Incidence, progression, and risk factors of age-related macular degeneration in 35- to 95-year-old individuals from three jointly designed German cohort studies

Brandl et al., 2021

SUPPLEMENTARY MATERIAL

Content

Supplementary Table 1. Response- and participant-proportions in the KORA and AugUR follow-up enrolment. Shown are the numbers and percentages of the total baseline sample, the net sample of follow-up participants, the final number of follow-up participants included in this analysis (i.e. color fundus images gradable for AMD for at least one eye at baseline and follow-up) for **(A)** KORA-Fit, **(B)** KORA-FF4 and **(C)** AugUR. Also shown are telephone-based self-reported reasons for non-response.

(A) KORA-Fit	**Number**	**Gross sample**	**Net sample**
	n	%	%
Baseline participants (KORA-S4) eligible for fundus sub-study (i.e. examined in study center equipped with fundus camera)[1]	**1831**	**100%**	
Died	73		
Not agreed to re-contact	123		
Consent withdrawn	6		
Moved outside the study area	226		
Moved, unknown destiny, postal return	9		
Net sample	**1394**	**76.13 %**	**100%**
No contact	102		
No participation due to health reasons	44		
Nursing case	5		
No sufficient communication possible	0		
Health reasons not further specified	39		
Refusal to participate	291		
No time, dependents in need of care	10		
No time, not specified	55		
Lack of interest	104		
Following medical expert suggestion	3		
Without giving reasons	119		
Follow-up participants	**957**	**52.27%**	**68.65%**
Examined at study center until August 2nd, 2018 and thus eligible for the fundus sub-study	**856**	**46.75%**	**61.40%**
Of those: re-examined at University Eye Clinic Augsburg	**50**		
Color fundus images acquired for at least one eye in baseline and follow-up	**856**		
Color fundus images gradable for AMD for at least one eye in baseline and follow-up (analyzed sample)	**506**		

Supplementary Table 1 continued.

(B) KORA-FF4	Number	Gross sample	Net sample
	n	%	%
Baseline participants (KORA-S4) eligible for fundus sub-study (i.e. examined in study center equipped with fundus camera)[1]	**1653**	**100%**	
Died	376		
Not agreed to re-contact	86		
Consent withdrawn	3		
Moved outside the study area	50		
Moved, unknown destiny, postal return	2		
Net sample	**1136**	**68.72%**	**100%**
No contact	33		
No participation due to health reasons	208		
Nursing case	31		
No sufficient communication possible	0		
Health reasons not further specified	177		
Refusal to participate	217		
No time, dependents in need of care	35		
No time, not specified	18		
Lack of interest	77		
Following medical expert suggestion	3		
Without giving reasons	84		
Follow-up participants examined at study center	**678**	**41.02%**	**59.68%**
Color fundus images acquired for at least one eye in baseline and follow-up	**678**		
Color fundus images gradable for AMD for at least one eye in baseline and follow-up (analyzed sample)	**350**		

Supplementary Table 1 continued.

(C) AugUR	Number	Gross sample	Net sample
	n	%	%
Baseline participants examined at study center	**1133**	**100%**	
Died	67		
Not agreed to re-contact	3		
Consent withdrawn	0		
Moved outside the study area	5		
Moved, unknown destiny, postal return	32		
Net sample	**1026**	**90.56%**	**100%**
No participation due to health reasons	121		
Nursing case	22		
No sufficient communication possible	1		
Health reasons not further specified	98		
Refusal to participate	117		
No time, dependents in need of care	4		
No time, not specified	9		
Lack of interest	89		
Following medical expert suggestion	1		
Without giving reasons	14		
Follow-up participants	**788**	**69.55%**	**76.80%**
Interview-based questionnaire via telephone	**55**		
Examined at study center	**733**	**64.70%**	**71.44%**
Color fundus images acquired for at least one eye in baseline and follow-up	**733**		
Color fundus images gradable for AMD for at least one eye in baseline and follow-up (analyzed sample)	**657**		

Supplementary Text 1. Details on the assessment of lifestyle, metabolic parameters, and genetic risk score.

Information on lifestyle factors (smoking, physical activity, healthy diet), as well as metabolic parameters (body-mass-index [BMI], type 2 diabetes mellitus [T2DM], hypertension, high and low density lipoprotein cholesterol [HDL-C, LDL-C]) were gathered via a standardized face-to-face interview and medical exams by trained medical staff as well as laboratory measurements. Participants were classified as current smokers (including regular smokers, currently smoking ≥ 1 cigarette per day, and occasional smokers, currently smoking < 1 cigarette per day), ex-smokers, and never smokers. Physical activity was assessed as regular activity during leisure time in summer and/or winter weekly for ≥ 1 hour (active) or less (not active).[2] A score for healthy diet was computed based on a 24-item standardized questionnaire[3] and dichotomized at the median of 15.00 (healthy diet: score ≥ 15.00, no healthy diet: score < 15.00). BMI (kg m-2) was computed based on measured weight in kg (in light clothing, to nearest 0.1 kg) and height in m (to nearest 0.5 cm) as weight divided by squared body height.[4] T2DM was assessed as self-reported type 2 diabetes or reported anti-diabetic therapy intake.[1] Hypertension was assessed as actually measured systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg or corresponding medication taken, given that the participants were aware of having hypertension.[1] HDL-C and LDL-C was measured as described previously.[5]

For genetic data, KORA and AugUR study participants were genotyped via the Affymetrix Axiom (Thermo Fisher Scientific, Santa Clara, California, USA) or the Illumina Infinium Global Screening Array (Illumina, San Diego, California, USA) and genetic information was imputed (1000 Genomes Reference panel, phase 3, version 5).[6] We derived information for 50 of 52 variants identified from case-control studies for late AMD[7] (49 variants directly and a proxy for rs142450006, rs1888235, with r^2=0.96 in IAMDGC data[7]). The variants rs121913059 and rs141853578 were rare (minor allele frequency in IAMDGC <= 1%) and unavailable in AugUR and KORA. Most of these 50 genetic variants were also documented

risk factors for early AMD.[8] We computed a genetic risk score (GRS) by adding the dosages of AMD risk alleles, weighed by the respective variant's effect size (log odds ratio from fully conditioned regression model[7]) and divided by the theoretical maximum of the weighted sum (i.e., the sum of two times the effect size for each variant). This resulted in a percentage of the (maximum) GRS for each study participant, ranging theoretically from 0% to 100%, observed from 32.0% to 54.0% (mean±standard deviation: 43.3±3.9, 43.1±3.9, 43.7±3.7 for KORA-Fit, KORA-FF4 and AugUR, respectively).

Supplementary Text 2. Details on the acquisition, processing, and grading of color fundus images.

In order to achieve comparable image quality across all three studies and all follow-up visits, the same camera type, settings and protocol were used in all studies/visits conducted in 2013-2019. KORA-S4 was conducted in 1999-2001; here, color fundus images of the central retina were acquired using the 45° non-mydriatic TRC-NW5S fundus camera (Topcon, Willich, Germany). As described previously[1], at least one non-stereoscopic color fundus photograph of the central retina of each eye, including full macular region and optic disc, was acquired. Images were available as.jpg-files with a resolution of 768 x 576 pixels. In AugUR1-BL, AugUR1-FU1, KORA-FF4 and KORA-Fit, conducted in 2013-2019, the automatized DRS camera (Digital Retinography System; CenterVue, Padova, Italy) with identical settings was applied as described before[9,10]: at least two color fundus images of each eye were acquired capturing the central or the central nasal field of the retina within a 45° view, including the full macular region and optic disc. Color fundus images were exported as .jpg-files with a resolution of 2,592 x 1,944 pixels from the DRS camera.

As it is known that the quality of fundus photography depends on pupil size and that pupil size decreases with age[11], mild pharmacological mydriasis was administered for the majority of the individuals aged 70+ as described previously.[9] Additionally, KORA-Fit participants with non-gradable images for at least one eye were re-invited to the Department of Ophthalmology, University Hospital Augsburg, where a total of 50 individuals were then re-

examined in mild mydriasis using the Zeiss FF450 plus color fundus camera (Carl Zeiss AG, Oberkochen, Germany; **Supplementary Table 1A**).

