Supplementary Information:

Supplementary Table 1. Characteristics of the study participants (N = 102, 318). The fields "N,%" and "mean, se", "median, IQR" denote a number of the study participants, percentage, means, standard errors, medians and interquartile range respectively. Spherical equivalent cut-off points that were used to define emmetropia, hyperopia and myopia are provided in brackets

Demographic characteristics	
Age (N= 102,218) (median, IQR)	59 (51-64)
Sex (N = 102,218) (N, %)	
women	54,444 (53)
men	47,874 (47)
Townsend deprivation index (N = 102, 218) (median, IQR)	-2.01 (-3.53-0.45)
Years of education (N = 101, 470) (mean, se)	13 (10-20)
Refractive error-related variables	
Age of first spectacle wear (N = 93,357) (mean, se)	32 (16.2)
Spherical equivalent (N =102,318) (mean, se)	-0.3 (2.7)
Emmetropia (-0.5 < SpE< 0.5 Diopters) (N, %)	45,322 (44)
Hyperopia (SpE >=1 Diopters) (N, %)	28,944 (28)
Myopia (SpE <= -1 Diopters) (N, %)	28,052 (27)

Supplementary Table 2. Associations between polypharmacy and socioeconomic and demographic factors. The fields "beta", "se", "OR", "p-value" denote the regression coefficient (ln(OR), the coefficients standard errors of estimation, odds ratios and the association p-values from the logistic regression model

Factor	Beta	OR	se	p-value
Sex (male)	-0.005	0.99	0.016	0.73
Age	0.04	1.03	0.003	1.92×10^{-36}
Years of education	-0.03	0.97	0.002	1.30×10^{-60}
Townsend deprivation index	0.12	1.13	0.008	1.09×10^{-52}
Birth cohort (1940 - 1949)	-0.74	0.47	0.07	1.68×10^{-25}
Birth cohort (1950 - 1959)	-1.01	0.36	0.08	1.39×10^{-35}
Birth cohort (1960 - 1970)	-1.38	0.25	0.1	3.95×10^{-42}

Supplementary Table 3. Results of mixed linear model regression analyses, testing association between refractive error and analgesic medications. Models were adjusted for sex, age, age^2, years of education, Townsend deprivation index, polypharmacy and measures of physical activity. Columns "Medication" and "Physical activity measures" list the names of the tested drugs as well as physical activity measures that were entered into a model as covariates to adjust for potential confounding. The fields "Beta", "se", "95% CI" and "p-value" denote respectively the regression coefficient (slope), the standard errors of the coefficient estimation, the coefficients lower and upper bonds of the 95% confidence intervals, and p-values for each tested medication. The results are shown for medications that passed the sensitivity analyses. The analyses were performed in the sub-sample of study participants with AOSW between 5 and 35 years (N = 38,960)

Physical activity measures	Medication	Beta	se	95% CI	p-value
Frequency of walking (days per week)	tramadol	0.97	0.17	0.64 - 1.30	8.08×10^{-09}
	codeine	0.64	0.09	0.47 - 0.81	1.07×10^{-13}
	acetaminophen	0.26	0.04	0.18 - 0.35	2.05×10^{-09}
	ibuprofen	0.19	0.05	0.09 - 0.28	9.58×10^{-05}
Frequency of moderate physical activity (days per week)	tramadol	0.90	0.17	0.56 - 1.23	1.99×10^{-07}
	codeine	0.63	0.09	0.46 - 0.80	1.09×10^{-12}
	acetaminophen	0.26	0.04	0.17 - 0.34	6.71×10^{-09}
	ibuprofen	0.19	0.05	0.09 - 0.28	0.0001
Frequency of vigorous physical activity (days per week)	tramadol	0.94	0.17	0.60 - 1.27	3.32×10^{-08}
	codeine	0.69	0.09	0.52 - 0.86	3.80×10^{-15}
	acetaminophen	0.26	0.04	0.17 - 0.35	4.48×10^{-09}
	ibuprofen	0.18	0.05	0.09 - 0.28	0.0002
Duration of daily walking (minutes)	tramadol	1.00	0.19	0.63 - 1.37	1.04×10^{-07}
	codeine	0.64	0.10	0.43 - 0.84	9.74×10^{-10}
	acetaminophen	0.28	0.05	0.19 - 0.37	2.08×10^{-09}
	ibuprofen	0.23	0.05	0.12 - 0.32	1.01×10^{-05}
Duration of daily moderate physical (minutes)	tramadol	0.95	0.21	0.54 - 1.36	5.26×10^{-06}
	codeine	0.66	0.11	0.44 - 0.89	4.77×10^{-09}
	acetaminophen	0.28	0.05	0.18 - 0.38	3.26×10^{-08}
	ibuprofen	0.18	0.05	0.07 - 0.29	0.0009
Duration of daily vigorous physical (minutes)	tramadol	1.14	0.25	0.65 - 1.62	4.23×10^{-06}
	codeine	0.52	0.13	0.27 - 0.77	5.52×10^{-05}
	acetaminophen	0.28	0.06	0.17 - 0.39	4.85×10^{-07}

Physical activity measures	Medication	Beta	se	95% CI	p-value
	ibuprofen	0.20	0.06	0.08 - 0.31	0.00097
24-hour recall of light physical activity	tramadol	0.95	0.21	0.53 - 1.37	9.54×10^{-06}
	codeine	0.56	0.12	0.33 - 0.80	2.95×10^{-06}
	acetaminophen	0.22	0.05	0.11 - 0.32	3.87×10^{-05}
	ibuprofen	0.20	0.06	0.09 - 0.31	0.0004
24-hour recall of moderate physical activity	tramadol	0.96	0.21	0.53 - 1.38	8.57×10^{-06}
	codeine	0.58	0.11	0.37 - 0.79	1.10×10^{-07}
	acetaminophen	0.22	0.05	0.11 - 0.32	3.15×10^{-05}
	ibuprofen	0.20	0.06	0.09 - 0.31	0.0004
24-hour recall of vigorous physical activity	tramadol	0.97	0.21	0.55 - 1.39	6.78×10^{-06}
	codeine	0.57	0.12	0.34 - 0.81	1.99×10^{-06}
	acetaminophen	0.22	0.05	0.11 - 0.32	3.94×10^{-05}
	ibuprofen	0.20	0.06	0.09 - 0.31	0.0004

Supplementary Table 4. Results of Mendelian randomisation analyses testing the causal association between refractive error and 12 different traits. Column "Exposure" lists the names of the tested traits. Field "PMID" contains PubMed database publication numbers for the studies that provided MR exposure instruments. The studies that used UK Biobank data are marked with "*". The instruments for the outcome –refractive error, were selected from the most recent GWAS meta-analysis (PMID: 32231278). Number of instrumental variables (IVs) is the number of SNPs used in the analyses, and can be found in the column "Number of IVs". Column "Test" includes the names of the tests that were used to test causality. The fields "Beta", "se", "95% CI" and "p-value" denote respectively the MR coefficient estimated by each method, the standard errors of the coefficient estimation, the coefficients lower and upper bonds of the 95% confidence intervals and p-values for each tested trait. The units of the coefficients denote the number of Diopters (positive or negative) change when the exposure changes by 1 unit of the exposure (if the exposure is quantitative), or the difference of Diopters between cases and controls if the exposure is a categorical variable.

