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ORIGINAL RESEARCH

Economic and Medical Burden of Non-Exudative Age-Related Macular Degeneration in Germany: A Retrospective Observational Claims Data Study

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Introduction: Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the elderly in higher-income countries. This study aimed to explore the medical and economic burden of non-exudative AMD patients living in Germany.

Methods: German claims data (AOK PLUS) were utilized in this retrospective analysis. Prevalent non-exudative AMD only patients were compared to (i) non-exudative AMD patients with a concomitant exudative AMD diagnosis and (ii) propensity score matched non-AMD controls in terms of patient characteristics and eye-related diagnostic/monitoring patterns during baseline (in 2020) as well as in terms of the healthcare resource use and associated costs during the follow-up (in 2021).

Results: The sample comprised 25,439 patients diagnosed with non-exudative AMD only and 7,153 diagnosed with both types of AMD (mean age: 79/81 years | female: 64.3%/64.5%). The total health insurance costs for non-exudative AMD only patients were estimated to be 6,500 € per person-year (pPY), which was about 500 € pPY higher than in matched non-AMD controls. The total costs further increased by about 3,500 € pPY in the presence of concomitant exudative AMD. Also, the healthcare resources (especially related to ophthalmological care) were utilized more frequently by non-exudative AMD patients compared to non-AMD controls, and even more so by patients with concomitant exudative AMD.

Conclusion: Non-exudative AMD patients were associated with an increased medical and economic burden compared to non-AMD individuals living in Germany.

Keywords: age-related macular degeneration, burden of disease, health insurance claims, healthcare resource utilization and associated costs, Germany

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the elderly in higher-income countries,[1,2] including Germany.[3,4] In 2020, it affected some 200 million worldwide, and due to population aging, the projections predict 288 million for 2040,[2] indicating a substantial global burden. In Germany, more than 7 million people have been estimated to have AMD in 2017.[5]

AMD occurs in two forms: non-exudative (dry) and exudative (wet). The majority of people with AMD have the non-exudative type, which includes early and intermediate stages of AMD as well as the advanced form called geographic atrophy (GA).[6] The latter is characterized by sharply demarcated lesions resulting from loss of photoreceptors as well as degeneration of retinal pigment epithelium and underlying choriocapillaris.[7] The exudative AMD type is also considered an advanced stage of AMD and is characterized by choroidal neovascularization with intraretinal or subretinal leakage, hemorrhage, and retinal pigment epithelium detachments.[6] GA and exudative AMD develop from intermediate stages of non-exudative AMD and are not mutually exclusive, such that both of these late AMD stages can develop in the same eye.[8,9]

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Both advanced AMD stages result in irreversible vision loss when not treated. There have been significant advances in the management of exudative AMD with the introduction of anti-angiogenesis therapies starting in 2004, and since then exudative AMD patients have effective treatment options that can prevent blindness and, in many cases, improve vision.[10,11] Yet, for non-exudative AMD patients, until recently, disease management focused solely on risk factor (e.g., smoking, obesity) reduction and on the use of dietary supplements, such as high-dose antioxidants (vitamins C and E) and minerals (zinc, copper), in the intermediate stage of the disease. In February 2023, the first treatment for the advanced stage of non-exudative AMD (ie, geographic atrophy [GA]) was approved by the US Food and Drug Administration (FDA) as the complement C3 and C3b inhibitor pegcetacoplan which slows down further disease progression.[12]

Although non-exudative AMD accounts for most AMD cases, there are substantial gaps in the published literature, particularly regarding the economic burden of non-exudative AMD, including all stages of the disease. A small number of past studies evaluated the healthcare resource utilization (HCRU) and direct medical costs for non-exudative AMD patients living in Europe or the United States.[13–16] Notably, based on the findings from a survey-based study, the financial costs resulting from non-exudative AMD in Germany were estimated to be nearly 500 million € per year.[16] Analyses of German statutory health insurance claims data provide the opportunity to examine real-world disease management and health economic aspects across different sectors that could ultimately help close gaps in the knowledge of non-exudative AMD and its economic burden in Germany. This retrospective claims data study aimed to describe the HCRU and associated direct medical costs in 2021 for prevalent non-exudative AMD patients living in Germany. The analysis was stratified by the presence or absence of concurrent exudative AMD.