The following steps of processing and grading were exactly the same across the three studies and for baseline and follow-up. (1) All images were imported into the K-DRS software, a self-developed application for image analysis: images are displayed with a standardized front end on a 27 inch color-calibrated monitor, information on quality and grading can be entered, and results are linked with image number, participant identifier (IDGenerator[12]). (2) All images were assessed for gradability and for AMD by the same grader (C.B.). (3) Images were defined as gradable for AMD, if they fulfilled the following quality criteria allowing for the assessment of AMD: sufficient brightness and color contrast as well as full macular region captured. Images were excluded from AMD grading, if they revealed obscuring lesions (e.g. cataract) or lesions considered to be the result of a competing retinal disease hampering AMD grading (such as advanced diabetic retinopathy, high myopia, trauma, congenital diseases, or photocoagulation unrelated to choroidal neovascularization). (4) Details of assessing AMD features for each eye have been described previously[1,9]: The presence of drusen and pigment abnormalities (hyperpigmentation or depigmentation) on color fundus images was assessed. Only lesions within 2 standard disc diameters (approx. 3000 µm) of the centre of the macula/fovea were considered. To determine drusen size category (small, intermediate, large), the smallest drusen diameter was compared to the width of a major branch retinal vein crossing the optic disc margin, considered to be approximately one-twelfth disc diameter (i.e. 125 µm, assuming the average disc diameter to be 1500 µm). Drusen were defined as small drusen when their diameter were ≤ half the diameter of the vein (i.e. ≤ 63 µm), as large drusen for ≥ full diameter of the vein (i.e. ≥ 125 µm), and as intermediate drusen if anything in between (> 63 µm and < 125 µm). For borderline findings, the K-DRS image analysis software semi-automatically facilitated the measurement of drusen diameter, when the two distant points of the smallest drusen diameter were manually clicked by the grader. To assess total drusen area, the K-DRS software allowed for digitally placing a circle with 650 µm in diameter on the image, which helped the grader to categorize total drusen area as < or ≥ the circle area. GA was defined as

an area of RPE atrophy ≥ a circle with 350 µm in diameter, central or paracentral localization, and the presence of at least two of the following features: sharply demarcated boarder, lack of RPE, visible choroidal vessels, and circular shape. Pure GA was defined if central or paracentral GA, but no MNV was present; pure MNV was defined if MNV, but no GA was present; mixed GA/MNV was defined if both, GA and MNV were detected. This information on the assessed AMD features was then transferred into AMD stages for each eye at baseline and follow-up by a SAS-algorithm, according to two well-established classification systems: (i) the Three Continent AMD Consortium Severity Scale (3CACSS)[13], which separates mild early from moderate or severe early AMD stages depending on drusen size, drusen area, or the presence of pigmentary abnormalities and (ii) the Clinical Classification (CC)[14], which distinguishes between early and intermediate AMD depending on the presence of large drusen and/or pigmentary abnormalities (further details as described previously[9]). These two classification systems differ in how they define “early” or “intermediate” AMD, but the definition of late AMD as presence of GA and/or MNV is fairly similar. (5) AMD status of a participant was derived as the AMD status of the eye with the more severe AMD stage (“worse eye”) when both eyes were gradable, and as the grade of the one available eye otherwise. Participants with gradable images for at least one eye at baseline and follow-up were included in the present analysis.

Of note, among the analyzed KORA subjects, eight participants had available AMD status in Fit as well as FF4 (same AMD status) and we chose to assign these individuals to KORA-Fit (younger age at baseline, longer time to follow-up).

Supplementary Text 3. Details on double grading and baseline versus follow-up comparisons.

All images, from baseline and follow-up in each of the three studies (KORA-S4, KORA-FF4, KORA-Fit, AugUR1-BL, AugUR1-FU1), were graded for AMD features by the same experienced and trained ophthalmological consultant (C.B.) as described before[1,9]; questionable findings were discussed with a second trained grader (ophthalmological

consultant, T.B.). Double grading was performed by these two graders for AugUR, KORA-S4 and FF4; inter-rater reliability was high in AugUR (quadratic weighted kappa=0.97)[9,15], as well as in KORA (quadratic weighted kappa=0.80 and 0.91 for KORA-S4 and KORA-FF4, respectively).

Initially, images were graded sequentially and independently for baseline and follow-up, i.e. the grader was masked for the follow-up or baseline grading, respectively. Images that showed regression in AMD status in follow-up compared to baseline were re-graded comparatively in a side-by-side view to evaluate potential misclassification.[16] Regression from early to no AMD was found in 32 participants (e.g. for 3CACSS: n=8, n=3, n=21 in KORA-Fit, KORA-FF4 and AugUR, respectively), regression from late to early/no AMD in one participant (KORA-Fit). After the update via the side-by-side comparison, regression from early to no AMD remained in six participants (n=0, n=1 and n=5 participants of KORA-Fit, KORA-FF4, and AugUR, respectively). These results were used for further analysis.

Supplementary Text 4. Details on statistical analyses.

We computed cumulative incidence and progression estimates, per study and also by refined five- to ten-year age-groups within study, as the number of “events” divided by the number of “persons at risk”, as defined above.

The classification of “early AMD” differs between 3CACSS and CC and, consequently, also the classification of “no AMD” (i.e. absence of early and late AMD). The “late AMD” classification is basically the same. We thus computed cumulative incidence and progression for 3CACSS-based AMD and for CC-based AMD. We compared the two classifications of “early AMD” by computing the Positive Predictive Value (PPV) for late AMD as the ratio of the total number of incident late AMD cases among individuals with the respective no/early AMD category divided by the total number of persons within that particular category. We also computed the sensitivity and specificity of no/early AMD baseline categories (consecutively combined based on increasing severity) to predict late AMD development and the respective area under the receiver operating curve (AUROC).

We estimated the association of reported risk factors with incident early AMD, incident late AMD (definition-2), or progression, for each study separately. For this, we applied multiple logistic regression including all risk factors as covariates with early AMD (yes/no) or late AMD (yes/no) at follow-up as outcome and restricting the respective analyses to no AMD at baseline (incident early), no/early AMD at baseline (incident late definition-2), or early AMD at baseline (progression), respectively. Odds ratios (OR) were derived and tested for statistically significant difference from unity. Association with progression was only computed in AugUR, since the number of participants with progression from early to late AMD in the other two studies was not sufficient for stable association estimation. All models were adjusted for the individual's time in follow-up, which was close to 18-year, 14-years, or 3-years in the three studies.