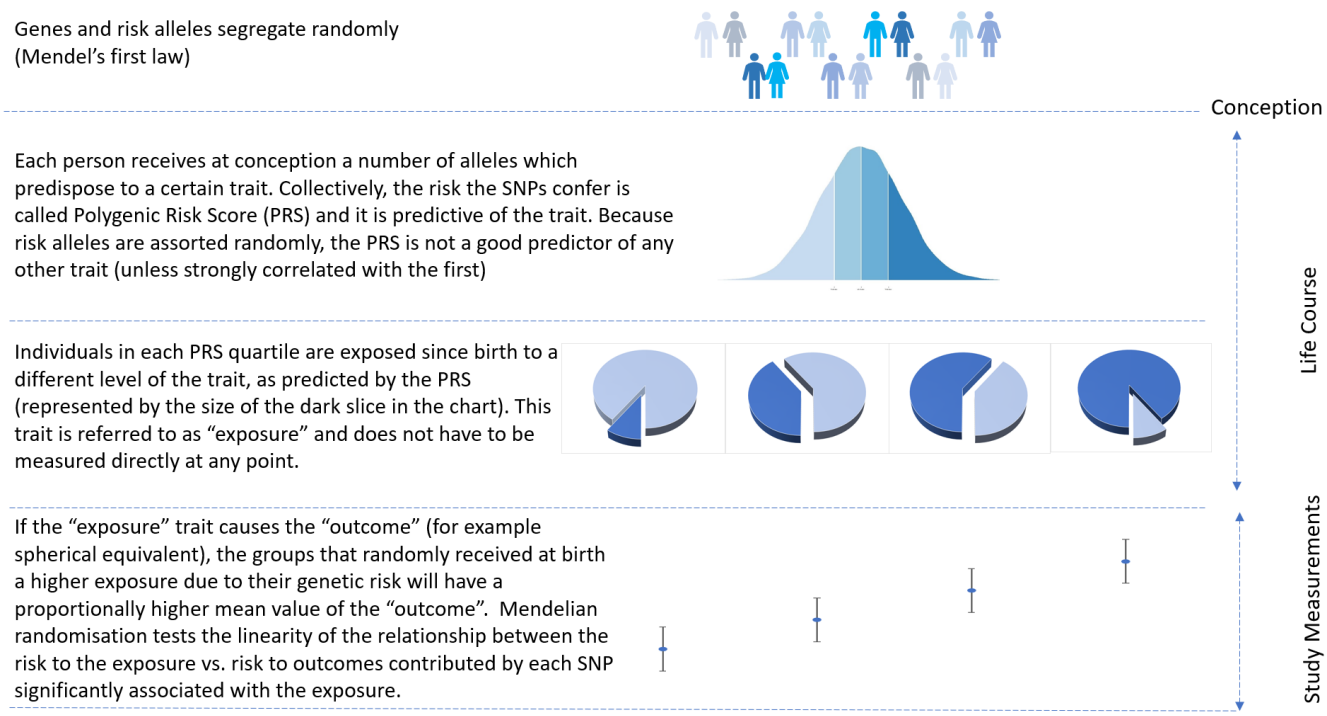
Exposure	PMID	Number of IVs	Test	Beta	Se	95 % CI	p-value
Intraocular pressure	29785010*	73	Simple median	-0.04	0.02	-0.088 - -0.009	0.016
			IVW	-0.045	0.013	-0.075 - -0.023	< 0.001
			MR-Egger	-0.087	0.038	-0.16 - -0.01	0.02
			(intercept)	-0.005	0.004	-0.004 - 0.01	0.256
			Maximum-likelihood method	-0.046	0.014	-0.073 - -0.02	0.001
IOP-lowering drugs	31015401*	14	Simple median	-0.043	0.007	-0.056 - -0.029	< 0.001
			IVW	-0.043	0.011	-0.064 - -0.022	< 0.001
			MR-Egger	-0.053	0.036	-0.124 - 0.018	0.15
			(intercept)	0.002	0.006	-0.01 - 0.014	0.78
Diabetes	30054458*	139	Simple median	-0.022	0.006	-0.033 - -0.01	< 0.001
			IVW	-0.022	0.008	-0.037 - -0.007	0.004
			MR-Egger	-0.071	0.017	-0.105 - -0.038	< 0.001
			(intercept)	0.004	0.001	0.001 - 0.006	0.001
Drugs used in diabetes	31015401*	56	Simple median	-0.024	0.0001	-0.024 - -0.024	< 0.001
			IVW	-0.028	0.007	-0.042 - -0.015	< 0.001
			MR-Egger	-0.049	0.016	-0.081 - -0.017	0.003
			(intercept)	0.003	0.002	-0.001 - 0.006	0.166
Chronic multisite pain	31194737*	38	Simple median	0.195	0.04	0.116 - 0.274	< 0.001
			IVW	0.201	0.044	0.115 - 0.287	< 0.001
			MR-Egger	0.505	0.218	0.079 - 0.932	0.02
			(intercept)	-0.005	0.004	-0.012 - 0.002	0.153
			Maximum-likelihood method	0.204	0.046	0.114 - 0.295	< 0.001

Exposure	PMID	Number of IVs	Test	Beta	Se	95 % CI	p-value
Anti-inflammatory and antirheumatic products, non-steroids	31015401*	6	Simple median	0.006	0.032	-0.057 - 0.07	0.844
			IVW	-0.02	0.072	-0.16 - 0.12	0.779
			MR-Egger	-0.541	0.411	-1.345 - 0.264	0.188
			(intercept)	0.025	0.019	-0.013 - 0.063	0.199
Salicylic acid and derivatives	24390342*	10	Simple median	0.011	0.016	-0.021 - 0.042	0.51
			IVW	0.026	0.015	-0.003 - 0.054	0.08
			MR-Egger	0.007	0.041	-0.074 - 0.088	0.873
			(intercept)	0.001	0.003	-0.004 - 0.007	0.621
Rheumatoid arthritis	24390342*	30	Simple median	0.008	0.004	0.000 - 0.016	0.05
			IVW	0.008	0.003	0.001 - 0.014	0.022
			MR-Egger	0.008	0.005	-0.002 - 0.017	0.134
			(intercept)	0	0.001	-0.001 - 0.002	0.958
Adrenergics inhalants	31015401*	54	Simple median	0.001	0.007	-0.013 - 0.015	0.91
			IVW	-0.003	0.01	-0.022 - 0.016	0.77
			MR-Egger	-0.031	0.028	-0.086 - 0.024	0.265
			(intercept)	0.003	0.002	-0.002 - 0.007	0.28
Chronic obsructive pulmonary disease	30804561*	47	Simple median	-0.015	0.021	-0.056 - 0.026	0.487
			IVW	-0.018	0.023	-0.064 - 0.027	0.434
			MR-Egger	-0.081	0.068	-0.215 - 0.052	0.23
			(intercept)	0.003	0.003	-0.002 - 0.008	0.321
Gout	27899376	9	Simple median	-0.011	0.014	-0.038 - 0.017	0.435
			IVW	-0.005	0.013	-0.031 - 0.02	0.675
			MR-Egger	0.067	0.03	0.007 - 0.126	0.027
			(intercept)	-0.013	0.005	-0.024 - -0.003	0.011
Uric acid	24816252	1	Simple median	-0.6678	0.2466	-0.914 - -0.421	0.007
			IVW	-0.369	0.18	-0.549 - -0.189	0.04
			MR-Egger	0.216	0.306	-0.09 - 0.522	0.481
			(intercept)	-0.009	0.0036	-0.013 - -0.005	0.024

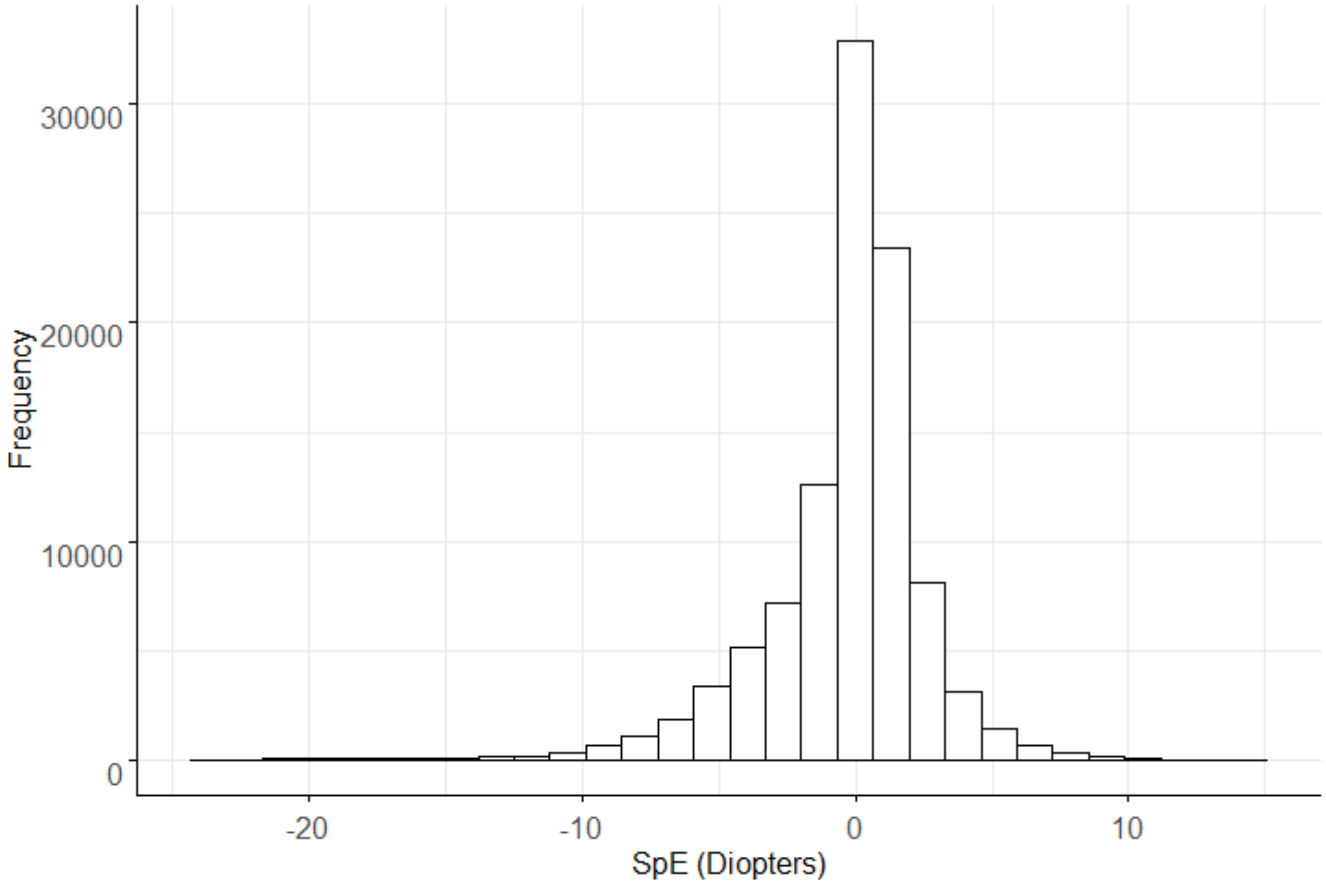
Supplementary Table 5. Association between SE and SNPs that have previously been shown to be associated with multisite chronic pain, in the UK Biobank. "Beta" denotes the linear regression coefficient, "SE" its standard errors, and "P-value" the association probabilities. The field "SNPs" contains the name of the associated polymorphisms, followed by the reference allele for which the effects are being reported in this table.