Methods

Data Source

This retrospective observational study used anonymized data from a statutory health insurance (SHI) fund in Germany, the AOK PLUS, covering approximately 3.5 million German patients (which corresponds to approximately 4.1% of the German population) living in two administrative regions in Germany (Saxony and Thuringia). The dataset contained data on patients' demographics (age, sex, level of care, insurance status, date of death). Moreover, data on treatments in outpatient and inpatient settings was available. For the treatments in the outpatient setting (visits to general practitioners and specialists identified via a physician code [*Facharztgruppenschlüssel*, FGS code]) the following data was taken into account: diagnosis codes (based on the International Statistical Classification of Diseases, German Modification [ICD-10-GM]), performed services (identified mainly via *Einheitlicher Bewertungsmaßstab* [German uniform evaluation standard; EBM codes], or for some predefined procedures identified also via the operation and procedure classification system [OPS] codes), and the costs associated with any service/procedure. For the treatments in inpatient settings (hospitalizations) the following data was available: diagnosis codes (ICD-10-GM), performed procedures (identified via OPS codes), length of stay, rehabilitations, and associated costs. Lastly, outpatient prescriptions (dispensed and reimbursed drug prescriptions and associated costs) were also evaluated.

Study Population

ICD-10 codes specifying the AMD subtypes have been introduced in Germany only in 2020 (exudative AMD: H35.30; non-exudative AMD: H35.31). Before 2020 only one common code existed for AMD in general, ICD-10 H35.3. Two AMD study cohorts were defined to describe, firstly, prevalent non-exudative AMD only patients and, secondly, prevalent non-exudative AMD patients with a concomitant exudative AMD diagnosis. The respective cut-off date for both cohorts was 31.12.2020 (index date). Non-exudative AMD patients without a concomitant diagnosis for exudative AMD (ie, "non-exudative AMD only" patients) were required to fulfill the following selection criteria: (1) alive on 31.12.2020, (2) at least one inpatient diagnosis and/or at least two confirmed outpatient diagnoses of AMD (ICD-10 H35.3) documented by an ophthalmologist (FGS code 05) in two different quarters between 01.01.2019 and 31.12.2020, whereby at least one of the diagnoses must be coded as non-exudative AMD (ICD-10 H35.31) between 01.01.2020 and 31.12.2020, (3) no inpatient or outpatient diagnosis of exudative AMD (ICD-10 H35.30) documented between 01.01.2020 and 31.12.2020, and (4) continuously insured at AOK PLUS between 01.01.2020 and 31.12.2020.

Moreover, non-exudative AMD patients with a concomitant exudative AMD diagnosis were selected according to the following criteria: (1) alive on 31.12.2020, (2) at least one inpatient diagnosis and/or at least two confirmed outpatient diagnoses of AMD (ICD-10 H35.3) documented by an ophthalmologist (FGS code 05) in two different quarters between 01.01.2019 and 31.12.2020, (3) at least one inpatient diagnosis and/or at least one confirmed outpatient diagnosis of non-exudative AMD (ICD-10 H35.31) documented by an ophthalmologist (FGS code 05) between 01.01.2020 and 31.12.2020, (4) at least one inpatient diagnosis and/or at least one confirmed outpatient diagnosis of exudative AMD (ICD-10 H35.30) documented by an ophthalmologist (FGS code 05) between 01.01.2020 and 31.12.2020, and (5) continuously insured at AOK PLUS between 01.01.2020 and 31.12.2020. Hence, the second cohort included patients with non-exudative AMD (any stage) in one eye and exudative AMD in the fellow eye as well as patients with non-exudative late-stage AMD (GA) and exudative AMD in the same eye combined with any of the following scenarios in the fellow eye: (i) no AMD or (ii) non-exudative AMD of any stage only or (iii) exudative AMD or (iv) non-exudative late-stage AMD (GA) and exudative AMD. Moreover, patients who transitioned from non-exudative to exudative AMD during the baseline period (ie, these would show both diagnosis codes during baseline) were included too.