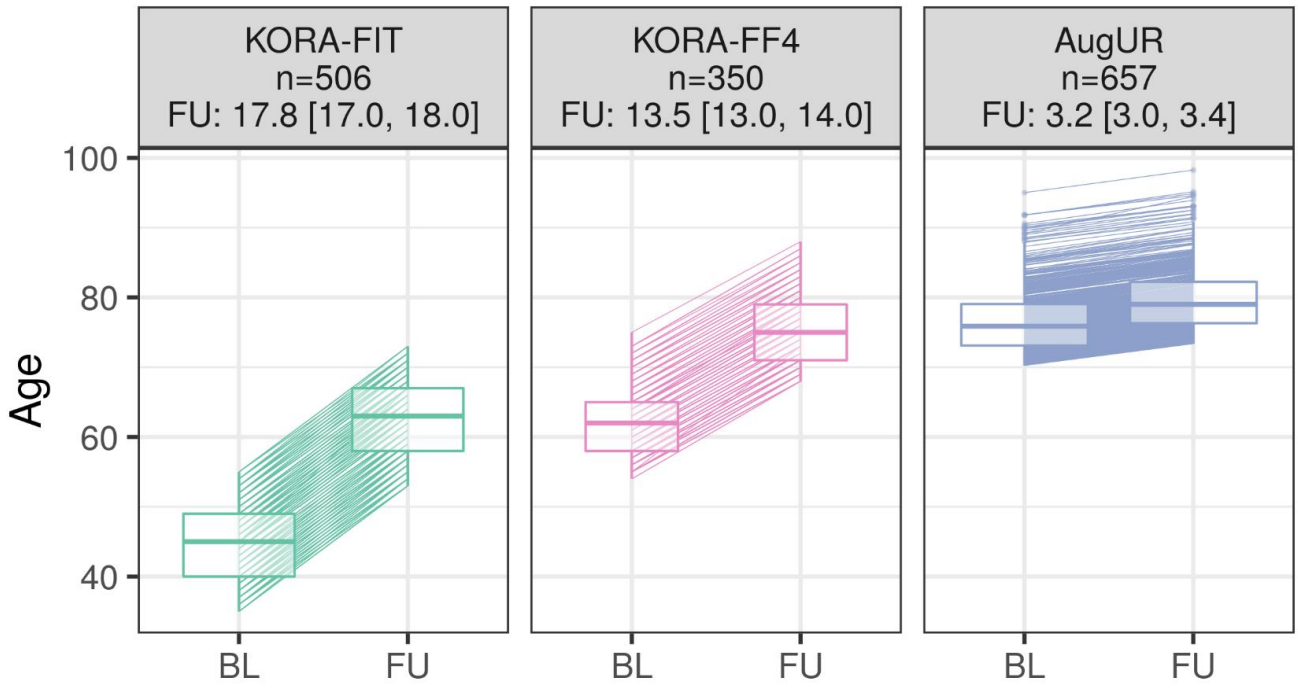
For comparison between our studies and to published studies, we estimated incidence and progression rates per 1,000 person-years by study and refined age-groups. For each age-group, the rate is derived as the fraction of the number of events divided by the number of person-years at risk, multiplied by 1,000. Each individual contributed the number of years at risk to one or several age-groups corresponding to the person's age at baseline and follow-up, which covered the age range of 35 years up to nearly 100 years (minimum baseline age and maximum age at follow-up).

Supplementary Table 2. Baseline characteristics of analyzed subjects compared to participants not in follow-up. Shown are baseline characteristics for subjects with available AMD status at baseline and follow-up (i.e. gradable color fundus images for at least one eye at baseline and follow-up; =analyzed subjects) and for eligible subjects with available AMD status at baseline but not at follow-up (=no follow-up). Also indicated is a significant P-value for difference via logistic regression adjusting for age and/or sex (where applicable).

	KORA-Fit		KORA-FF4		AugUR	
	Analyzed (n=506)	**No follow-up (n=675)**	**Analyzed (n=350)**	**No follow-up (n=566)**	**Analyzed (n=657)**	**No follow-up (n=383)**
General characteristics						
Age [years] at BL, mean ± SD (min-max)	44.6 ± 5.5 (35-55)	44.9 ± 6.4 (35-55)	61.9 ± 4.8 (54[h]-75)	64.4 ± 5.5*** (55-75)	76.6 ± 4.4 (70-95)	79.1 ± 5.7*** (70-94)
Men, % (n)	44.3 (224)	51.6 (348)*	52.9 (185)	52.8 (299)	56.3 (370)	50.7 (194)*
Lifestyle factors						
Current smoker[a], % (n)	26.3 (133)	39.1 (263)**	14.6 (51)	18.4 (104)**	5.5 (36)	7.3 (28)*
Ex-smoker, % (n)	37.8 (191)	28.9 (194)	39.1 (137)	40.4 (228)	38.5 (253)	36.6 (140)
Physically active[b], % (n)	59.1 (299)	48.4 (322)**	49.6 (173)	41.3 (231)*	95.0 (624)	90.9 (348)
Healthy diet[c], % (n)	57.5 (291)	51.3 (341)	64.2 (224)	69.3 (388)	71.4 (469)	64.2 (246)**
Metabolic parameters						
BMI [kg/m²][d], mean ± SD	26.5 ± 4.5	27.3 ± 5.1*	27.8 ± 4.0	28.5 ± 4.5*	27.9 ± 4.4	28.1 ± 4.5
T2DM[e], % (n)	1.6 (8)	3.0 (20)	4.0 (14)	8.9 (50)*	20.9 (137)	20.6 (79)
Hypertension[f], % (n)	29.3 (148)	33.5 (223)	50.4 (176)	57.65 (324)	73.5 (482)	71.7 (273)
HDL-C [mg/dl], mean ± SD	58.9 ± 17.6	56.1 ± 17.3	57.5 ± 16.0	57.5 ± 16.9	59.0 ± 14.8	59.7 ± 15.5
LDL-C [mg/dl], mean ± SD	131.1 ± 39.6	137.7 ± 41.8*	149.1 ± 40.2	154.9 ± 41.3*	144.7 ± 33.5	147.1 ± 35.4
AMD status at baseline						
Early AMD[g], % (n)	8.9 (45)	10.1 (68)	15.7 (55)	17.1 (97)	16.7 (110)	16.2 (62)
Late AMD, % (n)	0.2 (1)	0.0 (0)	0.0 (0)	0.9 (5)	4.4 (29)	8.9 (34)

Abbreviations: BL = baseline; SD = standard deviation; BMI = body-mass-index; T2DM = type 2 diabetes; HDL-C, LDL-C = high and low density lipoprotein cholesterol; AMD=age-related macular degeneration; NA = data not available;
P-value for difference adjusted for age and sex: *) P=0,05-0,01; **) P=0,01-0,001; ***) P<0,001
[a]) regular smokers currently smoking ≥ 1 cigarette day or occasional smokers with < 1 cigarette per day;
[b]) ≥ 1 hour of regular activity per week during leisure time in summer and/or winter;
[c]) healthy diet score above the median score of 15;
[d]) measured weight divided by squared measured body height;
[e]) self-reported diagnosis of T2DM or anti-diabetes medication intake;
[f]) measured systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg or corresponding medication taken, given that the participants were aware of having hypertension;
[g]) for AugUR, based on Three Continent AMD Consortium Severity Scale with "mild/moderate/severe early AMD" collapsed to "early AMD"[11]; for KORA, based on extended AREDS 9stepSeverity Scale (step 1=no AMD, step 2-9 early AMD, step 10-12 late AMD)[1], because AMD grading of participants not in follow-up was available only with this scale; [h]) minimum age of 54 years for the analyzed sample is due to rounding effects of the age at exam;

Supplementary Figure 1. Age distribution of analyzed KORA and AugUR study participants. Depicted are numbers of individuals, mean follow-up time [25th and 75th percentile], age at baseline and follow-up for each of the three studies: the younger adults (baseline age 35-55 years; KORA-FIT), the older adults (54-75 years; KORA-FF4) and the old-aged (70-95 years; AugUR).



