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Age-Related Macular Degeneration and Associated Risk Factors in the Population-Based Study of Health in Pomerania (SHIP-Trend)

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Age-related macular degeneration (AMD) is the leading cause of visual impairment in developed countries, especially in the older population. The Study of Health in Pomerania (SHIP) is a population-based study designed to investigate risk factors and clinical disorders in the general population. In the present study, we analysed the AMD prevalence and risk factors in the north-eastern German population.





Material/Methods: From 2008 to 2012, we collected data among participants ages 29–79 years. The study population consisted of 4420 individuals. Non-mydratiac retinal photographs were taken of 3934 participants. AMD stages were graded according to the Rotterdam Classification System and the International Classification System.

Results: Photographs from 1854 participants were available for grading. The baseline examinations showed small hard drusen (<63 μm, stage 0b and 0c) were present in 10.7% of the participants (stage 0b in 7.5% and stage 0c in 3.2%). Earliest signs of AMD were detected in 28.68% (stage 0b in 7.5% and stage 1b in 21.18%). Late AMD (geographic atrophy and neovascular AMD, stages 4a and 4b) were identified in 0.43% (stage 4a in 0.16% and stage 4b 0.27%). Risk of AMD increased significantly with age and higher body mass index, waist circumference, hip circumference, and weight-waist-ratio. Smoking, sex, systolic and diastolic blood pressure, HbA1c, cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride were not associated with AMD in this study.

Conclusions: The prevalence of AMD increases with age and obesity-associated factors. These results must be verified in the follow-up. Data concerning the incidence of AMD will be available after the 5- and 10-year follow-ups.

MeSH Keywords: **Epidemiologic Studies • Epidemiology • Macular Degeneration • Prevalence**

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Background

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment in developed countries [1–4]. Earliest subclinical stages have been defined by the presence of yellow deposits called drusen below the retinal pigment epithelium (RPE) and/or areas of pigmentary abnormalities. Late AMD can be classified into geographic atrophy and choroidal neovascularization. These late stages lead to visual impairment. There is currently no effective treatment for the atrophic forms of AMD. The signs and progression of early AMD can be limited using antioxidant supplementation [5–7]. Clinically relevant AMD is most prevalent in the elderly population, but early signs of AMD can also be found in individuals below 50 years of age [8].

The region of north-east Germany has a much higher prevalence of AMD-associated risk factors, such as arterial hypertension, lipometabolic disorders, and obesity, than other German regions. Additionally, a demographic change is in progress, with the result that we can expect a higher incidence of age-related diseases like AMD in the coming years. With this in mind, the opportunity to explore a population with a broad risk spectrum provides us with further information about AMD. The SHIP data can be used to evaluate associations between systemic findings and ophthalmological conditions. Furthermore, risk factors and their progression over time can be identified [9]. The aim of this study was to describe the prevalence of AMD and associated risk factors in the north-eastern region of Germany.

Material and Methods

Study characteristics

SHIP is a population-based study carried out in north-east Germany. The study was designed to assess the prevalence and incidence of common risk factors, subclinical disorders, and clinical diseases to investigate the complex associations between risk factors, subclinical disorders, and clinical diseases, and to assess the prevalence of subclinical findings defined by highly innovative non-invasive methods. The baseline examination for the SHIP-Trend study was performed between 2008 and 2012. The SHIP-Trend study included participants ages 29–79 years. Study participants were recruited from the cities of Stralsund, Greifswald, Anklam, and surrounding communities. The study sample was drawn from the local resident registration offices. All the participants were informed of the purpose and assessments of the study, and gave their written informed consent. Local ethics committee approval was obtained to perform this study. From a sample of 8016 subjects, a total of 4420 subjects participated in the baseline examinations of the SHIP-Trend study [9–11], with a response rate of

55.14%. The examination of 486 participants took place in regional study centers without the opportunity for funduscopy. Consequently, the number of participants examined was reduced to 3934. A further 691 fundus images had to be excluded due to poor image quality and 1389 photographs due to lesions of undefined origin and the difficulty in determining pigmentary abnormalities. The final sample size for the analyses was 1854 participants. Of these, 32.9% (609 subjects) were under age 40 years.

Ophthalmological examination

Trained and certified study nurses obtained an ophthalmological history from all the participants and performed non-mydratric fundus photography. The examiners followed standardized operational procedures for all examinations, and all data were documented electronically. The ophthalmological examinations and all the other assessments are described in detail elsewhere [11].