Patient Characteristics at Baseline

Baseline characteristics were measured either at the index date (age, sex, insurance status) or based on 12 months before the index date (including the index date). In addition to age, sex, insurance status, and long-term care levels, comorbidities were reported. To assess the burden of comorbidities at baseline, the Charlson Comorbidity Index (CCI) was calculated,[17] whereby the age factor (ie, adding 1 point to the score for each decade ≥50 years of age) was not included in this calculation. Information on the smoking status is not available in German claims data. Hence, nicotine dependence (ICD-10 F17) was used as a proxy. In the absence of weight data, information on obesity was extracted based on ICD-10 E66. Furthermore, proportions of patients with a visual disturbance diagnosis (ICD-10 H53; which includes among others visual field defects, diplopia, and night blindness, ie, more general restrictions of visual acuity) or with documented visual impairment levels (ICD-10 H54 subcodes) were determined. The H54 subcodes define a mild, moderate, severe or a high-grade visual impairment (with high-grade visual impairment including blindness), measured monocularly or binocularly. Moreover, the top-10 most frequently observed comorbidities were reported for the non-exudative only AMD cohort and an age/sex-matched non-AMD control. Based on the top-10 comorbidities list of non-exudative AMD patients, comorbidities were also reported for non-exudative AMD patients with concomitant exudative AMD. Lastly, whether non-exudative AMD was affecting one or both eyes was reported, whenever the disease location was documented in association with ICD-10 H35.31.

Eye-Related Diagnostic and Monitoring Procedures at Baseline

In German claims data, performed procedures were documented via (1) EBM codes, which are used in the outpatient setting only, and (2) via OPS codes, which are used mainly in the inpatient setting (and for selected examples also in the outpatient setting). To describe the diagnostic and monitoring procedures received during baseline (01.01.2020–-31.12.2020) by prevalent non-exudative AMD patients with or without a concomitant exudative AMD diagnosis, the 20 most frequently observed eye-related EBM and OPS codes were evaluated. The number and proportion of non-exudative AMD patients (with or without a concomitant exudative AMD diagnosis) with a record of at least one of the respective codes were reported for each of the top-20 listings. In addition, for a clearer presentation of the results in the main text, superordinate categories for EBM-coded procedures or services (from the top-20 lists) were formed whenever equivalent procedures or services were coded by more than one EBM code. Specifically, superordinate categories were created for the following codes: (1) optical coherence tomography (OCT) for diagnostics on the right eye (EBM code: 06336) and on the left eye (EBM code: 06337) were combined to OCT for diagnostics on any eye; (2) OCT for therapy monitoring on the right eye (EBM code: 06338) and on the left eye (EBM code: 06339) were combined to OCT for therapy monitoring on any eye; (3) intravitreal administration of medication into the right eye (EBM code: 31371) and into the left eye (EBM code: 31372) were combined to intravitreal administration of medication into any eye.

Healthcare Resource Utilization & Associated Costs

The utilization of healthcare resources and associated costs was determined for non-exudative AMD patients without concomitant exudative AMD diagnosis and compared to non-AMD controls in year 2021 (01.01.2021–31.12.2021). In addition, HCRU and costs were calculated for non-exudative AMD patients with a concomitant exudative AMD diagnosis. The observation period ended with whichever of the following events occurred first: loss-to-follow-up (end of insurance with AOK PLUS), end of the study period (31/12/2021), or death. Additional censoring criteria were applied to the non-exudative AMD only cohort. Here, patients were censored as soon as an exudative AMD diagnosis (ICD-10 H35.30) was documented or when an exudative AMD therapy (incl. dispensation of anti-VEGF [vascular endothelial growth factor] agents or intraocular injections of medication or photodynamic therapy; Table S1) was initiated during the follow-up. Out of 25,439 non-exudative AMD only patients, 1,280 were censored during the follow-up in 2021 for at least one of reasons above. For the calculation of the total number of observed person-years, all follow-up days within a study cohort were summed up and divided by 365.25, the average number of days per calendar year (to account for leap years with 366 days).