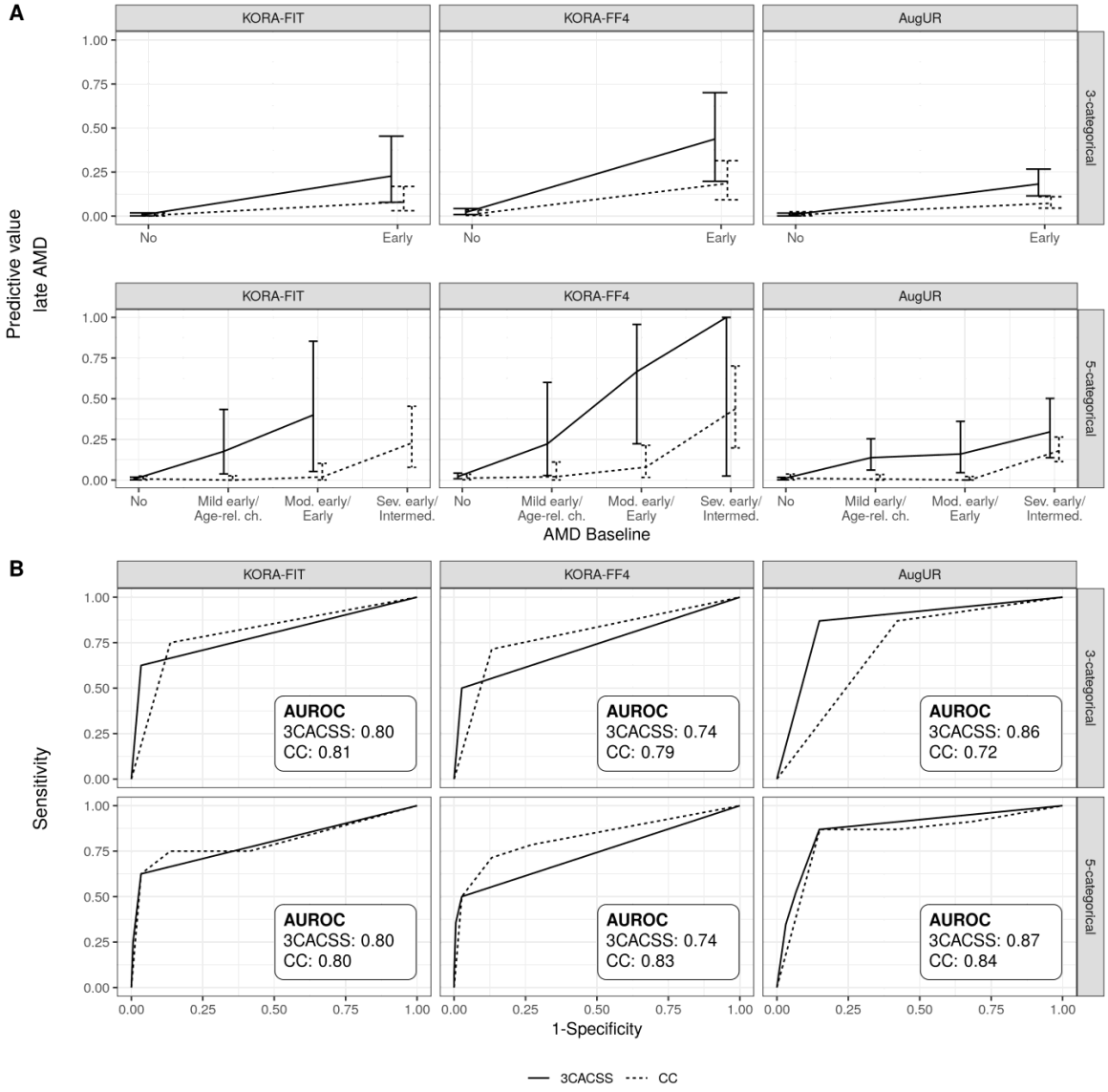
Supplementary Table 3. Cumulative estimates for incident early AMD, incident late AMD, and progression by study and refined age-groups based on the Clinical Classification (CC). Shown are 18-year, 14-year, and 3-year cumulative estimates and 95%-confidence intervals (CI) for incidence and progression for the three studies (KORA-Fit, KORA FF4, AugUR, respectively), overall and by refined age-groups. For AMD classification, CC[14] was applied here (analogous estimates for 3CACSS[13] in **Table 1**).

	A) Cumulative incidence of early AMD				B) Cumulative incidence of late AMD (definition-1)[c]		
Study	**Age [years][a]**	**N events / n[b]**	**Incidence (%)**	**95%-CI**	**N events / n[b]**	**Incidence (%)**	**95%-CI**
KORA-Fit	All	104 / 432	24.1	[20.1, 28.4]	2 / 432	0.5	[0.1, 1.7]
	[34,45]	54 / 244	22.1	[17.1, 27.9]	0 / 244	0.0	[0.0, 1.5]
	[45,50]	28 /121	23.1	[16.0, 31.7]	1 / 121	0.8	[0.0, 4.5]
	[50,55]	22 / 67	32.8	[21.8, 45.4]	1 / 67	1.5	[0.0, 8.0]
KORA-FF4	All	122 / 294	41.5	[35.8, 47.4]	4 / 294	1.4	[0.4, 3.4]
	[53,60]	53 / 133	39.8	[31.5, 48.7]	1 / 133	0.8	[0.0, 4.1]
	[60,65]	43 / 100	43.0	[33.1, 53.3]	1 / 100	1.0	[0.0, 5.4]
	[65,75]	26 / 61	42.6	[30.0, 55.9]	2 / 61	3.3	[0.4, 11.3]
AugUR	All	61 / 353	17.3	[13.5, 21.6]	3 / 353	0.8	[0.2, 2.5]
	[70,75]	26 / 166	15.7	[10.5, 22.1]	1 / 166	0.6	[0.0, 3.3]
	[75,80]	18 / 130	13.8	[8.4, 21.0]	1 / 130	0.8	[0.0, 4.2]
	[80,96]	17 / 57	29.8	[18.4, 43.4]	1 / 57	1.8	[0.0, 9.4]

	C) Cumulative incidence of late AMD (definition-2)[d]				D) Cumulative progression from early to late AMD		
Study	**Age [years][a]**	**N events / n[b]**	**Incidence (%)**	**95%-CI**	**N events / n[b]**	**Progression (%)**	**95%-CI**
KORA-Fit	All	8 / 506	1.6	[0.7, 3.1]	6 / 76	8.1	[3.0, 16.8]
	[34,45]	1 / 275	0.4	[0.0, 2.0]	1 / 31	3.2	[0.1, 16.7]
	[45,50]	2 / 144	1.4	[0.2, 4.9]	1 / 23	4.3	[0.1, 21.9]
	[50,55]	5 / 87	5.7	[1.9, 12.9]	4 / 20	20.0	[5.7, 43.7]
KORA-FF4	All	14 / 348	4.0	[2.2, 6.7]	10 / 54	18.5	[9.3, 31.4]
	[53,60]	4 / 151	2.6	[0.7, 6.6]	3 / 18	16.7	[3.6, 41.4]
	[60,65]	3 / 120	2.5	[0.5, 7.1]	2 / 20	10.0	[1.2, 31.7]
	[65,75]	7 / 77	9.1	[3.7, 17.8]	5 / 16	31.2	[11.0, 58.7]
AugUR	All	23 / 628	3.7	[2.3, 5.4]	20 / 275	7.3	[4.5, 11.0]
	[70,75]	6 / 267	2.2	[0.8, 4.8]	5 / 101	5.0	[1.6, 11.2]
	[75,80]	11 / 244	4.5	[2.3, 7.9]	10 / 114	8.8	[4.3, 15.5]
	[80,96]	6 / 177	5.1	[1.9, 10.8]	5 / 60	8.3	[2.8, 18.4]

[a]) age at baseline
[b]) number of events / number of persons at risk
[c]) considering individuals with no AMD at baseline (definition-1);
[d]) considering individuals with no or early AMD at baseline (definition-2);

Supplementary Figure 2. Comparing two classification systems for prediction of late AMD development. An individual´s no or early AMD classification at baseline can be considered a screening test to predict development of late AMD. We evaluated 3CACSS[13] and CC[17] as 3-category and 5-category version. For each of the three studies (18-, 14-, or 3-year follow-up, respectively), we derived (**A**) positive predictive value (PPV) for incident late AMD by baseline categories for no/early AMD (i.e. cumulative number of incident late AMD cases per no/early AMD category at baseline divided by total number of persons in the category). We also provide (**B**) sensitivity and 1-specificity per baseline category to discriminate correctly who developed late AMD during follow-up (sensitivity) or wrongly those who did not (1-specificity) and area-under-the-curve of the receiver-operating characteristics (AUROC) as measure for discriminatory ability.