SNPs	Beta	se	P-value
rs10888692_C	0.017	0.012	0.15
rs197422_C	0.036	0.012	0.0031
rs59898460_T	0.010	0.012	0.40
rs12071912_C	0.012	0.013	0.34
rs1443914_T	0.005	0.012	0.68
rs12435797_G	0.039	0.015	0.01
rs2006281_C	0.027	0.012	0.03
rs2386584_T	0.015	0.012	0.21
rs285026_G	-0.019	0.012	0.11
rs11871043_T	0.019	0.012	0.12
rs11079993_G	0.014	0.012	0.25
rs62098013_G	0.019	0.012	0.11
rs4852567_A	0.008	0.013	0.53
rs2424248_G	0.021	0.017	0.23
rs7628207_T	0.014	0.016	0.39
rs28428925_G	-0.006	0.017	0.72
rs6770476_C	-0.019	0.013	0.14
rs34811474_G	0.009	0.014	0.55
rs13135092_A	0.101	0.021	8.18×10^{-07}
rs13136239_G	0.024	0.012	0.05
rs6869446_T	-0.003	0.012	0.80
rs1976423_A	0.006	0.012	0.61
rs17474406_G	0.049	0.036	0.17
rs1946247_T	0.014	0.017	0.42
rs11751591_G	0.018	0.016	0.28
rs6907508_A	0.025	0.018	0.18
rs6926377_A	0.019	0.013	0.15
rs10259354_G	0.004	0.013	0.79
rs7798894_A	0.010	0.014	0.45
rs6966540_T	0.021	0.012	0.08
rs12537376_A	-0.007	0.012	0.55
rs11786084_G	0.033	0.012	0.007
rs10992729_C	0.019	0.013	0.14
rs6478241_A	0.003	0.012	0.81
chr9:140251458_G_A_G	0.019	0.018	0.29
rs2183271_T	0.004	0.012	0.74
rs11599236_T	0.031	0.012	0.009
rs12765185_T	-0.003	0.013	0.79
rs61883178_C	-0.004	0.016	0.82

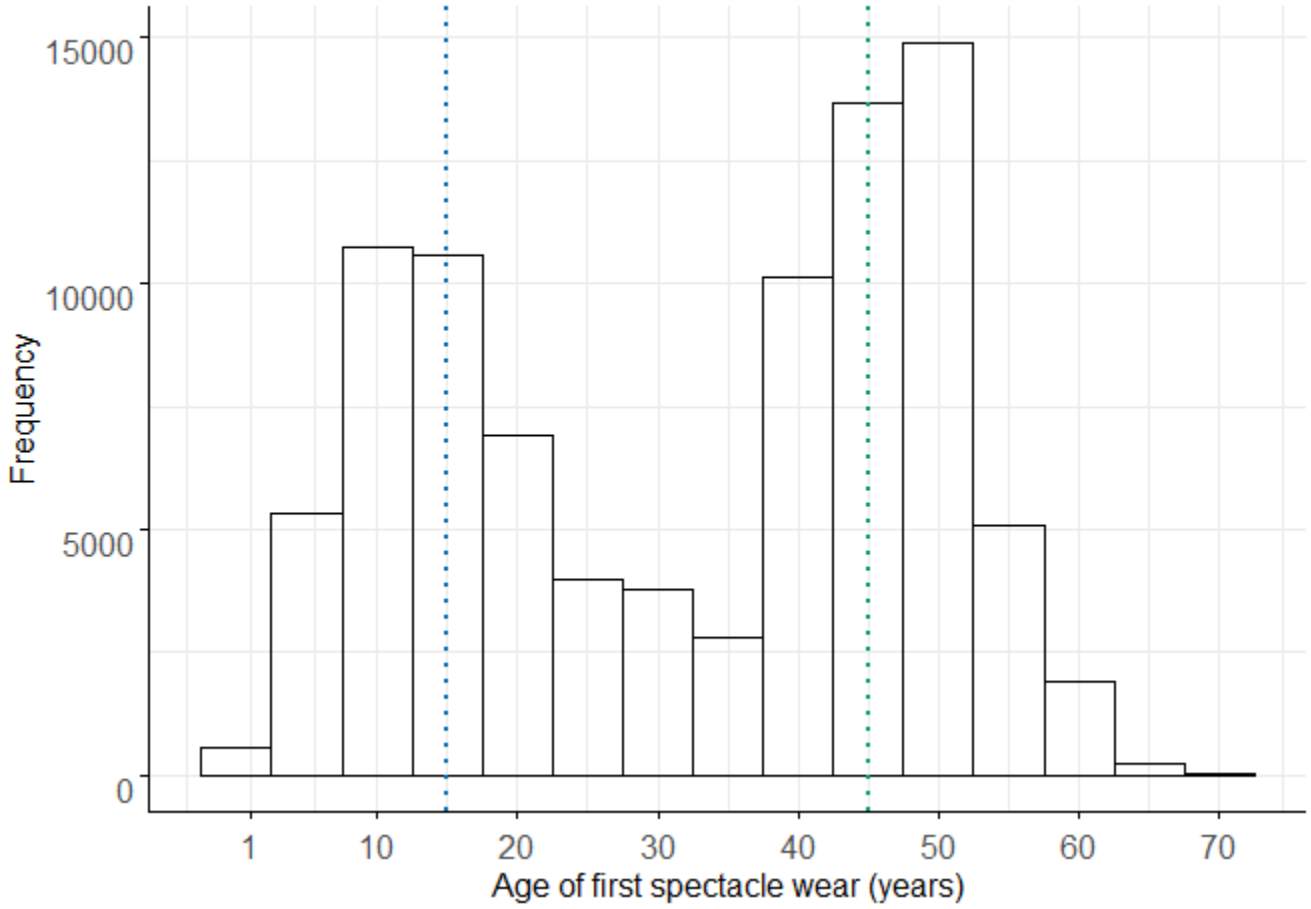
Supplementary Figure 1. The general principles of Mendelian Randomization. From top to bottom: the risk alleles are re-shuffled after each meiosis, they are assorted independently and randomly so they create unique risk profiles predicting only one trait (the "exposure"). When increased levels of "exposure" lead the specific outcome, progressively higher levels of the outcome phenotype will be observed with proportionally higher levels of randomly assigned levels of genetic risk.



