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# Five-year change in refractive error and its risk factors: results from the Gutenberg Health Study

Julia V. Stingl ,[1] Sol A Ban,[1] Markus Nagler,[2] Irene Schmidtmann,[3] Philipp S. Wild,[2,4,5] Karl J. Lackner,[6] Thomas Münzel,[7] Manfred E. Beutel,[8] Norbert Pfeiffer,[1] Alexander K. Schuster[1]

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For numbered affiliations see end of article.

**Correspondence to**
Dr Julia V. Stingl, Department of Ophthalmology, Johannes Gutenberg Universitat Universitätsmedizin Universitäts-Augenklinik Mainz, Mainz 55131, Germany; Julia.stingl@unimedizin-mainz.de

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## ABSTRACT

**Background/Aims** To examine the 5-year change in refractive error in phakic eyes and its risk factors in the general population.

**Methods** The Gutenberg Health Study (GHS) is a population-based cohort study including 15 010 participants from Germany aged 35–74 years at baseline examination (2007–2012). After 5 years, a follow-up examination was carried out (83% participation). 5-year change of spherical equivalent (SE) was computed as difference between follow-up and baseline objective refraction. Linear and logistic regression analysis were conducted analysing potential risk factors. Only phakic eyes at follow-up examination were included.

**Results** Right eyes of 10 175 subjects were included. An age-related shift of refractive error was identified, namely −0.12 D for age 35–44 years, 0.25 D for age 45–54 years, 0.25 D for age 55–64 years and 0.12 D for age 65–74 years during the 5-year follow-up. Smokers had a hyperopic shift (OR=1.31; p<0.001), while baseline SE (OR=0.89 per dioptre; p<0.001) and female sex (OR=1.49; p<0.001) were linked with a myopic shift. Education, occupation and other cardiovascular parameters were not associated with change in refractive error.

**Conclusions** The GHS demonstrates a parabolic shift in refractive error with a myopic shift at age 35–44 years, followed by a hyperopic shift at age 45–64 years which decreases at higher age. Smoking is associated with a hyperopic shift whereas female sex and myopic baseline SE is associated with a myopic shift. Educational level and occupation were not linked to a change in refractive error at age 35–74 years.

## INTRODUCTION

Refractive error is the main cause of visual impairment worldwide.[1 2] It is the inability of the eye to display a sharp picture on the retina. Refractive error can be corrected by spectacles, contact lenses or refractive surgery, but still constitutes an important risk factor for different ophthalmological diseases such as angle closure glaucoma in hyperopic individuals or open angle glaucoma,[3] retinal detachment[4] and myopic maculopathy in the case of myopia.[5]

The global prevalence for myopia is 26.5%, and 30.9% for hyperopia,[6] whereas in Germany prevalence for myopia and hyperopia is 35.1% and 31.8%, respectively.[7] The prevalence of myopia is steadily increasing and is estimated to affect about 5 billion individuals worldwide by 2050.[8]

The development of myopia is decisively influenced by both hereditary and environmental risk factors.[9 10] Various genes were identified to be responsible for myopia, most of them affecting the retinal and choroidal tissue, their signal transduction and cell-cycle mechanisms supporting the hypothesis of light-dependent globe growth.[10 11] A higher educational level was associated with a more myopic refraction,[12 13] and there are two major theories explaining this relation: first, near work over longer periods may lead to reduced accomodation ability resulting in hyperopic defocus on the retina and in eye growth, as shown in animal models.[14] Second, bright light seems to release dopamine which is postulated to inhibit axial elongation,[15] and increased time spent outside showed a preventive effect regarding myopia in adolescents.[16 17]

It is well known that refractive error can change over lifetime. A hyperopic shift is described in younger subjects between 35 and 64 years, whereas people aged 65 and older undergo a myopic shift.[18 19] The hyperopic shift in younger adults has been attributed to decreasing lens power, and the myopic shift to nuclear cataract.[20] Interestingly, people with high myopia seem to have a smaller hyperopic shift than emmetropic or hyperopic people.[18] Furthermore, higher education was associated with a higher hyperopic shift after 6 years in a Chinese cohort aged ≥35 years and in the Blue Mountains Eye Study cohort aged ≥49 years after 5 years.[18 19]

In previous studies, not only associations with age, lens opacification or baseline refractive error, but also with cardiovascular risk factors such as arterial hypertension or diabetes mellitus were found.[21 22] Diabetes mellitus can cause lens swelling by blood glucose fluctuations and is further a known risk factor for cataract development.[23 24] Also, dyslipidaemia has been identified as risk factor for cortical opacification,[25] which may affect the course of refractive error.