Supplementary Table 4. Risk factor association with incident early AMD, incident late AMD, and progression. We estimated absolute risk (i.e. probability, Prob, of an individual to be in the reference group) and relative risk (Odds Ratios, OR) including 95%-confidence intervals (CI) and P-values via logistic regression models. Shown are estimates of (**A**) incident early, (**B**) incident late AMD (definition-2), and (**C**) progression. Covariates were age, sex, follow-up (FU) time, smoking, HDL-C (model I), adding the 50-variant genetic risk score (GRS) (model II) and, for (B), also early AMD at baseline (BL; 3CACSS, without and with GRS, model III and IV, respectively). Model II results for incident early AMD and progression and Model IV results for incident late AMD are depicted in **Figure 1**.

(A) Incident early AMD (among individuals with no AMD at baseline)

	Model I*			**Model II****		
	Prob/OR	**95%-CI**	**P-value**	**Prob/OR**	**95%-CI**	**P-value**
KORA-Fit						
Reference, Prob(event)	0.1	[0.0, 0.1]	-	0.1	[0.0, 0.1]	-
Age [10 years, centered]	1.9	[1.0, 3.8]	0.06	1.9	[1.0, 3.8]	0.07
Sex [female vs. male]	0.6	[0.3, 1.4]	0.25	0.6	[0.3, 1.5]	0.31
FU time [per year, centered]	1.2	[0.6, 2.2]	0.57	1.2	[0.6, 2.2]	0.62
Smoking [current vs. never]	1.2	[0.4, 3.2]	0.78	1.2	[0.4, 3.5]	0.67
Smoking [former vs. never]	1.5	[0.7, 3.7]	0.31	1.6	[0.7, 3.9]	0.27
HDL-C [per 10 mg/dl, centered]	1.2	[0.9, 1.4]	0.23	1.2	[0.9, 1.4]	0.22
GRS [per 5%, b-weighted, centered]	-	-	-	1.5	[0.9, 2.4]	0.11
KORA-FF4						
Reference, Prob(event)	0.1	[0.1, 0.2]	-	0.1	[0.1, 0.2]	-
Age [10 years, centered]	1.8	[0.9, 3.6]	0.09	2.0	[1.0, 4.2]	**0.048**
Sex [female vs. male]	1.4	[0.6, 2.9]	0.44	1.4	[0.7, 3.1]	0.35
FU time [per year, centered]	1.3	[0.7, 2.4]	0.47	1.3	[0.7, 2.4]	0.48
Smoking [current vs. never]	0.3	[0.0, 1.2]	0.15	0.3	[0.0, 1.2]	0.13
Smoking [former vs. never]	1.2	[0.6, 2.5]	0.57	1.1	[0.6, 2.3]	0.72
HDL-C [per 10 mg/dl, centered]	1.1	[0.9, 1.3]	0.47	1.1	[0.8, 1.3]	0.64
GRS [per 5%, b-weighted, centered]	-	-	-	1.8	[1.2, 2.7]	**0.01**
AugUR						
Reference, Prob(event)	0.1	[0.1, 0.2]	-	0.1	[0.1, 0.2]	-
Age [10 years, centered]	1.5	[0.7, 2.8]	0.27	1.7	[0.9, 3.4]	0.12
Sex [female vs. male]	0.6	[0.3, 1.2]	0.13	0.6	[0.3, 1.2]	0.16
FU time [per year, centered]	0.9	[0.3, 2.3]	0.84	0.8	[0.3, 2.0]	0.70
Smoking [current vs. never]	2.2	[0.7, 6.0]	0.16	1.9	[0.6, 5.5]	0.24
Smoking [former vs. never]	1.1	[0.6, 2.2]	0.68	1.2	[0.6, 2.2]	0.66
HDL-C [per 10 mg/dl, centered]	1.0	[0.8, 1.3]	0.83	1.0	[0.8, 1.2]	0.91
GRS [per 5%, b-weighted, centered]	-	-	-	1.9	[1.2, 2.9]	**0.01**

(B) Incident late AMD (among individuals with no or early AMD at baseline, definition-2)

	Model I*			Model II**		
	Prob/OR	**95%-CI**	**P-value**	**Prob/OR**	**95%-CI**	**P-value**
KORA-Fit						
Reference, Prob(event)	0.0	[0.0, 0.0]	-	0.0	[0.0, 0.0]	-
Age [10 years, centered]	26.4	[3.2, 570.2]	**0.01**	28.8	[3.0, 789.7]	**0.02**
Sex [female vs. male]	0.6	[0.1, 3.2]	0.52	0.9	[0.1, 6.4]	0.95
FU time [per year, centered]	2.3	[0.6, 9.1]	0.23	1.3	[0.3, 5.5]	0.76
Smoking [current vs. never]	4.3	[0.4, 98.5]	0.26	5.2	[0.4, 124.9]	0.21
Smoking [former vs. never]	2.9	[0.4, 60.5]	0.36	3.1	[0.4, 64.6]	0.35
HDL-C [per 10 mg/dl, centered]	0.7	[0.4, 1.2]	0.24	0.7	[0.4, 1.3]	0.28
GRS [per 5%, b-weighted, centered]	-	-	-	4.5	[1.5, 17.1]	**0.01**
KORA-FF4						
Reference, Prob(event)	0.0	[0.0, 0.0]	-	0.0	[0.0, 0.0]	-
Age [10 years, centered]	7.0	[2.0, 28.0]	**0.004**	11.1	[2.6, 60.4]	**0.002**
Sex [female vs. male]	2.1	[0.5, 9.1]	0.31	2.1	[0.5, 9.6]	0.34
FU time [per year, centered]	1.5	[0.5, 5.0]	0.52	1.6	[0.5, 6.2]	0.44
Smoking [current vs. never]	9.8	[1.8, 56.4]	**0.01**	11.3	[1.8, 83.2]	**0.01**
Smoking [former vs. never]	1.5	[0.3, 6.7]	0.55	1.4	[0.3, 6.3]	0.69
HDL-C [per 10 mg/dl, centered]	1.2	[0.8, 1.6]	0.43	1.1	[0.8, 1.6]	0.47
GRS [per 5%, b-weighted, centered]	-	-	-	3.9	[1.8, 8.8]	**0.001**
AugUR						
Reference, Prob(event)	0.0	[0.0, 0.1]	-	0.0	[0.0, 0.1]	-
Age [10 years, centered]	2.0	[0.8, 4.8]	0.13	3.0	[1.1, 8.0]	**0.03**
Sex [female vs. male]	0.3	[0.1, 0.9]	**0.04**	0.3	[0.1, 1.0]	0.07
FU time [per year, centered]	0.5	[0.1, 2.2]	0.45	0.5	[0.1, 2.3]	0.50
Smoking [current vs. never]	3.2	[0.7, 12.0]	0.10	3.1	[0.6, 12.0]	0.13
Smoking [former vs. never]	1.0	[0.4, 2.8]	0.93	0.9	[0.3, 2.6]	0.91
HDL-C [per 10 mg/dl, centered]	1.2	[0.9, 1.6]	0.21	1.1	[0.8, 1.5]	0.59
GRS [per 5%, b-weighted, centered]	-	-	-	4.1	[2.1, 8.4]	**$5.9*10^{-5}$**

(B) Incident late AMD *continued* (among individuals with no or early AMD at baseline, definition-2)