Statistical Analysis and Matching of Non-Exudative AMD Only Patients to Non-AMD Individuals Based on Propensity Scores

Statistical analyses were conducted using Stata version 17 software (Stata Statistical Software: Release 17. College Station, TX: StataCorp LP). Patient characteristics were descriptively analyzed for the study cohorts as well as the age/sex-matched non-AMD control. Frequency analysis of all categorical variables was performed, and the number and percentage of patients in each category were reported. Summary statistics, including mean and standard deviation (SD), were reported for continuous variables. Statistically significant differences between the non-exudative/exudative AMD and non-AMD control cohorts were determined using *t* tests for continuous variables and chi-square or Fisher exact tests for categorical variables.

HCRU and associated costs were described for non-exudative AMD patients with or without a concomitant exudative AMD diagnosis. For non-exudative AMD only patients, additional subgroup analyses were performed based on reported levels of visual impairment, as coded by ICD-10 H54. Regarding outpatient visits, patients with at least one visit at the general practitioner and the ophthalmologist, respectively, were counted. The frequency of the respective visits was determined per person-year. In terms of inpatient stays, patients with at least one all-cause hospitalization were counted and the frequency of hospitalizations as well as the days spent at the hospital were determined per person-year. Patients with at least one AMD-related hospitalization or at least one rehabilitation stay were counted. Total health insurance costs were determined for the same follow-up period for both study cohorts (in € per person-year). Total costs consisted of costs related to all-cause hospitalizations, inpatient rehabilitations, outpatient visits, outpatient prescriptions, medical aids, and remedies. For the non-exudative AMD only and non-AMD matched cohorts in the outpatient setting, only visits to the ophthalmologist (but not the general practitioner) were analyzed. Moreover, proportions of patients with at least one fracture-related hospitalization and burn-related hospitalization, respectively, were reported for the same follow-up period in addition to the outcomes listed above.

To compare the baseline characteristics of the non-exudative only AMD study cohort to non-AMD individuals, propensity score matching (PSM) based on age (at index) and sex (1 = female, 0 = male) was performed. Propensity scores were estimated using logistic regression models in which the dependent variable was a binary indicator of a group affiliation (AMD or non-AMD). Then, 1:1 nearest-neighbor matching with a caliper of 0.01 within the common support region and without replacement of control individuals was performed. To identify the pool of AOK PLUS insured persons that can potentially serve as a non-AMD control group for the study cohort, the following criteria were applied: (1) alive on 31.12.2020 (index date), (2) continuously insured at AOK PLUS between 01.01.2020 and 31.12.2020, and (3) without any inpatient or outpatient AMD diagnosis documented at any time point starting from 01.01.2010 (beginning of data availability) until 31.12.2020 (index date). This definition yielded 2,808,153 non-AMD patients which were employed to perform the PSM to the prevalent non-exudative AMD only patients. All patients were matched to a non-AMD control. For the balance diagnostics, the standardized mean difference (SMD) was evaluated before and

after the PSM, according to Zhang et al, 2019.[18] The SMD was the difference in the means of each covariate between comparison groups divided by the SD derived from both groups so that it is measured on a uniform scale. An SMD greater than 0.1 was considered a sign of imbalance.