However, apart from this, there is little knowledge about the course of refractive error in adults. The purpose of this study therefore is to analyse changes in refractive error of adults and to identify further risk factors associated with refractive error change.

## METHODS

The Gutenberg Health Study (GHS) is a prospective and observational population-based cohort study in the State of Rhine-Palatine, Germany. Fifteen thousand and ten residents, randomly sampled by the regional registration office, took part. The study participants had an age range from 35 to 74 years at inclusion. The study was launched in 2007 and comprises an extensive follow-up examination at an interval of 5 years. The study design has been previously published by Höhn *et al*.[26] Inclusion criteria for the GHS were mental and physical ability to visit the study centre and to pass through the examinations, sufficient knowledge of the German language.

The baseline examination took place between 2007 and 2012 and a follow-up examination after 5 years between 2012 and 2017 at the study center at University Medical Center Mainz.

An ophthalmological examination was conducted including a slit-lamp examination at baseline, corneal Scheimpflug imaging (baseline: Pachycam, follow-up examination: Pentacam, Oculus, Wetzlar, Germany), determination of visual acuity, objective refraction (Humphrey Automated Refractor/Keratometer (HARK) 599, Carl Zeiss Meditec AG, Jena, Germany) and non-contact tonometry (Nidek NT-2000, Nidec Co, Japan).

Refractive error measurement was conducted without cycloplegia. Refractive values were measured in spherical and cylindrical dioptres (D), cylindrical power was indicated in negative sign convention. Spherical equivalent (SE) was computed as SE=sphere+0.5×cylinder. No refractive change was defined as −0.5 to +0.5 D change in SE, myopic shift as <−0.5 D and hyperopic shift as >+0.5 D. Presence of cataract was evaluated during slit-lamp examination in neutral pupil size at baseline.

Educational level[12] and occupation were investigated. Job position was classified via KIdB 2010 ('Klassifikation der Berufe'—German classification of occupations) in nine categories with additional subgroups for unemployed subjects, retired subjects and homemaker. One military subject was added to the 'Traffic, logistics, protection and security' category.

Physical activity was assessed using the SQUASH (Short QUestionnaire to ASses Health-enhancing physical activity) physical activity questionnaire and is indicated as physical activity score in minutes×intensity per week.[27] Extensive laboratory measurements including glycated hemoglobin (HbA1c), vitamin D level and blood lipid levels were carried out. Anthropometric measurements were performed with calibrated digital scales (Seca 862, Seca, Hamburg, Germany) and a measuring stick (Seca 220, Seca, Hamburg, Germany), and body mass index (BMI) was computed as BMI=weight/height$^2$. Smoking information is provided as categorical variable with four levels: non-smoker, occasional smoker, smoker and former smoker.

### Study sample

All study participants with objective refraction measurement at both baseline and 5-year follow-up examination were included. Refractive change was computed as difference in SE between follow-up and baseline measurement. If data were only available for one eye at both time points, this eye was included. For descriptive statistics, only right eyes were included. Exclusion criteria were ocular surgeries and only phakic eyes were included.

### Statistics

Descriptive statistics were calculated for all primary and secondary variables. For categorical data, absolute and relative frequencies were computed. For continuous parameters, mean and SD was calculated for all approximately normally distributed variables, otherwise median and interquartile range (IQR).