	Model III*			Model IV**		
	Prob/OR	**95%-CI**	**P-value**	**Prob/OR**	**95%-CI**	**P-value**
KORA-Fit						
Reference, Prob(event)	0.0	[0.0, 0.0]	-	0.0	[0.0, 0.0]	-
Age [10 years, centered]	24.0	[2.1, 703.6]	**0.03**	21.2	[1.7, 698.0]	**0.04**
Sex [female vs. male]	0.6	[0.1, 4.6]	0.65	1.1	[0.1, 10.0]	0.96
FU time [per year, centered]	1.8	[0.5, 7.5]	0.39	1.1	[0.2, 4.9]	0.93
Smoking [current vs. never]	2.3	[0.2, 55.2]	0.55	3.0	[0.2, 80.3]	0.45
Smoking [former vs. never]	1.3	[0.1, 30.2]	0.82	1.8	[0.2, 41.8]	0.65
HDL-C [per 10 mg/dl, centered]	0.8	[0.5, 1.5]	0.58	0.7	[0.4, 1.4]	0.36
Early AMD BL	21.4	[3.4, 161.1]	**0.001**	21.1	[3.2, 164.5]	**0.002**
GRS [per 5%, b-weighted, centered]	-	-	-	4.3	[1.4, 18.4]	**0.02**
KORA-FF4						
Reference, Prob(event)	0.0	[0.0, 0.0]	-	0.0	[0.0, 0.0]	-
Age [10 years, centered]	5.2	[1.2, 27.4]	**0.04**	6.3	[1.2, 43.8]	**0.04**
Sex [female vs. male]	1.7	[0.3, 8.6]	0.53	1.5	[0.3, 8.6]	0.63
FU time [per year, centered]	1.3	[0.3, 5.1]	0.71	1.3	[0.3, 5.8]	0.69
Smoking [current vs. never]	28.3	[3.8, 295.9]	**0.002**	26.5	[3.3, 321.5]	**0.004**
Smoking [former vs. never]	1.6	[0.3, 9.7]	0.61	1.4	[0.2, 8.9]	0.73
HDL-C [per 10 mg/dl, centered]	1.4	[0.9, 2.1]	0.10	1.4	[0.9, 2.2]	0.09
Early AMD BL	57.7	[11.2, 372.3]	$\mathbf{3.3*10^{-6}}$	40.7	[7.2, 282.9]	$\mathbf{5.0*10^{-5}}$
GRS [per 5%, b-weighted, centered]	-	-	-	3.0	[1.3, 7.6]	**0.01**
AugUR						
Reference, Prob(event)	0.0	[0.0, 0.0]	-	0.0	[0.0, 0.0]	-
Age [10 years, centered]	1.3	[0.5, 3.6]	0.58	1.7	[0.5, 4.8]	0.35
Sex [female vs. male]	0.4	[0.1, 1.3]	0.14	0.4	[0.1, 1.4]	0.19
FU time [per year, centered]	0.7	[0.1, 2.9]	0.62	0.7	[0.1, 3.1]	0.67
Smoking [current vs. never]	4.6	[0.7, 26.3]	0.09	4.4	[0.7, 24.7]	0.09
Smoking [former vs. never]	1.0	[0.3, 2.8]	0.94	0.9	[0.3, 2.8]	0.91
HDL-C [per 10 mg/dl, centered]	1.2	[0.8, 1.6]	0.43	1.1	[0.7, 1.5]	0.69
Early AMD BL	54.6	[15.0, 354.9]	$\mathbf{1.9*10^{-7}}$	40.2	[10.5, 266.5]	$\mathbf{2.6*10^{-6}}$
GRS [per 5%, b-weighted, centered]	-	-	-	1.9	[1.0, 4.0]	0.06

(C) Progression from early to late AMD (among individuals with early AMD at baseline)

	Model I*			Model II**		
	Prob/OR	**95%-CI**	**P-value**	**Prob/OR**	**95%-CI**	**P-value**
KORA-Fit						
Reference, Prob(event)						
Age [10 years, centered]						
Sex [female vs. male]						
FU time [per year, centered]			Models did not converge.			
Smoking [current vs. never]						
Smoking [former vs. never]						
HDL-C [per 10 mg/dl, centered]						
GRS [per 5%, b-weighted, centered]						
KORA-FF4						
Reference, Prob(event)						
Age [10 years, centered]						
Sex [female vs. male]						
FU time [per year, centered]			Models did not converge.			
Smoking [current vs. never]						
Smoking [former vs. never]						
HDL-C [per 10 mg/dl, centered]						
GRS [per 5%, b-weighted, centered]						
AugUR						
Reference, Prob(event)	0.2	[0.1, 0.4]	-	0.1	[0.1, 0.3]	-
Age [10 years, centered]	1.0	[0.3, 3.1]	0.96	1.3	[0.4, 4.5]	0.64
Sex [female vs. male]	0.3	[0.1, 1.0]	0.07	0.3	[0.1, 1.2]	0.10
FU time [per year, centered]	0.5	[0.1, 2.6]	0.45	0.5	[0.1, 3.0]	0.51
Smoking [current vs. never]	7.2	[0.9, 69.2]	0.06	7.2	[1.0, 67.2]	0.06
Smoking [former vs. never]	0.9	[0.3, 3.0]	0.91	0.9	[0.3, 3.0]	0.87
HDL-C [per 10 mg/dl, centered]	1.3	[0.9, 1.9]	0.23	1.2	[0.8, 1.8]	0.47
GRS [per 5%, b-weighted, centered]	-	-	-	2.5	[1.2, 5.8]	**0.03**

Supplementary Table 5. Incidence and progression rates as well as derived 1-year and 3-year risk. Shown are estimates (Est), standard error (SE) and 95% confidence intervals (CI) of rates (per 1000 person-years; PY) and derived 1-year and 3-year risk (%) for (**A**) incident early AMD, (**B**) incident late AMD among individuals with no AMD at baseline (definition-1), (**C**) incident late AMD among individuals with no or early AMD at baseline (definition-2), and (**D**) progression from early to late AMD (also depicted in **Figure 2**). For AMD classification, 3CACSS was applied. These main analyses assumed that the event occurred at half of the follow-up time.

(A) Incident early AMD (among individuals with no AMD at baseline)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	33	8315.0	4.0	0.7	[2.8, 5.4]	0.4	[0.3, 0.5]	1.2	[0.8, 1.6]
	[35, 45]	3	1280.0	2.3	1.4	[0.9, 5.6]	0.2	[0.1, 0.6]	0.7	[0.3, 1.7]
	[45, 55]	13	3689.0	3.5	1.0	[2.1, 5.7]	0.4	[0.2, 0.6]	1.1	[0.6, 1.7]
	[55, 65]	17	2839.0	6.0	1.5	[3.8, 9.2]	0.6	[0.4, 0.9]	1.8	[1.1, 2.7]
KORA-FF4	All	46	4176.0	11.0	1.6	[8.3, 14.4]	1.1	[0.8, 1.4]	3.3	[2.5, 4.2]
	[55, 65]	13	1329.5	9.8	2.7	[5.8, 15.8]	1.0	[0.6, 1.6]	2.9	[1.7, 4.6]
	[65, 75]	24	2262.5	10.6	2.2	[7.2, 15.3]	1.1	[0.7, 1.5]	3.1	[2.1, 4.5]
	[75, 85]	9	576.0	15.6	5.2	[8.3, 27.4]	1.6	[0.8, 2.7]	4.6	[2.5, 7.9]
AugUR	All	63	1553.6	40.5	5.1	[31.7, 51.2]	4.0	[3.1, 5.0]	11.5	[9.1, 14.2]
	[70, 75]	19	451.4	42.1	9.7	[27.1, 63.0]	4.1	[2.7, 6.1]	11.9	[7.8, 17.2]
	[75, 80]	22	694.2	31.7	6.8	[21.0, 46.2]	3.1	[2.1, 4.5]	9.1	[6.1, 13.0]
	[80, 100]	22	408.0	53.9	11.5	[35.7, 78.7]	5.2	[3.5, 7.6]	14.9	[10.2, 21.0]

