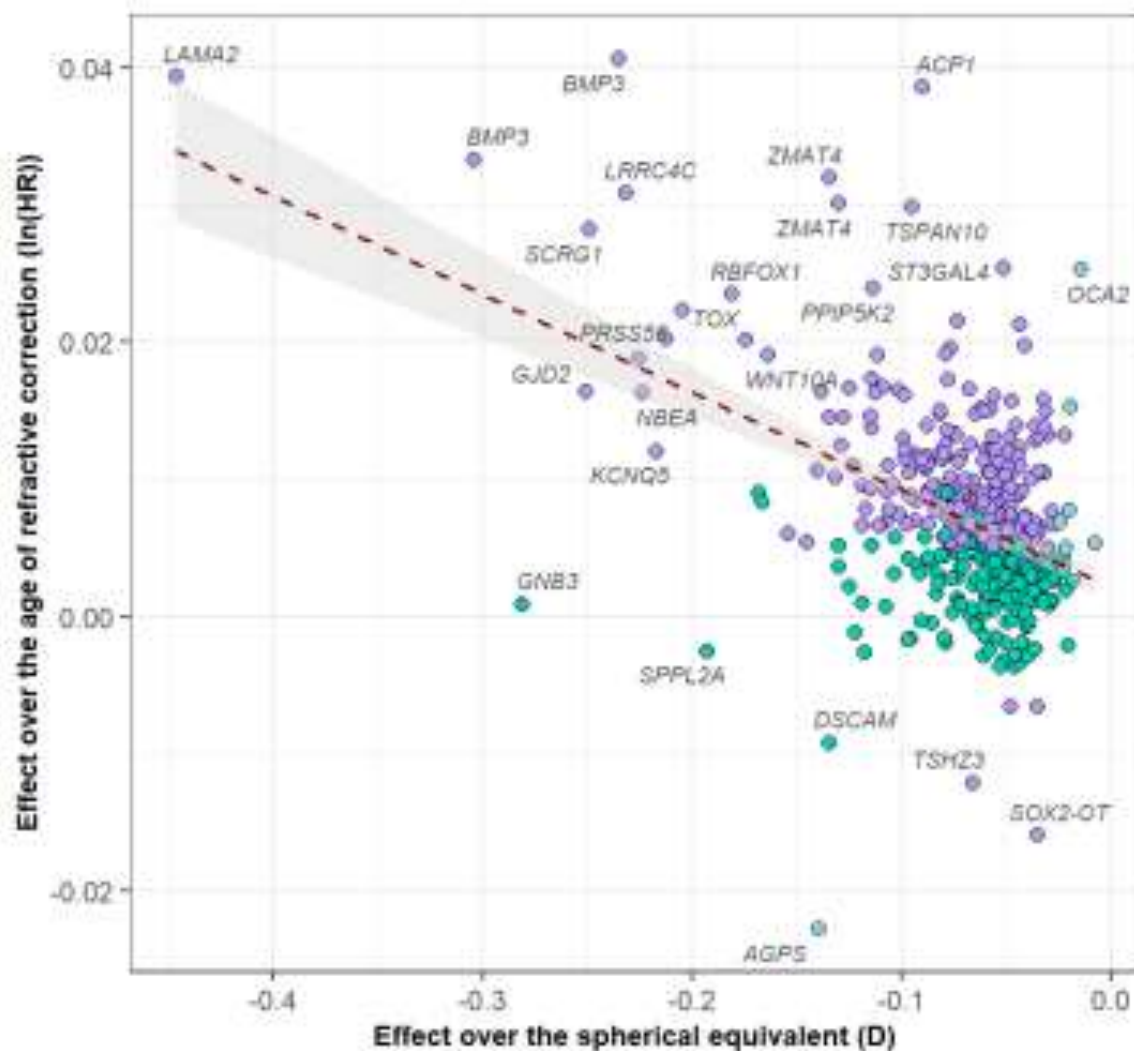
Table 1. Genetic correlations between SPHE GWAS effects and genome-wide survival analyses. Each value represents the pairwise genetic correlation (r_g) observed between the trait shown in the table headers and rows.

	AFSW all	AFSW, myopia only	AFSW, hyperopia only
Spherical Equivalent	-0.683	-0.968	0.808
AFSW all		0.889	-0.085
AFSW, myopia only			-0.651

Table 2. Replication of six novel loci associated with AFSW. Replication was carried out using the results of a genome-wide time to event study on age of first correction for myopia by Kiefer et al. (2013 PLoS Genetics 2013). The field "SNP" includes the polymorphic variants with the strongest associations (Discovery p-value) for each region, for which the Chromosome number (CHR) and genomic position (BP) are displayed. A1 lists the alleles at each SNP locus for which the effect sizes (Discovery HR as hazard ratios) and frequencies (Freq.) are reported, and the field "A2" lists alleles alternative to effect allele. "Gene" includes the symbol of transcript-coding gene nearest to the most strongly associated variant in the region. The columns "Replication HR" and "Replication p-value" display hazard ratios and p-values for the genetic associations in Kiefer et al. genome-wide survival analyses. The associations with replication p-value below the threshold of multiple testing correction (p=0.01) are shown in bold font. * The rs1194277 SNP, the second-best associated SNP in the AFSW analysis, was used as a replacement for rs1204700722, which was not available in the *23andMe* dataset

CHR	BP	SNP	Gene	A1	A2	Freq.	Discovery HR	Discovery p-value	Replication HR	Replication p-value
1	72720383	rs1194277*	*NEGR1*	G	T	0.69	1.013	3.72×10^{-08}	1.009	0.96
2	**13042958**	**rs10164589**	***TRIB2***	**T**	**G**	**0.48**	**1.013**	**3.96×10^{-08}**	**1.022**	**0.001**
3	**18192988**	**rs6577621**	***TBC1D5***	**G**	**A**	**0.45**	**1.014**	**8.15×10^{-09}**	**1.016**	**0.01**
12	106927958	rs7295942	*LOC100287944*	C	T	0.75	1.015	1.96×10^{-08}	1.007	0.38
17	**42847438**	**rs55882072**	***ADAM11***	**C**	**G**	**0.72**	**1.015**	**3.06×10^{-09}**	**1.028**	**0.0002**
21	**40575426**	**rs8131965**	***BRWD1***	**G**	**A**	**0.64**	**0.986**	**5.41×10^{-09}**	**0.974**	**0.00007**

Abbreviations

AFSW – Age of First Spectacle Wear

HRC – Haplotype Reference Consortium

GWAS – Genome-wide Associations Study