The distribution of 5-year change in SE was computed for the total analysis sample, as well as age-stratified and sex-stratified. Multiple linear and logistic regression analyses with generalised estimating equations (on eye-level) were performed to evaluate associated factors with 5-year change in SE. The included baseline parameters were sex, age (in linear and quadratic term), SE, intraocular pressure, presence of cataract, cardiovascular parameters such as HbA1c, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, BMI, physical activity and smoking as well as level of education and occupation. In logistic regression analysis, hyperopic and myopic shift was compared against no refractive change (−0.5 D≤x≤0.5 D). This is an exploratory study, p values were considered statistically significant if they were less than 0.05. Statistical analysis was performed with R (V.3.6.1).

## RESULTS

Among the initial 15 010 subjects, 12 423 visited the study centre for the 5-year follow-up examination. Two thousand two hundred and twenty-two subjects were excluded due to corneal surgery or cataract surgery in both eyes. Objective refractive data were not available from both baseline and 5-year follow-up examination in another 26 subjects resulting in the analysis sample of 10 175 subjects (9978 right eyes and 9952 left eyes). Table 1 shows the characteristics of analysis sample at baseline. The mean age was 53.0±10.4 years at baseline, and 52.6% were women.

The median value of refractive errors among included subjects was –0.12 (IQR: –1.25; 0.75) in right and in left eyes at baseline. The median value of refractive change over 5 years showed an overall hyperopic shift of 0.12 D in the right eyes. Separated into age decades, the 5 years change in SE was −0.12 D for age 35–44 years, 0.25 D for 45–54 years, 0.25 D for 55–64 years and 0.12 D for 65–74 years, respectively. At age 65–74 years, women showed no hyperopic shift in contrast to men (table 2). The scatterplot shows a quadratic relationship between 5-year change in SE and age with a hyperopic shift between age 44 and 70 years and a myopic shift at younger and higher age (figure 1).

The multivariable linear regression analysis showed a myopic shift over time in women compared with the men, age was associated in a negative quadratic relationship. Intraocular pressure (IOP), presence of cataract, HbA1c, HDL-cholesterol, LDL-cholesterol, triglycerides, BMI, physical activity, educational level and occupation were not associated with 5-year change of SE (table 3). In the logistic regression analysis, a myopic shift (more than −0.5 D) was related to lower age (p<0.001), female sex (OR=1.49, p<0.001) and baseline myopic SE (OR=0.89 per diopter, p<0.001) (online supplemental table 1). A hyperopic shift (more than 0.5 D) was more likely at higher age (p<0.001) and in regular smoker compared with non-smoker (OR=1.31, p<0.001), while former smoking or occasional smoking was not associated in logistic regression analysis (online supplemental table 2).

## DISCUSSION

Refractive error has a major impact on visual impairment worldwide, especially in low-income and middle-income countries. Change of refractive error is not only a phenomenon of childhood and young adulthood, as shown in large cohort studies involving individuals of European,[28] American,[20] Australian,[19] Carribean[29] and Asian[21] origin during the last two decades. The aim of this study was to analyse the 5-year change in SE and to identify risk factors in a large German cohort aged 35–74 years within the scope of the GHS.

The main findings of this study were a median age-related shift of refractive error of −0.12 D, 0.25 D, 0.25 D and 0.12 D for age groups 35–44, 45–54, 55–64 and 65–74 years. Regular