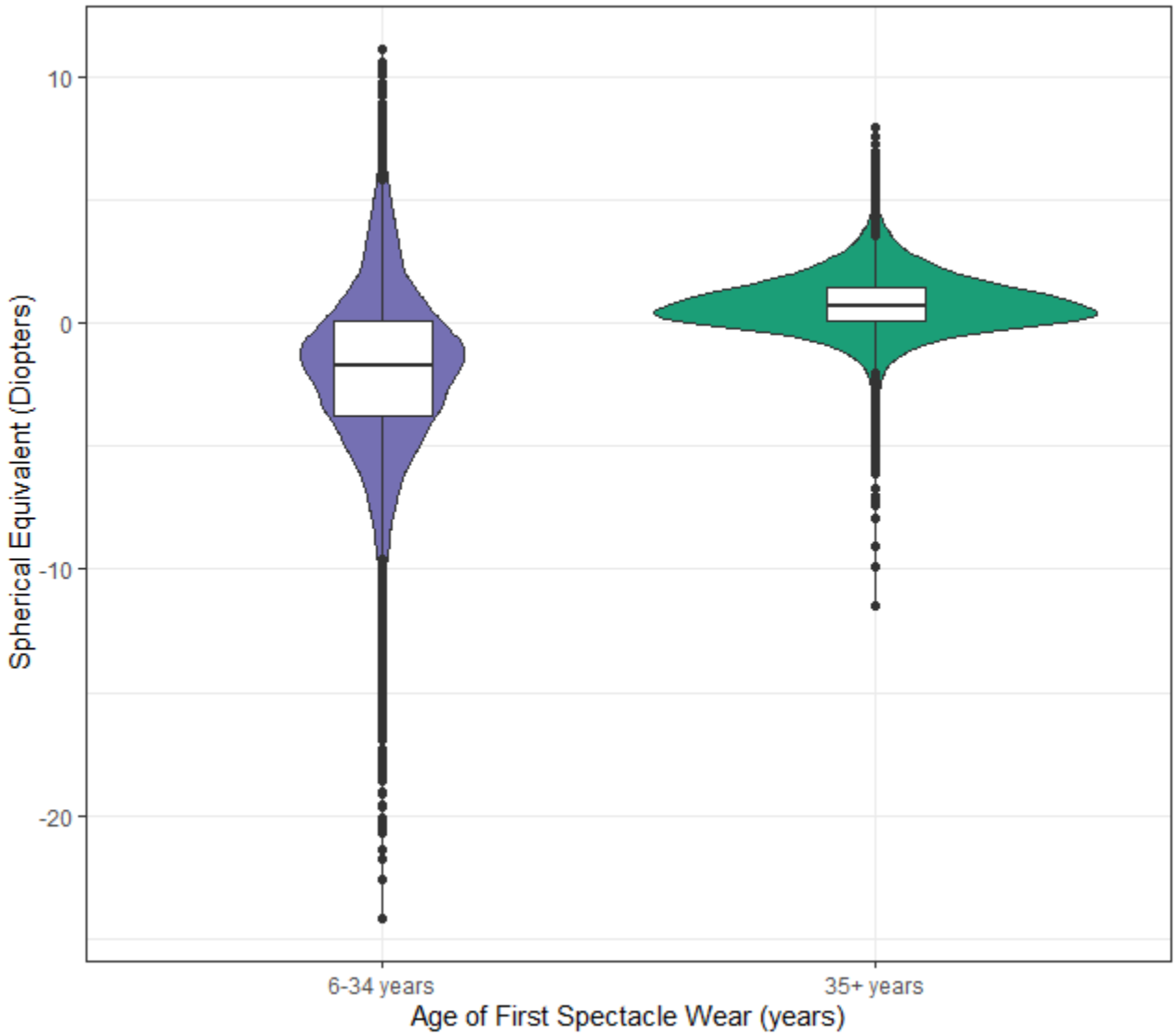
Supplementary Figure 2. Distribution of spherical equivalent (in Diopters) in UK Biobank cohort. The spherical equivalent is shown on the x-axis and the corresponding number of UK Biobank participants included in our work, for each spherical equivalent bracket, is given in the y-axis.



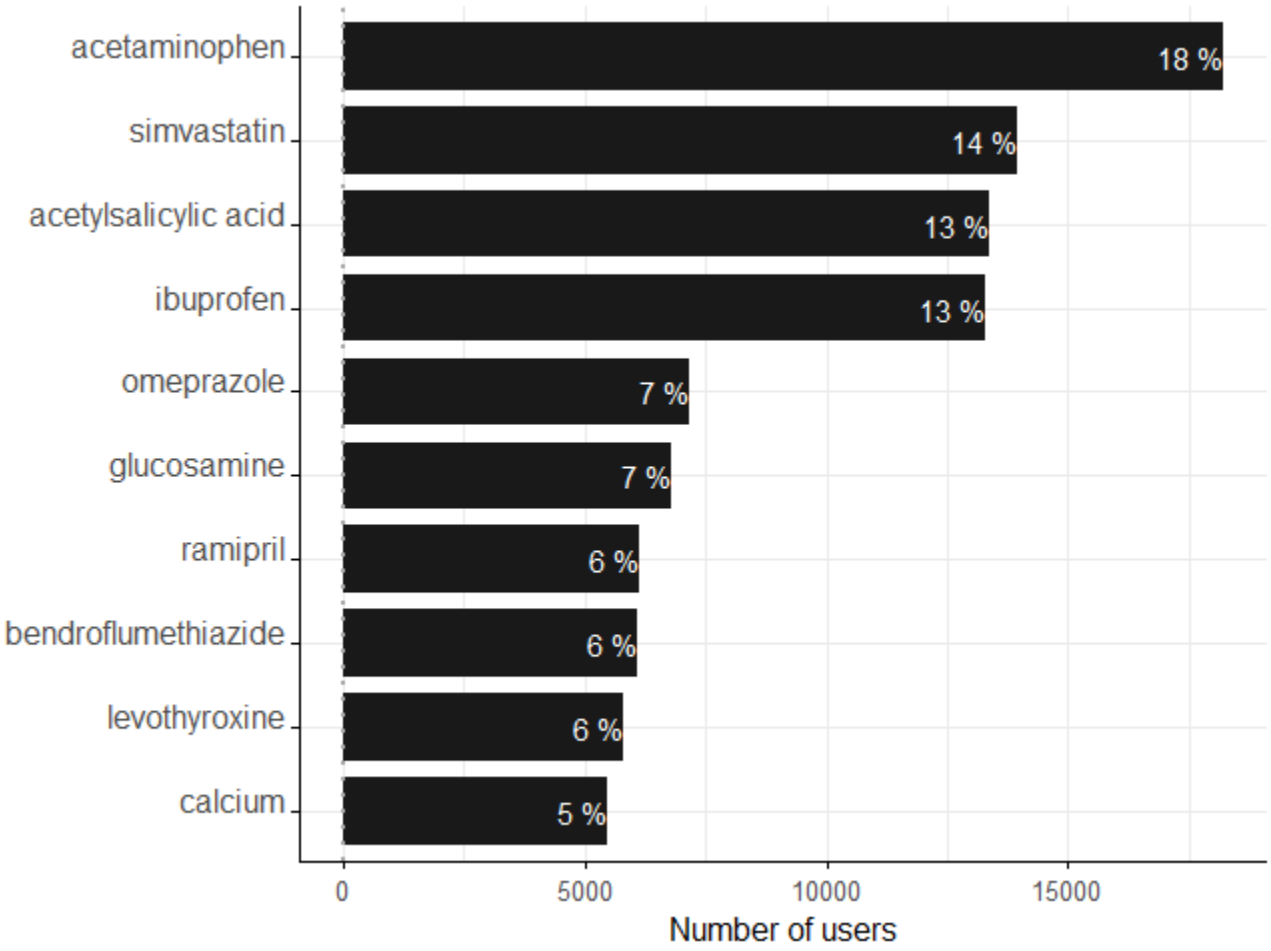
Supplementary Figure 3. Distribution of the age of first spectacle wear in UK Biobank cohort. The age of first spectacle wear is shown on the x-axis and the corresponding number of UK Biobank participants included in our work, for each spherical equivalent bracket, is given in the y-axis. The dashed lines represent the peaks of the modes of the distribution.