(B) Incident late AMD (among individuals with no AMD at baseline, definition-1)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	3	8583.0	0.3	0.2	[0.1, 0.8]	0.0	[0.0, 0.1]	0.1	[0.0, 0.3]
	[35, 45]	0	1281.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	0	3753.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[55, 65]	3	2984.0	1.0	0.6	[0.4, 2.4]	0.1	[0.0, 0.2]	0.3	[0.1, 0.7]
KORA-FF4	All	7	4441.0	1.6	0.6	[0.8, 2.9]	0.2	[0.1, 0.3]	0.5	[0.2, 0.9]
	[55, 65]	3	1341.5	2.2	1.3	[0.8, 5.4]	0.2	[0.1, 0.5]	0.7	[0.2, 1.6]
	[65, 75]	3	2412.0	1.2	0.7	[0.5, 3.0]	0.1	[0.0, 0.3]	0.4	[0.1, 0.9]
	[75, 85]	1	673.5	1.5	1.5	[0.4, 5.5]	0.1	[0.0, 0.5]	0.4	[0.1, 1.6]
AugUR	All	3	1649.0	1.8	1.1	[0.7, 4.4]	0.2	[0.1, 0.4]	0.5	[0.2, 1.3]
	[70, 75]	0	473.6	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[75, 80]	2	731.9	2.7	1.9	[0.8, 7.6]	0.3	[0.1, 0.8]	0.8	[0.3, 2.3]
	[80, 100]	1	443.5	2.3	2.3	[0.5, 8.3]	0.2	[0.1, 0.8]	0.7	[0.2, 2.5]

(C) Incident late AMD (among individuals with no or early AMD at baseline, definition-2)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	8	8935.0	0.9	0.3	[0.5, 1.6]	0.1	[0.0, 0.2]	0.3	[0.1, 0.5]
	[35, 45]	0	1301.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	1	3893.0	0.3	0.3	[0.1, 0.9]	0.0	[0.0, 0.1]	0.1	[0.0, 0.3]
	[55, 65]	7	3151.0	2.2	0.8	[1.1, 4.1]	0.2	[0.1, 0.4]	0.7	[0.3, 1.2]
KORA-FF4	All	14	4608.5	3.0	0.8	[1.8, 4.8]	0.3	[0.2, 0.5]	0.9	[0.5, 1.4]
	[55, 65]	3	1370.5	2.2	1.3	[0.8, 5.3]	0.2	[0.1, 0.5]	0.7	[0.2, 1.6]
	[65, 75]	6	2514.0	2.4	1.0	[1.1, 4.6]	0.2	[0.1, 0.5]	0.7	[0.3, 1.4]
	[75, 85]	5	710.0	7.0	3.1	[3.1, 14.4]	0.7	[0.3, 1.4]	2.1	[0.9, 4.2]
AugUR	All	23	1963.3	11.7	2.4	[7.8, 17.0]	1.2	[0.8, 1.7]	3.5	[2.3, 5.0]
	[70, 75]	5	551.0	9.1	4.1	[4.0, 18.6]	0.9	[0.4, 1.8]	2.7	[1.2, 5.4]
	[75, 80]	9	874.3	10.3	3.4	[5.5, 18.0]	1.0	[0.5, 1.8]	3.0	[1.6, 5.3]
	[80, 100]	9	538.0	16.7	5.6	[8.9, 29.3]	1.7	[0.9, 2.9]	4.9	[2.6, 8.4]

(D) Progression from early to late AMD (among individuals with early AMD at baseline)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	5	352.0	14.2	6.4	[6.3, 29.1]	1.4	[0.6, 2.9]	4.2	[1.9, 8.4]
	[35, 45]	0	20.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	1	140.0	7.1	7.1	[1.7, 26.3]	0.7	[0.2, 2.6]	2.1	[0.5, 7.6]
	[55, 65]	4	167.0	24.0	12.0	[9.7, 52.5]	2.4	[1.0, 5.1]	6.9	[2.9, 14.6]
KORA-FF4	All	7	167.5	41.8	15.8	[20.6, 78.0]	4.1	[2.0, 7.5]	11.8	[6.0, 20.9]
	[55, 65]	0	29.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[65, 75]	3	102.0	29.4	17.0	[10.7, 70.8]	2.9	[1.1, 6.8]	8.4	[3.2, 19.1]
	[75, 85]	4	36.5	109.6	54.8	[44.5, 240.2]	10.4	[4.4, 21.4]	28.0	[12.5, 51.4]
AugUR	All	20	314.3	63.6	14.2	[41.4, 94.9]	6.2	[4.1, 9.0]	17.4	[11.7, 24.7]
	[70, 75]	5	77.4	64.6	28.9	[28.4, 132.3]	6.3	[2.8, 12.4]	17.6	[8.2, 32.8]
	[75, 80]	7	142.4	49.2	18.6	[24.3, 91.7]	4.8	[2.4, 8.8]	13.7	[7.0, 24.1]
	[80, 100]	8	94.5	84.7	29.9	[43.6, 152.7]	8.1	[4.3, 14.2]	22.4	[12.3, 36.7]

Supplementary Table 6. Sensitivity analyses with alternative onset of events for incidence and progression rates and derived 1-year and 3-year risk. Shown are estimates and 95% confidence intervals (CI) of rates (per 1000 person-years) and derived 1-year and 3-year risk (%) for (**A**) incident early AMD, (**B**) incident late AMD among individuals with no AMD at baseline (definition-1), (**C**) incident late AMD among individuals with no or early AMD at baseline (definition-2), and (**D**) progression from early to late AMD. For AMD classification, 3CACSS was applied. These sensitivity analyses assumed event at 2/3rd of follow-up time.

(A) Incident early AMD (among individuals with no AMD at baseline)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	33	8413.3	3.9	0.7	[2.8, 5.4]	0.4	[0.3, 0.5]	1.2	[0.8, 1.6]
	[35, 45]	0	1281.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	9	3724.0	2.4	0.8	[1.3, 4.2]	0.2	[0.1, 0.4]	0.7	[0.4, 1.3]
	[55, 65]	19	2897.0	6.6	1.5	[4.2, 9.8]	0.7	[0.4, 1.0]	1.9	[1.3, 2.9]
KORA-FF4	All	46	4280.0	10.7	1.6	[8.1, 14.1]	1.1	[0.8, 1.4]	3.2	[2.4, 4.1]
	[55, 65]	2	1344.7	1.5	1.1	[0.5, 4.1]	0.1	[0.0, 0.4]	0.4	[0.1, 1.2]
	[65, 75]	32	2328.3	13.7	2.4	[9.8, 18.9]	1.4	[1.0, 1.9]	4.0	[2.9, 5.5]
	[75, 85]	12	599.0	20.0	5.8	[11.6, 32.9]	2.0	[1.1, 3.2]	5.8	[3.4, 9.4]
AugUR	All	63	1587.1	39.7	5.0	[31.1, 50.1]	3.9	[3.1, 4.9]	11.2	[8.9, 14.0]
	[70, 75]	18	461.6	39.0	9.2	[24.8, 59.0]	3.8	[2.4, 5.7]	11.0	[7.2, 16.2]
	[75, 80]	22	705.5	31.2	6.6	[20.7, 45.5]	3.1	[2.0, 4.4]	8.9	[6.0, 12.8]
	[80, 100]	23	420.0	54.8	11.4	[36.6, 79.3]	5.3	[3.6, 7.6]	15.2	[10.4, 21.2]

(B) Incident late AMD (among individuals with no AMD at baseline, definition-1)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	3	8592.0	0.3	0.2	[0.1, 0.8]	0.0	[0.0, 0.1]	0.1	[0.0, 0.3]
	[35, 45]	0	1281.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	0	3753.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[55, 65]	2	2992.3	0.7	0.5	[0.2, 1.9]	0.1	[0.0, 0.2]	0.2	[0.1, 0.6]
KORA-FF4	All	7	4456.7	1.6	0.6	[0.8, 2.9]	0.2	[0.1, 0.3]	0.5	[0.2, 0.9]
	[55, 65]	1	1345.3	0.7	0.7	[0.2, 2.7]	0.1	[0.0, 0.3]	0.2	[0.1, 0.8]
	[65, 75]	4	2421.0	1.7	0.8	[0.7, 3.6]	0.2	[0.1, 0.4]	0.5	[0.2, 1.1]
	[75, 85]	2	676.3	3.0	2.1	[0.9, 8.2]	0.3	[0.1, 0.8]	0.9	[0.3, 2.4]
AugUR	All	3	1650.6	1.8	1.0	[0.7, 4.4]	0.2	[0.1, 0.4]	0.5	[0.2, 1.3]
	[70, 75]	0	473.6	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[75, 80]	2	733.0	2.7	1.9	[0.8, 7.6]	0.3	[0.1, 0.8]	0.8	[0.3, 2.3]
	[80, 100]	1	444.1	2.3	2.3	[0.5, 8.3]	0.2	[0.1, 0.8]	0.7	[0.2, 2.5]