**Table 1** Baseline characteristics of the analysis sample with data on refractive error change in phakic eyes

| Characteristics | Total | Males | Females |
|---|---|---|---|
| n | 10 175 | 5243 | 4932 |
| Sex (female) | 48.5% | – | – |
| Age (years) | 53.5 (±10.5) | 53.7 (±10.6) | 53.2 (±10.4) |
| Ocular parameters (right eyes) | | | |
| Sphere (D) | 0 (−1.00; 1.00) | 0 (−1.00; 1.00) | 0 (−1.00; 1.00) |
| Cylinder (D) | −0.50 (−0.75; 0) | −0.50 (−0.75; −0.25) | −0.50 (−0.75; 0) |
| Spherical equivalent (D) | −0.12 (−1.25; 0.75) | −0.12 (−1.25; 0.75) | −0.12 (−1.12; 0.88) |
| IOP (mm Hg) | 14.10 (±2.78) | 14.16 (±2.86) | 14.03 (±2.68) |
| Ocular parameters (left eyes) | | | |
| Sphere (D) | 0 (−1.00; 1.00) | 0 (−1.00; 1.00) | 0 (−1.00; 1.00) |
| Cylinder (D) | −0.50 (−0.75; 0) | −0.50 (−0.75; 0) | −0.25 (−0.75; 0) |
| Spherical equivalent (D) | −0.12 (−1.25; 0.75) | −0.12 (−1.25; 0.75) | 0 (−1.25; 0.88) |
| IOP (mm Hg) | 14.25 (±2.83) | 14.37 (±2.91) | 14.11 (±2.72) |
| Ocular diseases | | | |
| Cataract (slitlamp examination) OD | 25.2% | 24.8% | 25.5% |
| Cataract (slitlamp examination) OS | 23.8% | 23.2% | 24.4% |
| Cardiovascular risk profile | | | |
| Smoking | | | |
| Never | 46.5% | 40.1% | 53.4% |
| Former smoker | 34.9% | 40.2% | 29.2% |
| Occasional smoker | 1.6% | 1.7% | 1.5% |
| Smoker | 17.0% | 18.0% | 16.0% |
| Obesity (yes) | 23.2% | 24.6% | 21.8% |
| Diabetes (yes) | 6.9% | 8.6% | 5.0% |
| Dyslipidaemia (yes) | 32.4% | 41.2% | 23.1% |
| Hypertension (yes) | 46.3% | 51.9% | 40.3% |
| Body mass index (kg/m$^2$) | 26.4 (23.8; 29.7) | 27.1 (24.8; 29.9) | 25.4 (22.6; 29.2) |
| Physical activity (minutes×intensity/week) | 7701.3 (±3909.0) | 7772.5 (±4231.5) | 7621.2 (±3510.1) |
| Laboratory measures | | | |
| HbA1c (%) | 5.5 (5.2; 5.8) | 5.5 (5.2; 5.8) | 5.4 (5.2; 5.7) |
| HDL-cholesterol (mg/dL) | 57.5 (±15.5) | 50.4 (±12.0) | 65.0 (±15.2) |
| LDL-cholesterol (mg/dL) | 139.0 (±35.0) | 139.5 (±34.5) | 138.5 (±35.5) |
| Triglycerides (mg/dL) | 103.0 (77.0; 144.0) | 116.0 (85.4; 162.0) | 93.0 (70.4; 124.0) |
| Education | | | |
| Secondary gerneral school ('Hauptschule') | 34.9% | 35.7% | 34.2% |
| Intermediate school ('Realschule') | 23.6% | 18.0% | 29.6% |
| High school ('Abitur') | 40.5% | 45.6% | 35.2% |
| Others | 0.5% | 0.4% | 0.6% |
| None | 0.4% | 0.4% | 0.5% |
| Occupation | | | |
| Housemaker, retried or none | 35.9% | 30.1% | 42.2% |
| Agriculture, forestry, animal husbandry and horticulture | 2.0% | 2.9% | 1.0% |
| Production and manufacturing | 8.7% | 14.5% | 2.5% |
| Construction and architecture | 3.2% | 5.7% | 0.5% |
| Natural and computer science | 4.6% | 7.3% | 1.8% |
| Transport, logistics, security and military | 5.2% | 7.8% | 2.5% |
| Commercial services and tourism | 6.3% | 5.6% | 7.0% |
| Business organisation, accounting, law and administration | 18.9% | 15.9% | 22.1% |
| Health and education | 12.2% | 7.2% | 17.6% |
| Humanities, media and culture | 2.9% | 3.0% | 2.9% |

Data from the German population-based Gutenberg Health Study (2007–2017). Analysis sample included 10 175 subjects (9978 right eyes and 9952 left eyes). Mean±SD are shown for normally distributed parameters, and median and IQR are shown for not normally distributed parameters.

HbA1c, Glycated hemoglobine; HDL, High-density lipoprotein; IOP, intraocular pressure; LDL, Low-density lipoprotein; OD, Oculus dexter; OS, Oculus sinister.

smokers were at higher risk for a hyperopic shift, and women were more likely to have a myopic shift. Education and occupation were not associated with refractive change after the age of 35 years.