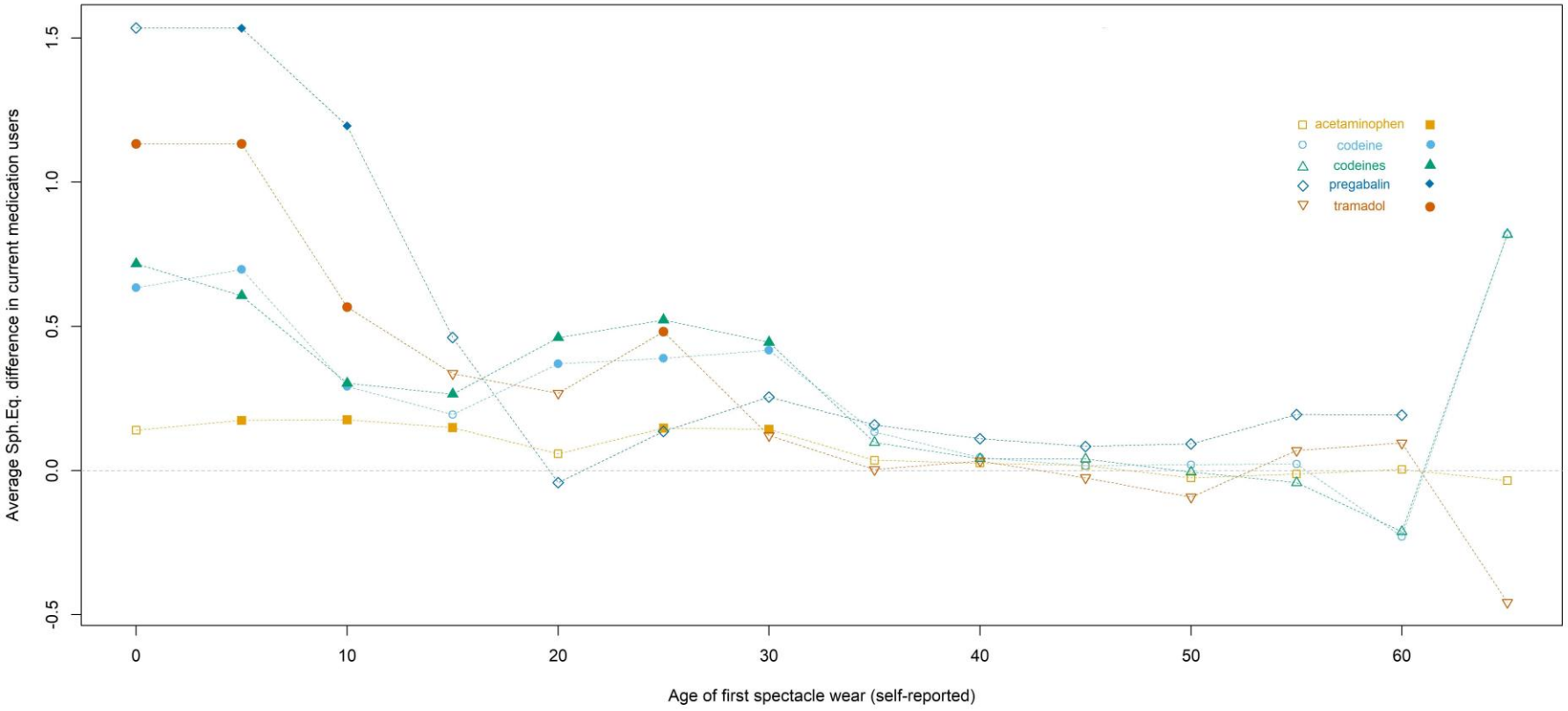
Supplementary Figure 4. Distribution of refractive error across the age of first spectacle wear in UK Biobank cohort (N = 87, 200). In the horizontal axes are shown the two main modes of the age of spectacle wear. The shape of the violin plots denotes the distribution of the spherical equivalent within the respective group. The central horizontal bar represents the mean spherical equivalent measurement (vertical axis) across all individuals in the respective categories; the box shows the interquartile range and the whiskers represent the observations in the 1.5 × IQR.



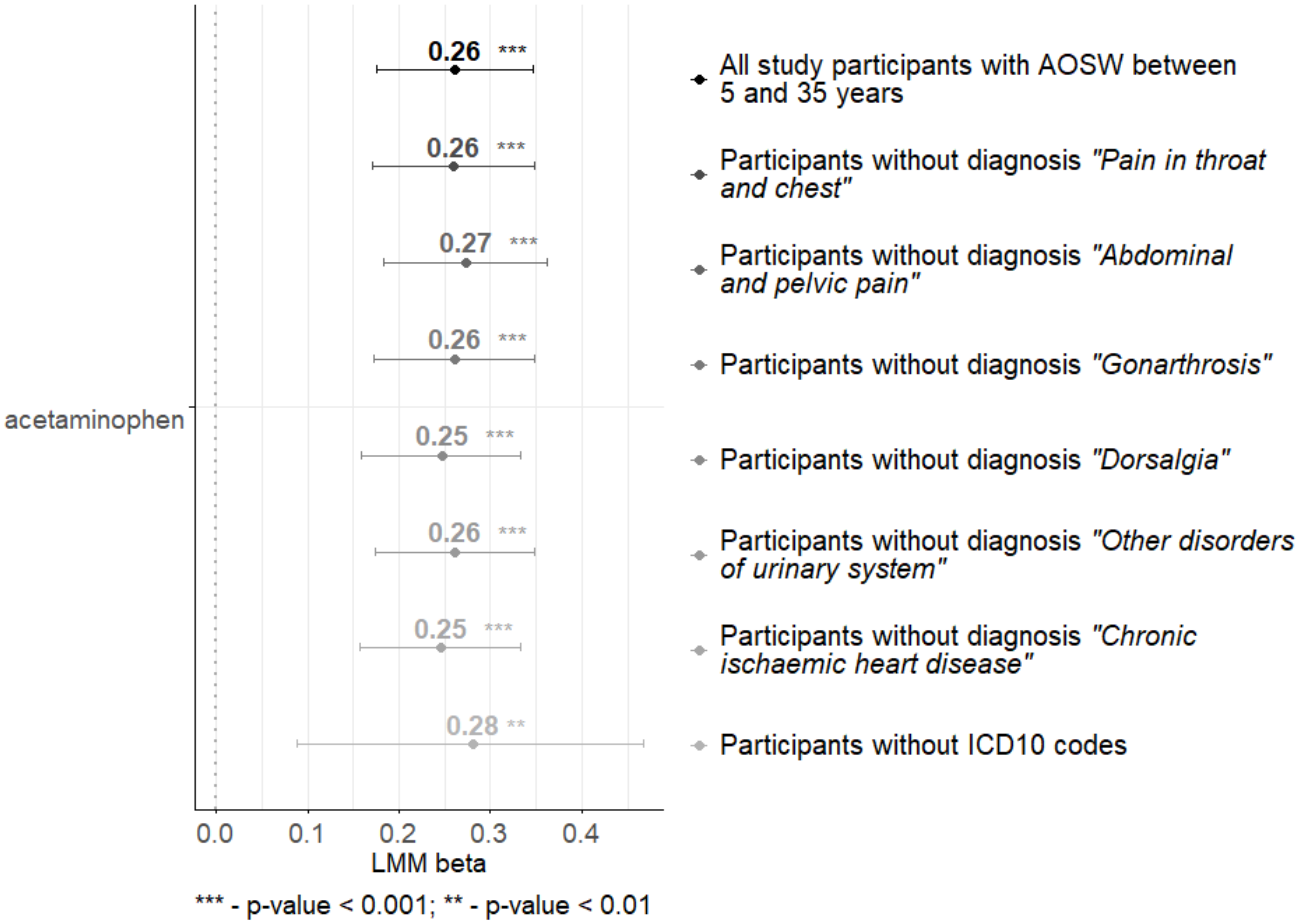
Supplementary Figure 5. Medication use in UK Biobank cohort. Information is limited to the ten most commonly reported drugs in the subset used in our study (N = 481). The numbers inside the bars represent the percentage of the study participants that reported taking medications.