Fundus photography

A TRC-NW 200 non-mydratric fundus camera (Topcon Corporation, Tokyo, Japan) was used to take the fundus photographs. All subjects were examined in a dark room for natural pupil dilation in preparation for posterior-segment photography. The image was centered within a 45° field on the optic disc. The right eye was photographed. The fundus images were recorded digitally using Visualis 2.62 image software (Imedos, Jena, Germany). After recording, only 1 experienced examiner characterized all the images for changes in the macula, retina, and optic disc, and then classified these into stages.

AMD grading

Wherever more than 1 photograph had been taken, we selected the photograph with the best image quality. The worse eye was graded when images from both eyes were available. The criteria for analysis were lesions closest to the fovea centralis and the most severe lesion. The grading of fundus photographs was performed without using any additional information about the age, sex, or other diseases of participants. AMD signs were graded based on the Rotterdam Classification [12] and the International Classification System [13]. The Rotterdam Classification ensures comparability with other European population-based studies. Macular changes were classified into earliest, early, and late maculopathy. Early signs were graded as stages 0b, 0c (Figure 1A), 1a, 1b, 2a, 2b, and 3 (Figure 1B), whereas for the earliest signs, only 0b and 1b were included. Late AMD was divided into stage 4a (Figure 1C) for atrophic changes and stage 4b (Figure 1D) for neovascular changes. Images with insufficient quality were excluded from AMD grading. The grading system is described in Table 1.