(C) Incident late AMD (among individuals with no or early AMD at baseline, definition-2)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	8	8959.0	0.9	0.3	[0.5, 1.6]	0.1	[0.0, 0.2]	0.3	[0.1, 0.5]
	[35, 45]	0	1301.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	1	3896.0	0.3	0.3	[0.1, 0.9]	0.0	[0.0, 0.1]	0.1	[0.0, 0.3]
	[55, 65]	5	3171.0	1.6	0.7	[0.7, 3.2]	0.2	[0.1, 0.3]	0.5	[0.2, 1.0]
KORA-FF4	All	14	4640.3	3.0	0.8	[1.8, 4.8]	0.3	[0.2, 0.5]	0.9	[0.5, 1.4]
	[55, 65]	1	1374.3	0.7	0.7	[0.2, 2.7]	0.1	[0.0, 0.3]	0.2	[0.1, 0.8]
	[65, 75]	6	2527.7	2.4	1.0	[1.1, 4.6]	0.2	[0.1, 0.5]	0.7	[0.3, 1.4]
	[75, 85]	7	724.3	9.7	3.7	[4.8, 18.0]	1.0	[0.5, 1.8]	2.9	[1.4, 5.3]
AugUR	All	23	1975.3	11.6	2.4	[7.8, 16.9]	1.2	[0.8, 1.7]	3.4	[2.3, 4.9]
	[70, 75]	2	553.1	3.6	2.6	[1.1, 10.1]	0.4	[0.1, 1.0]	1.1	[0.3, 3.0]
	[75, 80]	11	879.3	12.5	3.8	[7.1, 20.9]	1.2	[0.7, 2.1]	3.7	[2.1, 6.1]
	[80, 100]	10	543.0	18.4	5.8	[10.1, 31.5]	1.8	[1.0, 3.1]	5.4	[3.0, 9.0]

(D) Progression from early to late AMD (among individuals with early AMD at baseline)

Study	Age [years]	N events	PY at risk	Rate (per 1000 PY)			1-year risk (%)		3-year risk (%)	
				Est	SE	95%-CI	Est	95%-CI	Est	95%-CI
KORA-Fit	All	5	367.0	13.6	6.1	[6.0, 27.9]	1.4	[0.6, 2.8]	4.0	[1.8, 8.0]
	[35, 45]	0	20.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[45, 55]	1	143.0	7.0	7.0	[1.7, 25.8]	0.7	[0.2, 2.5]	2.1	[0.5, 7.4]
	[55, 65]	3	178.7	16.8	9.7	[6.1, 40.4]	1.7	[0.6, 4.0]	4.9	[1.8, 11.4]
KORA-FF4	All	7	183.7	38.1	14.4	[18.8, 71.1]	3.7	[1.9, 6.9]	10.8	[5.5, 19.2]
	[55, 65]	0	29.0	0.0	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]	0.0	[0.0, 0.0]
	[65, 75]	2	106.7	18.8	13.3	[5.8, 52.2]	1.9	[0.6, 5.1]	5.5	[1.7, 14.5]
	[75, 85]	5	48.0	104.2	46.6	[45.9, 213.4]	9.9	[4.5, 19.2]	26.8	[12.9, 47.3]
AugUR	All	20	324.7	61.6	13.8	[40.0, 91.4]	6.0	[3.9, 8.7]	16.9	[11.3, 24.0]
	[70, 75]	2	79.5	25.2	17.8	[7.8, 70.1]	2.5	[0.8, 6.8]	7.3	[2.3, 19.0]
	[75, 80]	9	146.3	61.5	20.5	[32.8, 107.7]	6.0	[3.2, 10.2]	16.9	[9.4, 27.6]
	[80, 100]	9	98.9	91.0	30.3	[48.5, 159.4]	8.7	[4.7, 14.7]	23.9	[13.5, 38.0]

References

1 Brandl C, Breinlich V, Stark KJ, *et al.* Features of Age-Related Macular Degeneration in the General Adults and Their Dependency on Age, Sex, and Smoking: Results from the German KORA Study. *PLoS One* 2016;**11**:e0167181. doi:10.1371/journal.pone.0167181

2 Meisinger C, Löwel H, Thorand B, *et al.* Leisure time physical activity and the risk of type 2 diabetes in men and women from the general population: The MONICA/KORA Augsburg Cohort Study. *Diabetologia* Published Online First: 2005. doi:10.1007/s00125-004-1604-3

3 Winkler G, Doring A. Validation of a short qualitative food frequency list used in several German large scale surveys. *Z Ernahrungswiss* 1998;**37**:234–41.http://www.ncbi.nlm.nih.gov/pubmed/9800314

4 Holzapfel C, Grallert H, Huth C, *et al.* Genes and lifestyle factors in obesity: results from 12,462 subjects from MONICA/KORA. *Int J Obes* 2010;**34**:1538–45.http://www.ncbi.nlm.nih.gov/pubmed/20386550

5 Wichmann HE, Gieger C, Illig T, *et al.* KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 2005;**67 Suppl 1**:S26-30.

6 Auton A, Abecasis GR, Altshuler DM, *et al.* A global reference for human genetic variation. Nature. 2015. doi:10.1038/nature15393

7 Fritsche LG, Igl W, Bailey JNC, *et al.* A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet* 2016;**48**:134–43. doi:10.1038/ng.3448

8 Winkler TW, Grassmann F, Brandl C, *et al.* Genome-wide association meta-analysis for early age-related macular degeneration highlights novel loci and insights for advanced disease. *bioRxiv* 2019;:1–18. doi:10.1101/2019.12.20.883801

9 Brandl C, Zimmermann ME, Gunther F, *et al.* On the impact of different approaches to classify age-related macular degeneration: Results from the German AugUR study. *Sci Rep* 2018;**8**:1–10. doi:10.1038/s41598-018-26629-5

10 Stark K, Olden M, Brandl C, *et al.* The German AugUR study: study protocol of a prospective study to investigate chronic diseases in the elderly. *BMC Geriatr* 2015;**15**:130. doi:10.1186/s12877-015-0122-0

11 Winn B, Whitaker D, Elliott DB, *et al.* Factors affecting light-adapted pupil size in normal human subjects. *Invest Ophthalmol Vis Sci* 1994;**35**:1132–7.http://www.ncbi.nlm.nih.gov/pubmed/8125724

12 Olden M, Holle R, Heid IM, *et al.* IDGenerator: unique identifier generator for epidemiologic or clinical studies. *BMC Med Res Methodol* 2016;**16**:120. doi:10.1186/s12874-016-0222-3

13 Klein R, Meuer SM, Myers CE, *et al.* Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. *Ophthalmic Epidemiol* 2014;**21**:14–23. doi:10.3109/09286586.2013.867512

14 Ferris 3rd FL, Wilkinson CP, Bird A, *et al.* Clinical classification of age-related macular degeneration. *Ophthalmology* 2013;**120**:844–51. doi:10.1016/j.ophtha.2012.10.036

15 Fleiss JL, Cohen J. Equivalence of Weighted Kappa and Intraclass Correlation Coefficient as Measures of Reliability. *Educ Psychol Meas* 1973;**33**:613–9.

16 Gangnon RE, Lee KE, Klein BEK, *et al.* Misclassification can explain most apparent regression of age-related macular degeneration: Results from multistate models with misclassification. *Investig Ophthalmol Vis Sci* Published Online First: 2014. doi:10.1167/iovs.13-12375

17 Ferris 3rd FL, Wilkinson CP, Bird A, *et al.* Clinical classification of age-related macular degeneration. *Ophthalmology* 2013;**120**:844–51. doi:10.1016/j.ophtha.2012.10.036