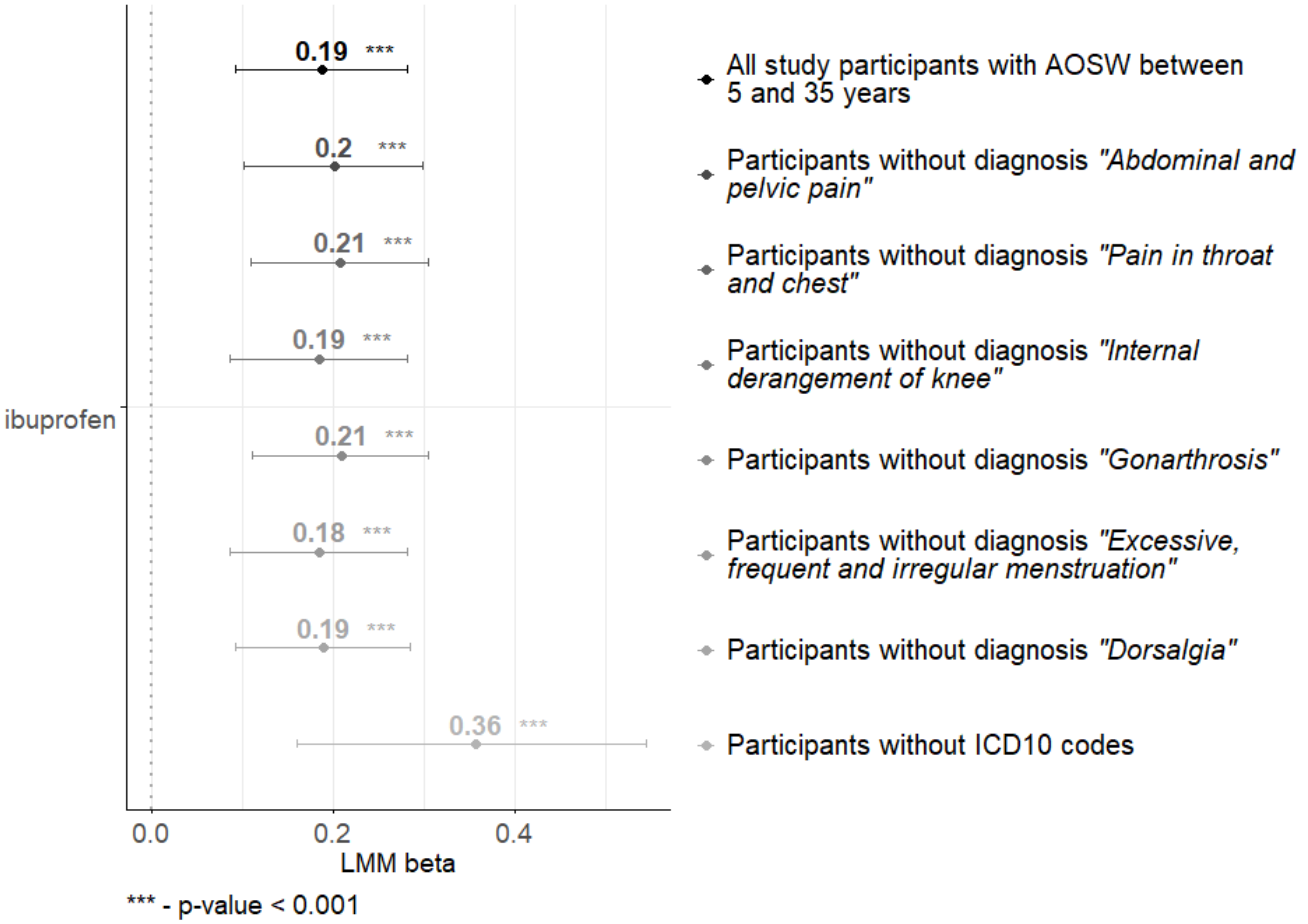
Supplementary Figure 6. The differences in spherical equivalent between subjects receiving analgesic medication and subjects who were not receiving them, by age of first spectacle wear. The AOSW shown in the x-axis is the first year of each of the 5-year periods in which the individuals started correcting their refractive error (i.e. 0-5, 5-10, etc.) and the y-axis denotes the adjusted difference in spherical equivalent observed in each group. The medications are specified in the Figure legend, with the symbol to the left of their names denoting results that are not statistically significant (see Methods) and the solid symbol to their right statistically significant differences.



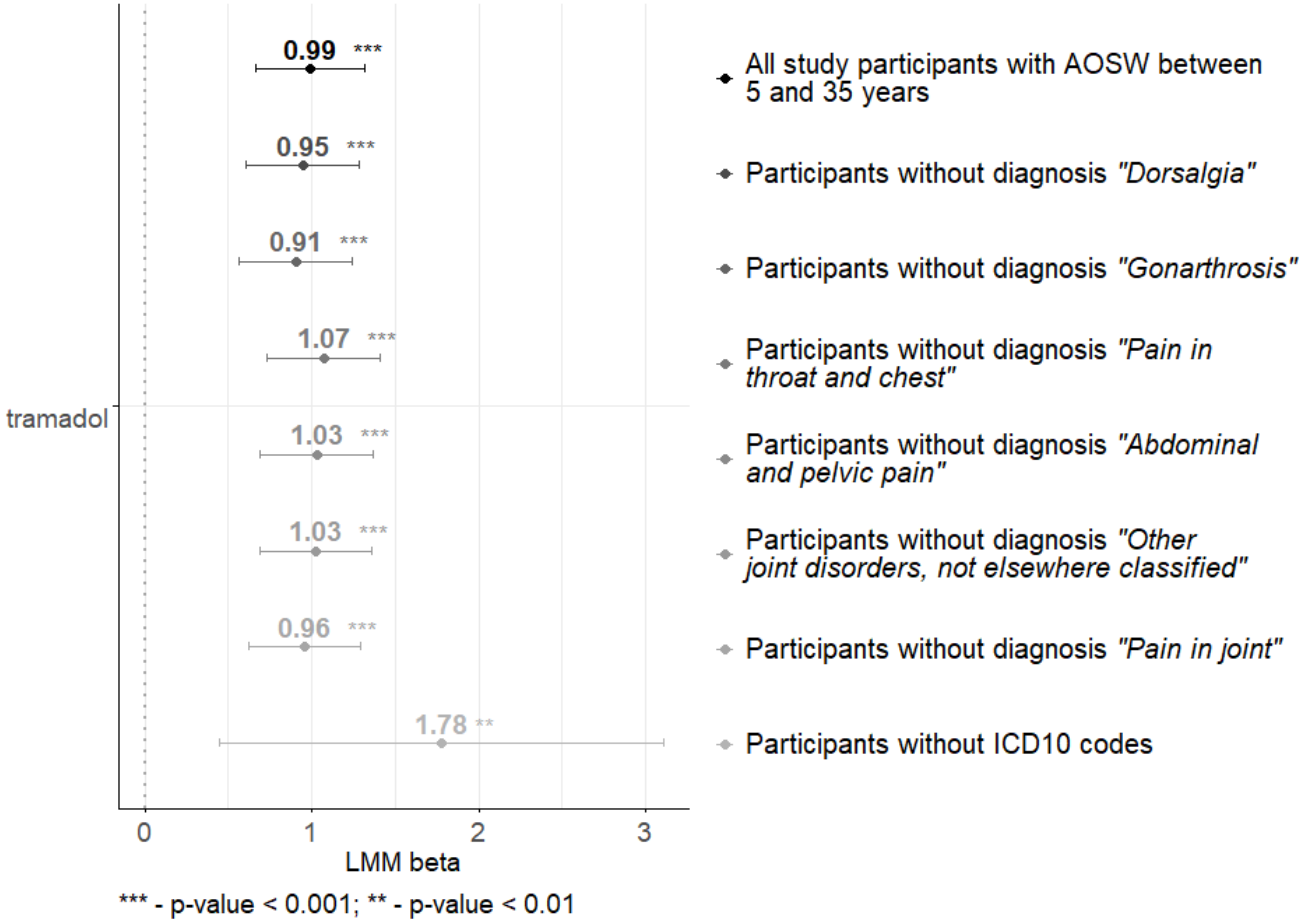
Supplementary Figure 7. Association between refractive error and acetaminophen use. Sensitivity analyses models' betas and their 95% confidence intervals are represented by error bar plots. Significance shown by the symbols ***, ** and * denote associations with p< 0.001, p < 0.01 and p < 0.05 respectively. Grey colour gradient represents the decreasing sample size. The legend keys follow the order of error bar plots. The resampling procedure was based on ICD10 codes – individuals with selected diagnoses were sequentially removed from the analyses



Supplementary Figure 8. Association between refractive error and ibuprofen use. Sensitivity analyses models linear model effect estimates, and their 95% confidence intervals are represented by error bar plots. Significance shown by the symbols ***, ** and * denote associations with p< 0.001, p < 0.01 and p < 0.05 respectively. Grey colour gradient represents the decreasing sample size. The resampling procedure was based on ICD10 codes – individuals with selected diagnoses were sequentially removed from the analyses