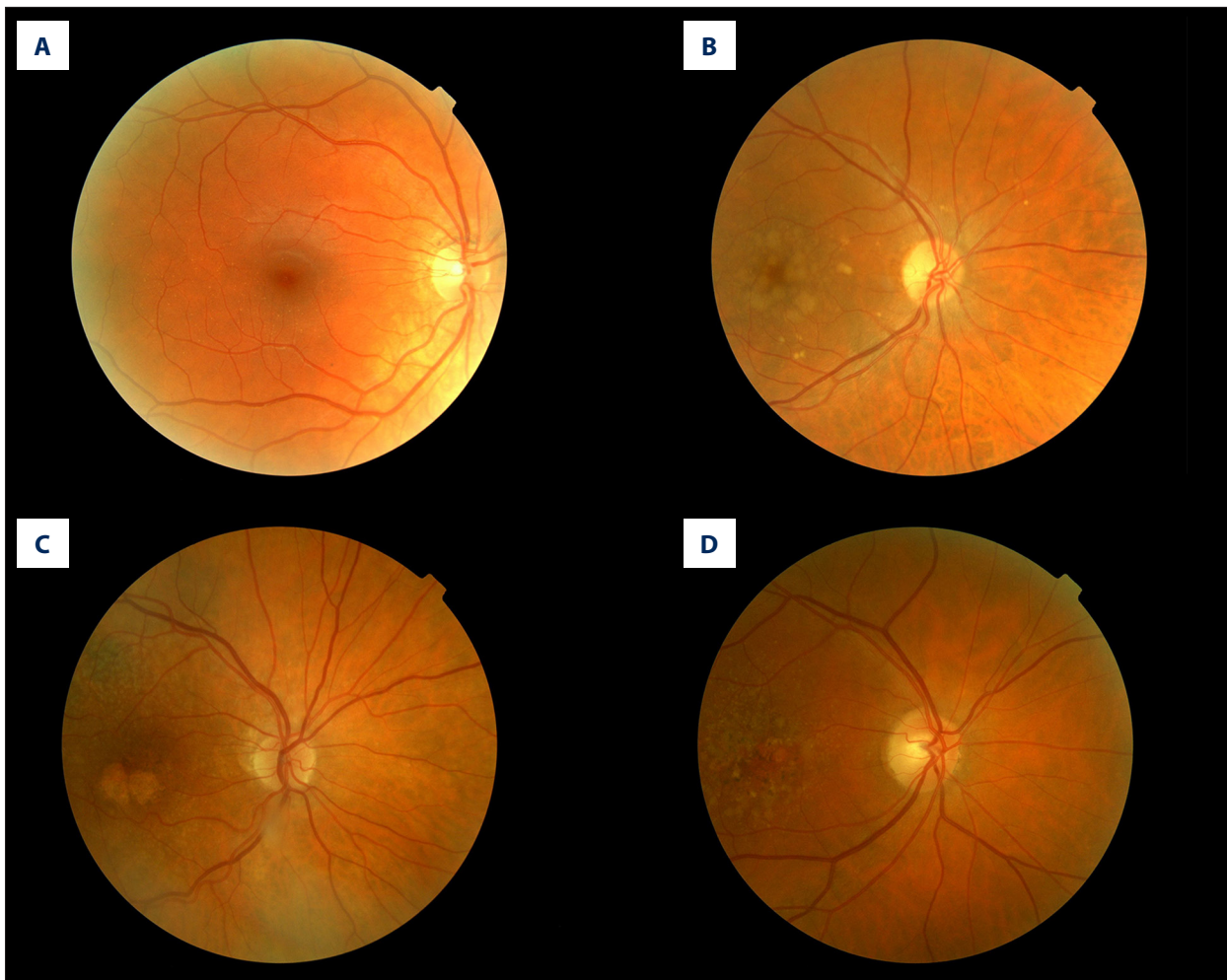


Figure 1. (A) Stage 0c: small, hard drusen. This fundus image shows a stage 0c with more than 10 hard drusen in the macular area of a 30-year-old subject. Referring to her general risk profile, she stated in the interview that she smoked and was largely inactive. The blood test revealed mild hyperlipidemia, while HbA1c was in the reference range. Her BMI was 25.4. There was no evidence of hypertension. (B) Stage 3: large, soft drusen. The progress of the AMD to large, soft drusen is recognizable in this fundus photograph of a 64-year-old subject. Her risk profile included hypertension under treatment at 143.5/79.5 mmHg and several years of nicotine use and hyperlipidemia. (C) Stage 4a: Geographic atrophy. In the end-stage, dry AMD is recognizable. Visible geographic atrophy was found in a 77-year-old subject. The general risk factors were hypertension at 153/62.5 mmHg, existing diabetes (HbA1c: 6%), a BMI of 34.99, and a longer period of nicotine consumption. (D) Stage 4b: choroidal neovascularization. Choroidal neovascularization is the final stage of wet AMD. This is a 66-year-old subject who reported recent use of nicotine and who had a BMI of 29.13.

Statistical analyses

All data were checked for correctness and completeness. The prevalence and mean values were weighted for the local population in West Pomerania. AMD prevalence was determined for the whole study population and for subgroups after stratifying for age and sex. We considered: (a) any type of AMD, (b) early stages of AMD (drusen and/or pigmentary abnormalities), (c) progression of early stages of AMD (drusen with pigmentary abnormalities), and (d) late stages of AMD (geographic atrophy and neovascular AMD). We excluded 2080 fundus photographs from the analysis because of reduced image

quality and difficulty in determination of retinal changes, especially pigmentary abnormalities. These basic images must be compared with follow-up images from the SHIP-Trend study to specify and correct the grading. Associations between potential risk factors and AMD categorized into 3 levels – no AMD, early AMD, and late AMD – were analysed using multinomial logistic regression models after adjustment for age, and were weighted for drop-out. In all analyses, $p < 0.005$ was considered to be statistically significant. All analyses were carried out using Stata 15.1 (Stata Corporation, College Station, TX, USA).

Table 1. Classification system of age-related maculopathy in SHIP-Trend.

| Stage | Legend |
|-------|--|
| 0a | No signs of AMD |
| 0b | Hard drusen (<63 µm, ≤10) |
| 0c | Hard drusen (<63 µm, >10) |
| 1a | Soft distinct drusen (≥63 µm) |
| 1b | Pigmentary abnormalities only |
| 2a | Soft indistinct drusen (≥125 µm) |
| 2b | Soft distinct drusen (≥63 µm) with pigmentary abnormalities |
| 3 | Soft indistinct drusen (≥125 µm) with pigmentary abnormalities |
| 4a | Atrophic AMD |
| 4b | Neovascular AMD |
| 5a | Cannot grade (photo quality) |
| 5b | Cannot grade (obscuring lesion) |

Results

We were able to use the fundus photographs of 1854 participants (880 men and 974 women) for grading. Because of inadequate image quality and the described examination criteria, 2080 fundus photographs could not be assessed. In the whole cohort, small hard drusen (<63 µm, stage 0b and 0c) were present in 10.7% of the participants (7.5% were stage 0b and 3.2% were stage 0c). Earliest signs of AMD were detected in 28.68% (7.5% were stage 0b and 21.18% were stage 1b). Late AMD (geographic atrophy and neovascular AMD, stages 4a and 4b) was identified in 0.43% (0.16% were stage 4a and 0.27% were stage 4b) (Table 2).