Several studies have described a hyperopic shift in age groups under 65 years, followed by a myopic shift beginning at the age of 60–65 years.[18–22 28–30] Our data confirmed this trend. While participants aged 35–44 years showed a myopic shift within the

**Table 2** Five-year change in spherical equivalent by age in phakic eyes (right eyes)

| | 5-year change in spherical equivalent (D) | | | Per cent with 5-year changes | | |
|---|---|---|---|---|---|---|
| Baseline age | n | Median | IQR | <−0.5 D | −0.5 to +0.5 D | >0.5 D |
| Both sexes | | | | | | |
| 35–44 | 2441 | −0.12 | −0.38; 0.25 | 12.0 | 80.4 | 7.6 |
| 45–54 | 2999 | 0.25 | 0; 0.50 | 3.4 | 81.3 | 15.3 |
| 55–64 | 2744 | 0.25 | 0; 0.50 | 4.2 | 79.9 | 15.9 |
| 65–74 | 1794 | 0.12 | −0.25; 0.38 | 13.3 | 76.8 | 9.9 |
| All ages | 9978 | 0.12 | −0.12; 0.38 | 7.5 | 79.9 | 12.6 |
| Males | | | | | | |
| 35–44 | 1208 | −0.12 | −0.38; 0.12 | 10.8 | 82.8 | 6.5 |
| 45–54 | 1537 | 0.25 | 0; 0.50 | 2.9 | 82.8 | 14.3 |
| 55–64 | 1402 | 0.25 | 0; 0.50 | 3.2 | 80.2 | 16.5 |
| 65–74 | 987 | 0.12 | −0.25; 0.38 | 12.2 | 77.2 | 10.6 |
| All ages | 5134 | 0.12 | −0.12; 0.38 | 6.6 | 81.0 | 12.4 |
| Females | | | | | | |
| 35–44 | 1233 | −0.12 | −0.38; 0.25 | 13.2 | 78.1 | 8.7 |
| 45–54 | 1462 | 0.25 | 0; 0.50 | 3.9 | 79.8 | 16.3 |
| 55–64 | 1342 | 0.25 | 0; 0.38 | 5.2 | 79.5 | 15.3 |
| 65–74 | 807 | 0 | −0.25; 0.26 | 14.6 | 76.3 | 9.0 |
| All ages | 4844 | 0.12 | −0.12; 0.38 | 8.4 | 78.7 | 12.9 |

Data from the German population-based Gutenberg Health Study (2007–2017).
*Small deviation from 100% in total may appear due to mathematical rounding of the numbers.

following 5 years, older participants (45–64 years) had a hyperopic shift which decreased in the oldest age group. The overall change of SE over a 5-year interval showed a hyperopic shift of +0.12 D slightly lower than in previous studies. The Blue Mountains Eye Study found a mean refractive error change of +0.19 D,[19] the Handan Eye Study of +0.17 D[21] and +0.29 D was reported in the Reykjavik Eye Study,[28] while the Beaver Dam Eye Study found the same hyperopic shift (+0.12 D),[22] implicating similar changes in both Caucasian and Asian eyes. Nevertheless, the studies had different age-ranges and the results are therefore not directly comparable. The age distribution of previous studies may explain the difference in overall refractive change because less subjects at younger age having a myopic shift were included in these studies.

The myopic shift at younger age, identified in our analysis, was also seen in the Handan Eye Study and might be attributable to continuing of progressive myopia into adulthood.[21] In accordance with this, we found more likely a myopic shift (over −0.5 D) in subjects with a higher myopic baseline refractive error.