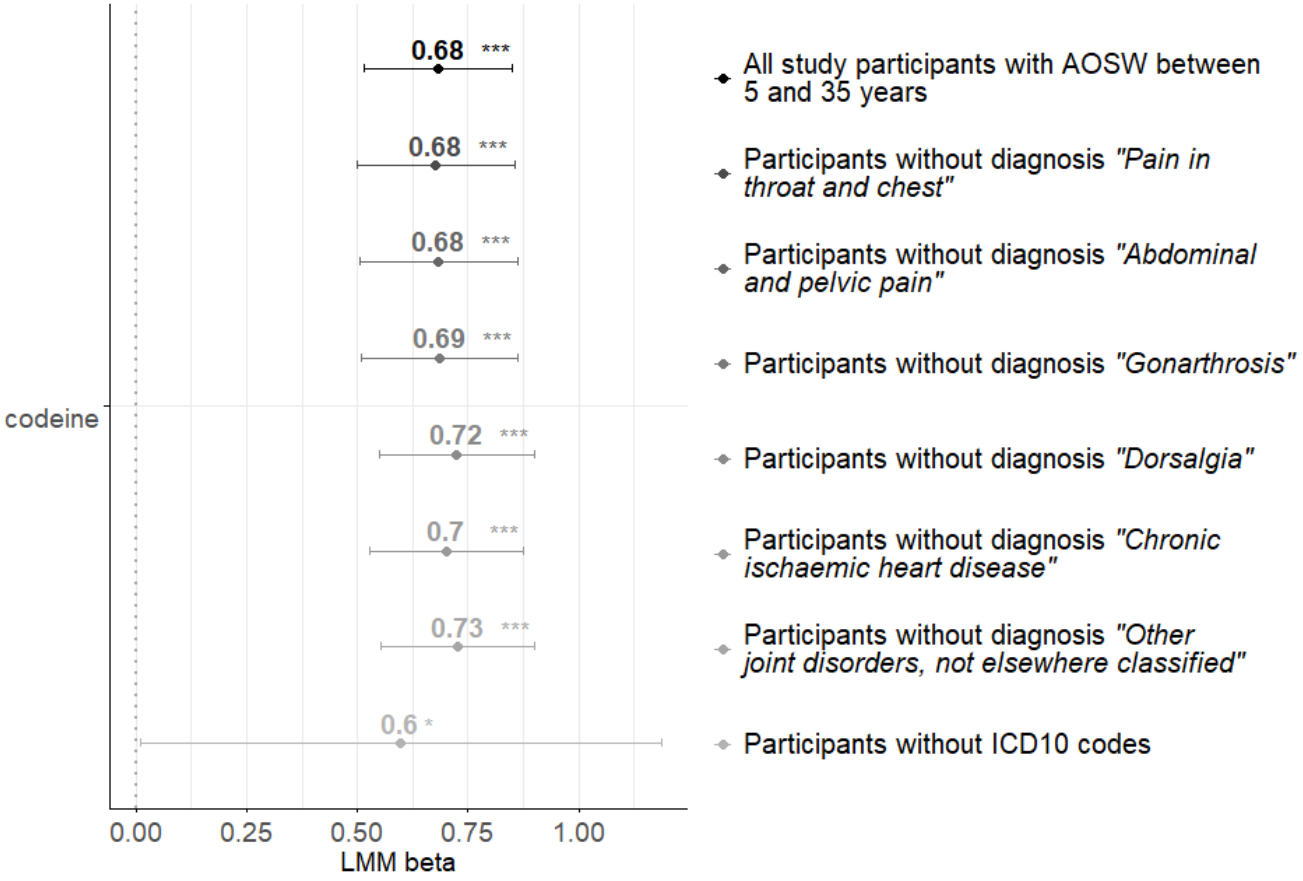


Supplementary Figure 9. Association between refractive error and tramadol use. Sensitivity analyses models' betas and their 95% confidence intervals are represented by error bar plots. Significance shown by the symbols ***, ** and * denote associations with p< 0.001, p < 0.01 and p < 0.05 respectively. Grey colour gradient represents the decreasing sample size. The resampling procedure was based on ICD10 codes – individuals with selected diagnoses were sequentially removed from the analyses



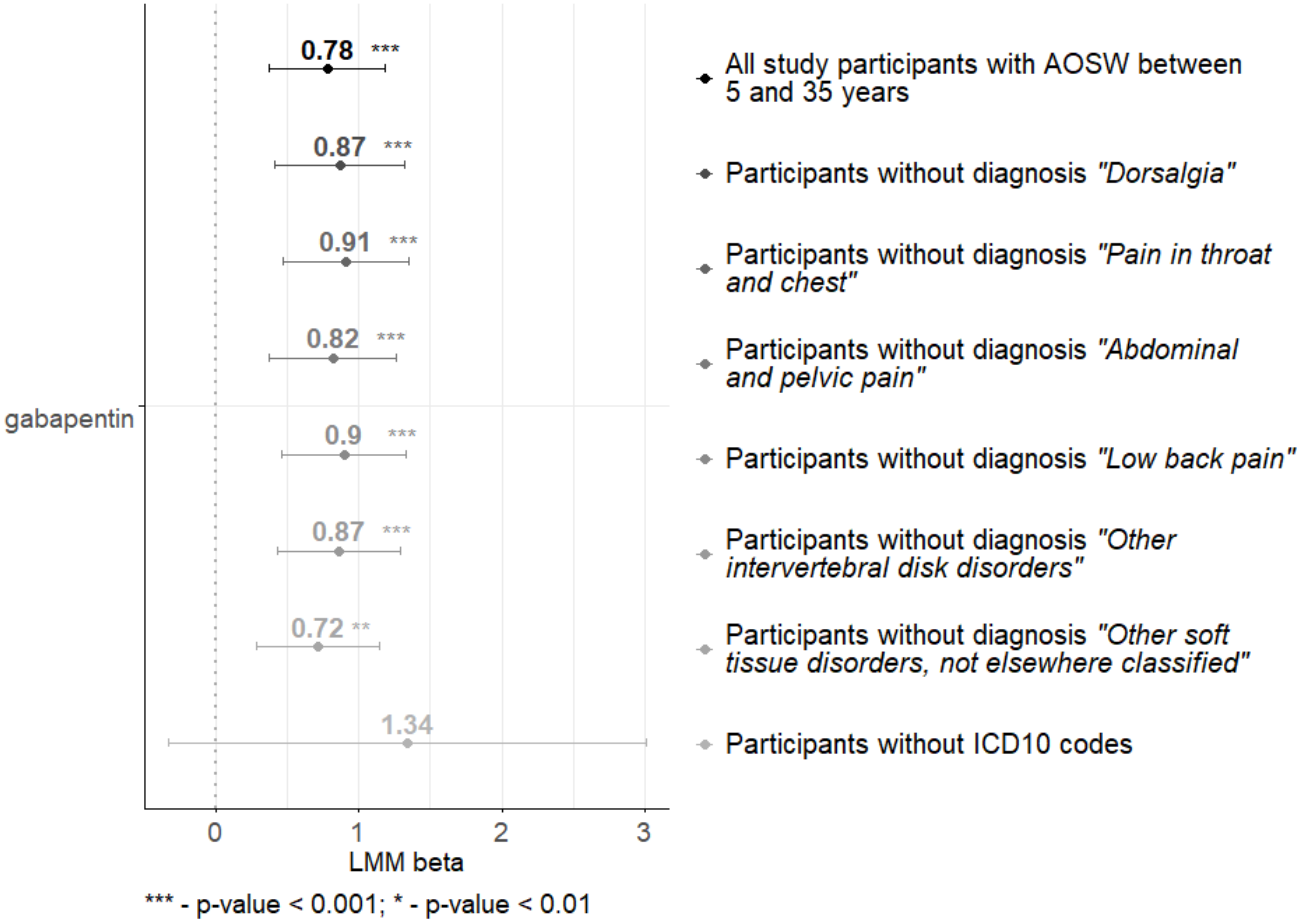
*** - p-value < 0.001; ** - p-value < 0.01

Supplementary Figure 10. Association between refractive error and codeine use. Sensitivity analyses models' betas and their 95% confidence intervals are represented by error bar plots. Significance shown by the symbols ***, ** and * denote associations with p< 0.001, p < 0.01 and p < 0.05 respectively. Grey colour gradient represents the decreasing sample size. The resampling procedure was based on ICD10 codes – individuals with selected diagnoses were sequentially removed from the analyses