Additionally, we analysed typical risk factors such as age, smoking, sex, cardiovascular factors, blood parameters (HbA1c, cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride), as well as fat intake and obesity. We found associations between age and (especially) late forms of AMD ($p=0.01$) and between AMD and increased body mass index ($p=0.005$), waist circumference ($p=0.016$), hip circumference ($p=0.011$), and weight-waist ratio ($p=0.006$). There was no significant association with smoking, HbA1c, cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, or cardiovascular disease (Tables 3, 4).

Table 2. Prevalence of age-related macular degeneration stages in the study population of SHIP-Trend.

| Classification | Participants at baseline | |
|----------------|--------------------------|--------|
| | n | % |
| 0a | 1088 | 59.10 |
| 0b | 138 | 7.50 |
| 0c | 59 | 3.20 |
| 1a | 90 | 4.89 |
| 1b | 390 | 21.18 |
| 2a | 30 | 1.63 |
| 2b | 26 | 1.41 |
| 3 | 12 | 0.65 |
| 4a | 3 | 0.16 |
| 4b | 5 | 0.27 |
| Total | 1841 | 100.00 |

Discussion

In this study, we report the prevalence of AMD in the general population. The data for analysis were collected in the Study of Health in Pomerania (SHIP-Trend), a population-based epidemiological study in north-east Germany.

The prevalence of age-related macular degeneration increased with age in the SHIP-Trend study. The presence of the earliest forms of AMD was 28.68% in the whole cohort and the prevalence of late AMD was 0.43%. Our results from the baseline examination are consistent with other comparable studies [8]. The grading of fundus photographs was performed without using any additional information about age, sex, or other diseases of participants. The determination of retinal changes proved to be inherently difficult, especially for pigmentary abnormalities. We assume there was a selection bias because of these uncertain lesions. Additional non-mydratic fundus photography was feasible but complicated in older individuals, and we had to exclude these individuals from grading because of reduced image quality.

The Rotterdam Eye Study in The Netherlands was the first European study to provide population-based data on AMD/ARM by grading fundus photographs. The study sample included 6251 participants ages 55–98 years. They reported an increase in the prevalence of drusen in persons ages 55–64 years, and an increase from 4.8% to 17.5% in persons 85 years and older. Late stages of AMD were present in 1.7% of the whole cohort. Atrophic AMD increased from 0.1% in persons aged 55–64 years to 3.7% in persons 85 years and older. Neovascular AMD increased from 0.1% to 7.4% in the same age groups [12].

Table 3. Graduation of the main risk factors in quantiles of 25%, 50%, and 75% of the study population.

| Classification | Variable | p25 | p50 | p75 |
|--------------------|---------------------|-------|-------|-------|
| No AMD | Age | 35 | 46 | 58 |
| | Cholesterin | 4.6 | 5.3 | 6 |
| | HDL | 1.17 | 1.4 | 1.69 |
| | LDL | 2.61 | 3.22 | 3.89 |
| | Triglyceride | 0.86 | 1.23 | 1.78 |
| | HbA1c | 4.8 | 5.2 | 5.5 |
| | BMI | 23.88 | 26.79 | 30.13 |
| | Waist circumference | 77.6 | 87.5 | 97.7 |
| | Hip circumference | 94.1 | 99.9 | 106.5 |
| | Waist-weight ratio | 0.46 | 0.51 | 0.57 |
| | Systole | 111.5 | 123.5 | 136 |
| | Diastole | 69.5 | 75.5 | 83 |
| | Pack-years | 0 | 0 | 10.45 |
| Early forms of AMD | Age | 35 | 45 | 55 |
| | Cholesterin | 4.7 | 5.4 | 6.1 |
| | HDL | 1.17 | 1.43 | 1.68 |
| | LDL | 2.77 | 3.33 | 3.88 |
| | triglyceride | 0.88 | 1.28 | 1.93 |
| | HbA1c | 4.9 | 5.2 | 5.55 |
| | BMI | 23.7 | 26.36 | 29.93 |
| | Waist circumference | 76.9 | 86.5 | 96 |
| | Hip circumference | 94 | 99.3 | 105.9 |
| | Waist-weight ratio | 0.45 | 0.5 | 0.56 |
| | Systole | 112.5 | 123 | 133.5 |
| | Diastole | 70.5 | 75.5 | 83 |
| | Pack-years | 0 | 0 | 10 |
| Late forms of AMD | Age | 43 | 53 | 64 |
| | Cholesterol | 4.7 | 5.7 | 6.2 |
| | HDL | 1.14 | 1.37 | 1.61 |
| | LDL | 2.74 | 3.5 | 4.11 |
| | Triglyceride | 1.05 | 1.49 | 2.08 |
| | HbA1c | 4.9 | 5.3 | 5.7 |
| | BMI | 25.28 | 28.56 | 32.01 |
| | Waist circumference | 84 | 92.9 | 103.6 |
| | Hip circumference | 97.45 | 102.5 | 110.1 |
| | Waist-weight ratio | 0.5 | 0.55 | 0.6 |
| | Systole | 117 | 131 | 142 |
| | Diastole | 71 | 77.5 | 85 |
| | Pack-years | 0 | 0 | 14 |