The aetiology of the hyperopic shift at age 43–70 years is so far not completely understood. Some authors hypothesised that the decreasing ability to accommodate is at least partially responsible, but studies using cycloplegic refraction as in Beaver Dam Eye Study also found a comparable hyperopic shift.[22] Another possible explanation is that the human lens power, which is formed by a refractive index gradient profile — unlike the homogeneous lens structures of intraocular lenses — decreases over the course of a lifetime. A maximum of lens fibre condensation in the central lens will be reached in adulthood, which causes an index plateau and acts like a homogeneous lens structure without a gradient, leading to a lower lens power.[31] The results of a recent population-based study in China support this theory as they found a relation between the hyperopic shift and the decreasing lens power.[18] At higher age, the identified myopic shift is in accordance to literature[32] and is known to be caused by nuclear cataract,[18] while other cataracts rather lead to a hyperopic shift.[33] This is explained by a combined effect of a refractive index change of the lens in nuclear cataract and a lens curvature change in cortical cataract.[33] The Beaver Dam Eye Study reported a 5-year refractive shift of −0.72 D in eyes with severe nuclear sclerosis compared with eyes with only mild nuclear sclerosis,[22] confirmed by other cohort studies describing a strong association between myopic shift and nuclear sclerosis.[19 22 28 29 34 35] Contrarily, in this study presence of cataract was not associated with a change in refractive error. This may be explained by missing differentiation of nuclear and cortical cataract in slit-lamp examination in neutral pupil size.

Although a higher educational level was found to be associated with a more myopic refractive error in the baseline GHS analysis,[12] both educational level and occupation did not influence

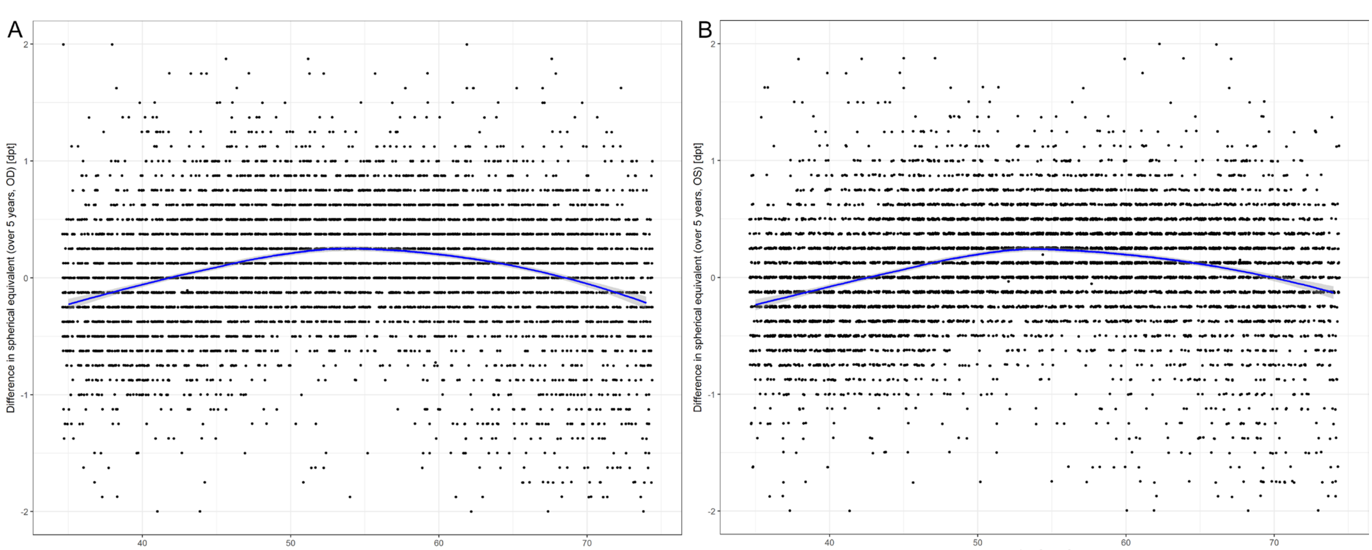


**Figure 1** Five-year change in spherical equivalent in phakic eyes and its relation to age. Data from the German population-based Gutenberg Health Study (2007–2017). (A) Right eyes; (B) left eyes.