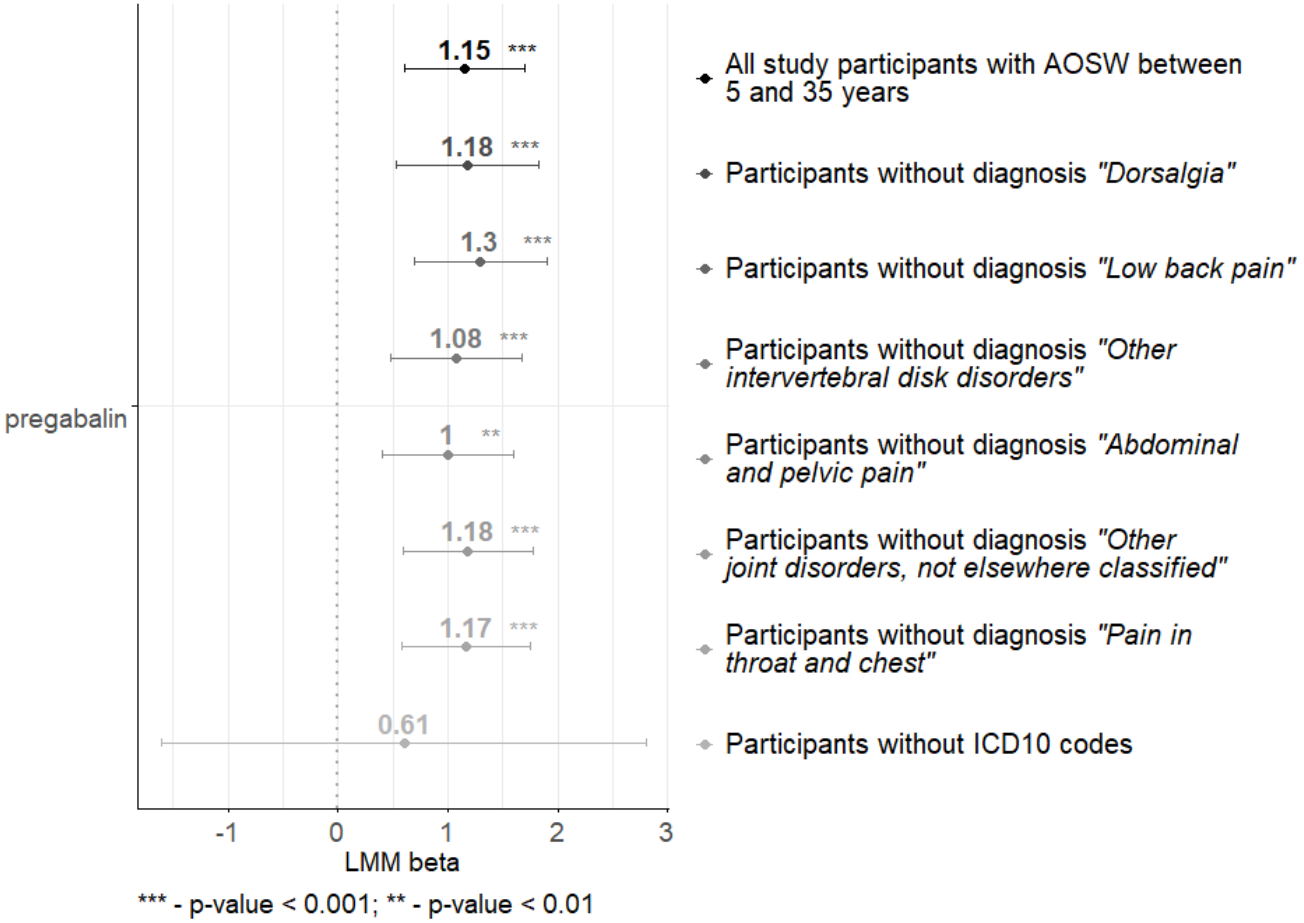


*** - p-value < 0.001; ** - p-value < 0.01, * - p-value < 0.05

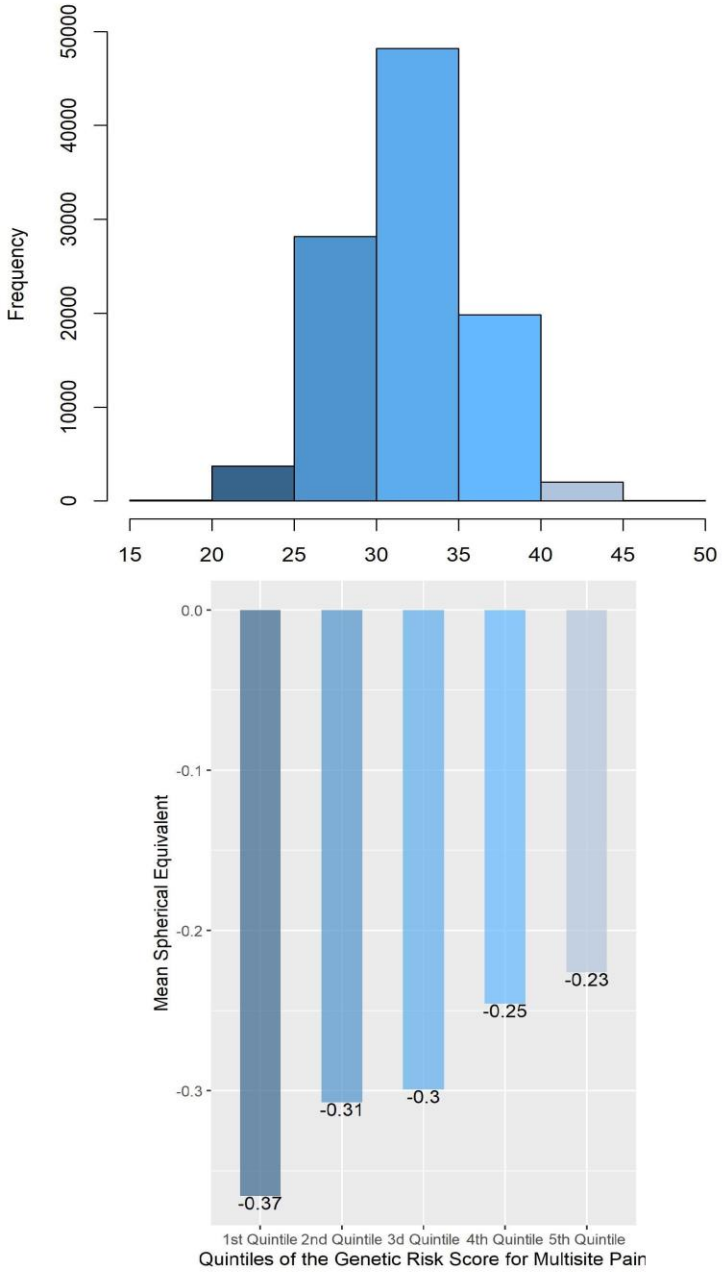
Supplementary Figure 11. Association between refractive error and gabapentin use. Sensitivity analyses models' betas and their 95% confidence intervals are represented by error bar plots. Significance shown by the symbols ***, ** and * denote associations with p< 0.001, p < 0.01 and p < 0.05 respectively. Grey colour gradient represents the decreasing sample size. The resampling procedure was based on ICD10 codes – individuals with selected diagnoses were sequentially removed from the analyses



Supplementary Figure 12. Association between refractive error and pregabalin use. Sensitivity analyses models' betas and their 95% confidence intervals are represented by error bar plots. Significance shown by the symbols ***, ** and * denote associations with p< 0.001, p < 0.01 and p < 0.05 respectively. Grey colour gradient represents the decreasing sample size. The resampling procedure was based on ICD10 codes – individuals with selected diagnoses were sequentially removed from the analyses



Supplementary Figure 13. The mean spherical equivalent observed in each quintile of the chronic multisite pain Polygenic Risk Score. Although chronic multisite pain and spherical equivalent are only weakly correlated (r=0.05), increasingly hypermetropic average levels of spherical equivalent are reliably observed for rising PRS values. The result of the test statistics for this relationship are reported in Supplementary Table 4.



Supplementary Figure 14. Results of Mendelian Randomisation tests for causality of multisite pain on spherical equivalent. Each of the points in the figure represents one instrumental variable (SNP) that has been selected on the basis of significant ($p < 5x10^{-08}$) association with multisite pain. The Mendelian randomization tests the relationship of the effect sizes of the associations of these instruments with multisite chronic pain ("exposure, x-axis) compared to the spherical equivalent (the "outcome", y-axis). The differently coloured lines represent the results of each of the tests used, as described in the Methods.