Table 4. Age-adjusted effect for the association with risk factors.

| Classification | Variable | Relative risk ratio | 95% confidence interval | p> z |
|---------------------|---------------------|---------------------|-------------------------|------------|
| Early forms of AMD | Age | 0.99 | 0.97; 1.01 | 0.419 |
| | Cholesterin | 1.14 | 1.03; 1.27 | 0.014 |
| | HDL | 1.06 | 0.79; 1.42 | 0.694 |
| | LDL | 1.14 | 1.01; 1.29 | 0.039 |
| | triglyceride | 1.07 | 0.97; 1.19 | 0.194 |
| | HbA1c | 1.09 | 0.92; 1.29 | 0.310 |
| | BMI | 0.99 | 0.97; 1.01 | 0.388 |
| | Waist circumference | 0.99 | 0.99; 1.00 | 0.174 |
| | Hip circumference | 0.99 | 0.98; 1.01 | 0.403 |
| | Waist-weight ratio | 0.34 | 0.07; 1.64 | 0.179 |
| | Systole | 1.00 | 0.99; 1.00 | 0.463 |
| | Diastole | 1.00 | 0.99; 1.01 | 0.862 |
| | Pack-years | 0.99 | 0.99; 1.01 | 0.639 |
| | Late forms of AMD | Age | 1.04 | 1.01; 1.06 |
| Cholesterol | | 1.08 | 0.94; 1.24 | 0.269 |
| HDL | | 0.79 | 0.52; 1.20 | 0.262 |
| LDL | | 1.11 | 0.95; 1.30 | 0.201 |
| Triglyceride | | 1.09 | 0.97; 1.23 | 0.130 |
| HbA1c | | 0.87 | 0.70; 1.09 | 0.240 |
| BMI | | 1.05 | 1.01; 1.08 | 0.005 |
| Waist circumference | | 1.01 | 1.00; 1.03 | 0.016 |
| Hip circumference | | 1.02 | 1.00; 1.03 | 0.011 |
| Waist-weight ratio | | 18.60 | 2.33; 148.37 | 0.006 |
| Systole | | 1.01 | 1.00; 1.02 | 0.025 |
| Diastole | | 1.01 | 0.99; 1.03 | 0.196 |
| Pack-years | | 0.99 | 0.99; 1.01 | 0.476 |

The Beaver Dam Eye Study included 4926 participants ages 43–86 years in the examination. They detected soft drusen in 2.1% of the individuals ages 43–54 years and in 5.8% of the individuals ages 55–64 years, and 10.7% of individuals ages 65–74 years were affected [2].

The Blue Mountain Eye Study detected early signs of AMD in 1.3% and no signs of late AMD in the age group 49–54 years. In the age group 55–64 years old, early AMD was found in 2.6% and late AMD in 0.2%, whereas early AMD was found in 8.5% and late AMD was found in 0.7% in those ages 65–74 years [14].