**Table 3** Associations with 5-year change in spherical equivalent in phakic eyes

| (n=15 836 eyes) | Beta | 95% CI | P value |
|---|---|---|---|
| Sex (female) | −0.043 | −0.080 to 0.005 | **0.027** |
| Age (per year) | | | |
| Linear term | 0.139 | 0.12 to 0.15 | **<0.001** |
| Quadratic term | −0.001 | −0.0014 to −0.0011 | **<0.001** |
| Cardiovascular parameters | | | |
| HbA1c (%) | 0.011 | −0.040 to 0.019 | 0.49 |
| HDL-cholesterol (mg/dL) | 0.000 | −0.0010 to 0.0015 | 0.69 |
| LDL-cholesterol (mg/dL) | 0.000 | −0.0002 to 0.0007 | 0.30 |
| Triglycerides (mg/dL) | 0.000 | −0.0003 to 0.0004 | 0.71 |
| BMI (kg/m$^2$) | −0.002 | −0.007 to 0.004 | 0.55 |
| Physical activity | 0.000 | >−0.001 to <0.001 | 0.14 |
| Smoking history | | | |
| Non-smoker | | *Reference* | |
| Smoker | 0.030 | 0.012 to 0.072 | 0.16 |
| Occasional smoker | −0.050 | −0.174 to 0.074 | 0.43 |
| Former smoker | 0.023 | −0.012 to 0.057 | 0.19 |
| Ocular parameters | | | |
| Spherical equivalent (D) | −0.015 | −0.033 to 0.002 | 0.085 |
| IOP (mm Hg) | −0.003 | −0.009 to 0.003 | 0.34 |
| Lens opacity | −0.001 | −0.039 to 0.039 | 0.98 |
| Education | | | |
| Secondary gerneral school ('Hauptschule') | | *Reference* | |
| Intermediate school ('Realschule') | 0.013 | −0.03 to 0.08 | 0.57 |
| High school ('Abitur') | 0.000 | −0.04 to 0.04 | 0.98 |
| Others | 0.031 | −0.12 to 0.17 | 0.66 |
| None | 0.049 | −0.11 to 0.21 | 0.55 |
| Occupation | | | |
| Housemaker, retried or none | | *Reference* | |
| Agriculture, forestry, animal husbandry and horticulture | −0.050 | −0.17 to 0.07 | 0.42 |
| Production and manufacturing | −0.006 | −0.05 to 0.06 | 0.83 |
| Construction and architecture | 0.009 | −0.10 to 0.12 | 0.87 |
| Natural and computer science | 0.054 | −0.03 to 0.14 | 0.21 |
| Transport, logistics, security and military | −0.051 | −0.11 to 0.01 | 0.10 |
| Commercial services and tourism | 0.004 | −0.06 to 0.06 | 0.89 |
| Business organisation, accounting, law and administration | 0.006 | −0.04 to 0.06 | 0.80 |
| Health and education | −0.001 | −0.05 to 0.05 | 0.98 |
| Humanities, media and culture | 0.038 | −0.05 to 0.13 | 0.42 |

Data from the German population-based Gutenberg Health Study (2007–2017). Multivariable linear regression analysis with generalised estimating equations was conducted. Bold values indicate statistical significance (p<0.05).
HbA1c, Glycated hemoglobin; HDL, High-density lipoprotein; IOP, intraocular pressure; LDL, Low-density lipoprotein.

the change of refractive error over the observed period of 5 years. This is in line with the Beaver Dam Eye Study and the Barbados Eye Study. In contrast, the Blue Mountains Eye Study and a Chinese population-based study showed that individuals with higher education had a higher hyperopic shift,[19 22 29] while the Handan Eye Study found an association between educational level and a myopic shift in univariate but not in multivariable analysis.[21] This study is the first to show that occupational activities do not affect refractive error beyond the age of 35 years on population-based level.