In the SHIP-Trend study, we found a strong association between higher body mass index and AMD. Additionally, we were able to identify waist circumference, hip circumference,

and weight-waist-ratio as risk factors for late AMD. These findings are consistent with findings from other similar studies [1,15,16]. Seddon et al. found an increased risk of progression to advanced stages of AMD with a higher body mass index. For body mass indices between 25 and 29, the relative risk was 2.32, and the relative risk increased to 2.35 in those with a body mass index of 30. Furthermore, an association between higher waist circumference and higher waist-hip ratio was reported [15]. Howard et al. also detected an association between body mass index, waist circumference, waist-hip-ratio and waist-height ratio, and for late stages of AMD, especially in female non-smokers [16]. Hence, obesity was considered to be a high-risk factor for progression to late stages of AMD.

The increased number of adipocytes due to obesity promotes oxidative stress in human cells through the production of inflammatory mediators, which play an important role in the pathogenesis of age-related macular degeneration. Therefore, obesity and an unhealthy lifestyle are considered to be major factors affecting the progression of AMD. Arslan et al. showed that dietary intake of antioxidants such as carotenoids, vitamins C and E, zinc, and omega 3 fatty acids, as well as optimizing waist circumference, reduces risk of progression of AMD [7]. Sheshasai et al. studied leptin concentration in the serum of AMD patients, finding an inverse association between decreased serum leptin levels and increased risk of AMD, especially in women and in former smokers. Sheshasai et al. suggested the existence of a newly discovered pathway in AMD pathogenesis that should be considered in future investigations [17].

Smoking was consistently associated with AMD in other studies [3,4,18–21], but the SHIP-Trend study found no association between this risk factor and AMD. The Rotterdam Study found an increased risk of neovascular AMD in individuals smoking more than 10 pack-years [18]. The Blue Mountain Eye Study and the Beaver Dam Eye Study detected an increased risk for pigmentary abnormalities and advanced AMD in smokers [3,19,20]. Myers et al. found a 24.4% incidence of early forms of AMD over a 20-year period. The later forms had an incidence of 4.5%. The risk of current smokers was increased from minimal stages to moderate stages of early AMD. With a high number of pack-years smoked, the risk of progression to a more severe stage of AMD was increased [21].

In the SHIP-Trend study, we found no association between diabetes and AMD. Klein et al. observed no significant association between diabetes and early AMD or geographic atrophy, but they did find a relationship between exudative AMD and diabetes in older men [22,23]. Borrone et al. also found more exudative AMD in subjects with diabetes, but also noted a low prevalence of AMD in diabetics [24], and Srinivasan et al. even found that diabetes protects against AMD [25]. Additionally, our search for a relationship between AMD and higher blood pressure detected no association. A comparison of the Beaver Dam Eye Study, the Blue Mountain Eye Study, and the Rotterdam Study also found no significant association between hypertension and AMD [1,26]. On the other hand, Klein et al. found an association between use of vasodilators and the incidence of AMD, reporting a 72% increase in the incidence of early forms of AMD of in individuals using vasodilators and a 71% increase in the incidence of exudative AMD in people taking beta blockers. These drugs are used in angina pectoris and

arterial hypertension and thus predominantly affect elderly patients who also have an increased risk of AMD [27].

The strength of this study is the population-based design and the large sample size. This is the first report to provide estimates of the prevalence of age-related macular degeneration in north-eastern Germany. Subsequent reports will use these data to generate information on the incidence of age-related macular degeneration at 5- and 10-year follow-ups.

A limitation of this study is the predominantly white study population, and our results cannot be generalized and extrapolated to other ethnic populations. In general, the classification systems vary among studies. Other study groups mainly used the International Classification System [13] or the Wisconsin Age-related Maculopathy grading system [2]. We classified using the Rotterdam Grading System to enable comparison with other European studies. The differences between the grading systems are subtle. For example, the categories such as pigmentary abnormalities are not subdivided, which causes variations between studies, especially in the early stages of AMD.

A further limitation of the present study is the large number of images of insufficient quality. Fundus photographs of 1316 participants were excluded from analysis because of reduced image quality and difficulty in determining pigmentary abnormalities. We used non-mydratic fundus images without any additional information about the participants or other diagnostic methods, such as OCT. We assumed that undilated pupils reduce image quality and therefore make accurate grading impossible.

Conclusions

In summary, we found small hard drusen in 10.7% of subjects in the baseline examinations, with earliest AMD in 28.68% and late AMD in 0.43%. The associations with risk factors were significant for age and late AMD, higher body mass index, higher waist circumference, higher hip circumference, and higher weight-waist ratio. Further data concerning the incidence of age-related macular degeneration will be available after the upcoming 5- and 10-year follow-ups.

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