Higher IOP is associated with longer axial length in children and also in young adulthood (18–27 years).[36 37] This effect possibly continues in older age groups but to a smaller amount, as published in the Barbados Eye Study, where individuals with ocular hypertension were at higher risk for incidence of myopia over an observation period of 9 years.[29] In our regression models, no association of IOP with change in refractive error was found. Furthermore, the Handan Eye Study reported that ocular hypertension was identified as a risk factor for a hyperopic shift in Asians.[21]

Although no association between smoking information and refractive error change was seen in the linear regression analysis, smokers were at higher risk to develop a hyperopic shift (more than +0.5 D) than non-smokers, former smokers or occasional smokers in the logistic regression analysis. Reykjavik Eye Study was the only other study that included the risk factor smoking in a regression model, but did not find any association with the change in SE.[28] The Salisbury Eye Evaluation Study reported that current smoking is associated with nuclear opacity incidence and progression, as well as cortical opacity progression.[38] This demonstrates that smoking leads to changes of the lens structure, that might result in a hyperopic refractive shift as found in our cohort.

We did not find any relation between refractive change and HbA1c-level as a marker for blood sugar control. In contrast, the Beaver Dam Eye Study found a more hyperopic shift in individuals with diabetes,[22] whereas Handan Eye study reported a more myopic shift and explained this by lens swelling leading to an increased refractive index,[21] while the Blue Mountains Eye Study did not find an association.[19] There was no association between HDL-cholesterol, LDL-cholesterol and triglycerides and the change in refractive error, though previous studies found an association between dyslipidaemia and cataract development,[25] which possibly might affect the refractive change. Furthermore, no relation between baseline refractive error and overall refractive change was present in the linear regression model, which is consistent with the 5-year data form the Beaver Dam Eye Study. Though in our study, logistic regression analysis showed a higher risk for a myopic shift in subjects with a higher myopic baseline refractive error. The Handan Eye Study reported a more myopic shift in individuals with longer axial length and postulated a higher fragility of the scleral tissue resulting in a higher tendency to expand.[21]

There are some limitations of our study. First, the recruitment efficacy proportion of our study was only 55.5% at baseline, nevertheless over 83% of the study participants took part in the 5-year follow-up examination. Second, we only had a slit-lamp examination with natural pupil at baseline and Scheimpflug imaging with natural pupil at 5-year follow-up examination and could therefore not evaluate the degree of lens opacity, subtypes of cataract and the cataract status after 5 years. Thus, the calculation of lens opacity influencing refractive error change might be imprecise. Nuclear sclerosis has been made responsible for the myopic shift in elderly people in previous studies.[19 22 28 29 34 35] In addition, ocular biometry was only carried out at the 5-year follow-up examination and we cannot report whether the change in refraction is due to an alteration of the ocular geometry or due to change in refractive index, especially of the human lens. Han *et al*[18] previously showed that lens power change was the most important biometric parameter for refractive changes at age 35 years and older. Another major limitation is the lacking information about the age of onset of myopia, which was associated with refractive change in both Blue Mountain Eye Study and Beaver Dam Eye Study.[19 22]

In summary, the GHS demonstrates a parabolic shift in refractive error with a myopic shift at age 35–44 years, while subjects at 45–64 years had a hyperopic shift which decreased in the oldest age group (65–74 years). Smoking was associated with a hyperopic shift whereas female sex and myopic baseline SE was associated with a myopic shift. Educational level and occupation did not have any effect on refractive change after 5 years at age 35–74 years.

**Author affiliations**
[1]Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[2]Preventive Cardiology and Preventive Medicine, Center for Cardiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[3]Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[4]Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[5]German Center for Cardiovascular Research (DZHK), partner site Rhine-Main, Mainz, Germany
[6]Institute for Clinical Chemistry and Laboratory Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[7]Center for Cardiology – Cardiology I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[8]Psychosomatic Medicine and Psychotherapy, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

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**Ethics approval** Each participant gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. Approvals of the local ethics committee (Ethics Commission of the State Chamber of Physicians of Rhineland-Palatinate, reference no. 837.020.07; original vote: 22.3.2007, latest update: 20.10.2015) and local and federal data safety commissioners were obtained.

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**Data availability statement** The written informed consent of GHS study participants does not approve public access to the data. This concept was requested by the local data protection officer and ethics committee (local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany). Access to data at the local database in accordance with the ethics vote is offered upon request at any time. Interested researchers can make their requests to the Principal Investigators of the Gutenberg Health Study (email: info@ghs-mainz.de).



**ORCID iD**
Julia V. Stingl http://orcid.org/0000-0002-9684-7753

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