Moreover, non-AMD individuals matched to prevalent non-exudative AMD only patients were also used for the assessment of healthcare-related costs. In addition to the age/sex-based PSM model, another, more extended matching was performed to adjust for commonly observable patient characteristics. Here, known risk factors, comorbidities, and common HCRU and cost drivers were included as covariates in addition to age and sex. Specifically, the covariates were: age at index, sex (1 = female, 0 = male), long-term care level at baseline (six categories: 0 = not reported; categories 1–5 = long-term care levels 1–5), number of non-AMD-related hospitalizations during baseline (five categories: 0 = none, 1–3 = 1–3 hospitalizations, 4 = ≥4 hospitalizations), and comorbidities during baseline as binary variables based on ICD-10 coding (nicotine dependence [F17], obesity [E66], cataract [H25-H28], chronic ischemic heart disease [I25], diabetes mellitus [E10-E14], disorders of refraction and accommodation [H52], dorsalgia [M54], glaucoma [H40], hyperlipidemia [E78.0-0.5], hypertension [I10-I15], osteoarthritis of the knee [M17], osteoporosis [M81]). Nicotine dependence, obesity, and osteoporosis were pre-defined to cover some of the presumed risk factors for AMD.[19–23] In addition, the presence of predefined comorbidities was assessed, including various forms of cataract, glaucoma, chronic ischemic heart disease, diabetes mellitus, hyperlipidemia, and hypertension. Matching was performed with the same pool of non-AMD individuals (2,808,153), which was defined for the age/sex-based matching above. Covariance balance diagnostics were performed as described above.

Results

Patient Baseline Characteristics

A total of 25,439 AOK PLUS insured individuals were identified as non-exudative AMD (ICD-10 H35.31) patients meeting the study's eligibility criteria for the prevalent non-exudative AMD only cohort in 2020 (Figure 1A). Prevalent non-exudative AMD patients with a concomitant exudative AMD diagnosis (H35.30) amounted to an additional 7,153 patients in the same year and constituted the prevalent non-exudative and exudative AMD study cohort (Figure 1B). All patients from the prevalent non-exudative AMD only cohort were propensity score matched to non-AMD controls based on age and sex. The covariates of the matching model were well balanced, as indicated by the comparison of the SMDs before and after the matching procedure (ie, all SMDs were below 0.1; Figure S1).

In line with an age-related disease, the vast majority of patients were pensioners (non-exudative AMD only: 94.1%, 23,949/25,439; non-exudative and exudative AMD: 96.0%, 6,866/7,153; Table 1). Non-exudative AMD patients with a concomitant exudative AMD diagnosis were on average slightly older than non-exudative AMD patients without concomitant diagnosis for exudative AMD (mean age (SD) for non-exudative AMD only: 79.0 (9.0) years; mean age (SD) for non-exudative and exudative AMD: 81.0 (7.7) years; Table 1). The proportion of women was very similar between the two study cohorts (non-exudative AMD only: 64.3%, 16,358/25,439; non-exudative and exudative AMD: 63.9%, 4,573/7,153; Table 1). For 61.4% (15,618/25,439) of the non-exudative AMD only patients, a disease location was reported – 12.6% (3,211/25,439) were diagnosed with a monocular non-exudative AMD and 48.8% (12,407/25,439) had a binocular manifestation of the disease. For the non-exudative and exudative AMD patients, 79.5% (5,685/7,153) showed a documentation of the non-exudative AMD location – 41.6% (2,972/7,153) of the patients were affected monocularly and 37.9% (2,713/7,153) binocularly.

Slightly more patients with non-exudative and exudative AMD were in need of long-term care than patients who were diagnosed with non-exudative AMD only (non-exudative AMD only: 29.9%, 7,595/25,439; non-exudative and exudative AMD: 34.7%, 2,484/7,153; Table 1). Patients with both forms of AMD were also slightly more comorbid during the baseline period, as indicated by the CCI scores (mean score (SD) for non-exudative AMD only: 3.5 (2.8); mean score (SD) for non-exudative and exudative AMD: 3.7 (2.9); Table 1). Both study cohorts showed a similar profile in the top-ranked most frequent diagnoses (Table 1). Interestingly, four eye-related diagnoses, namely disorders of refraction and accommodation, age-related cataract, other cataract, and glaucoma, were represented among the top-10 comorbidities for prevalent non-exudative AMD only patients (Table 1). Whether these ocular comorbidities occurred in the same or the

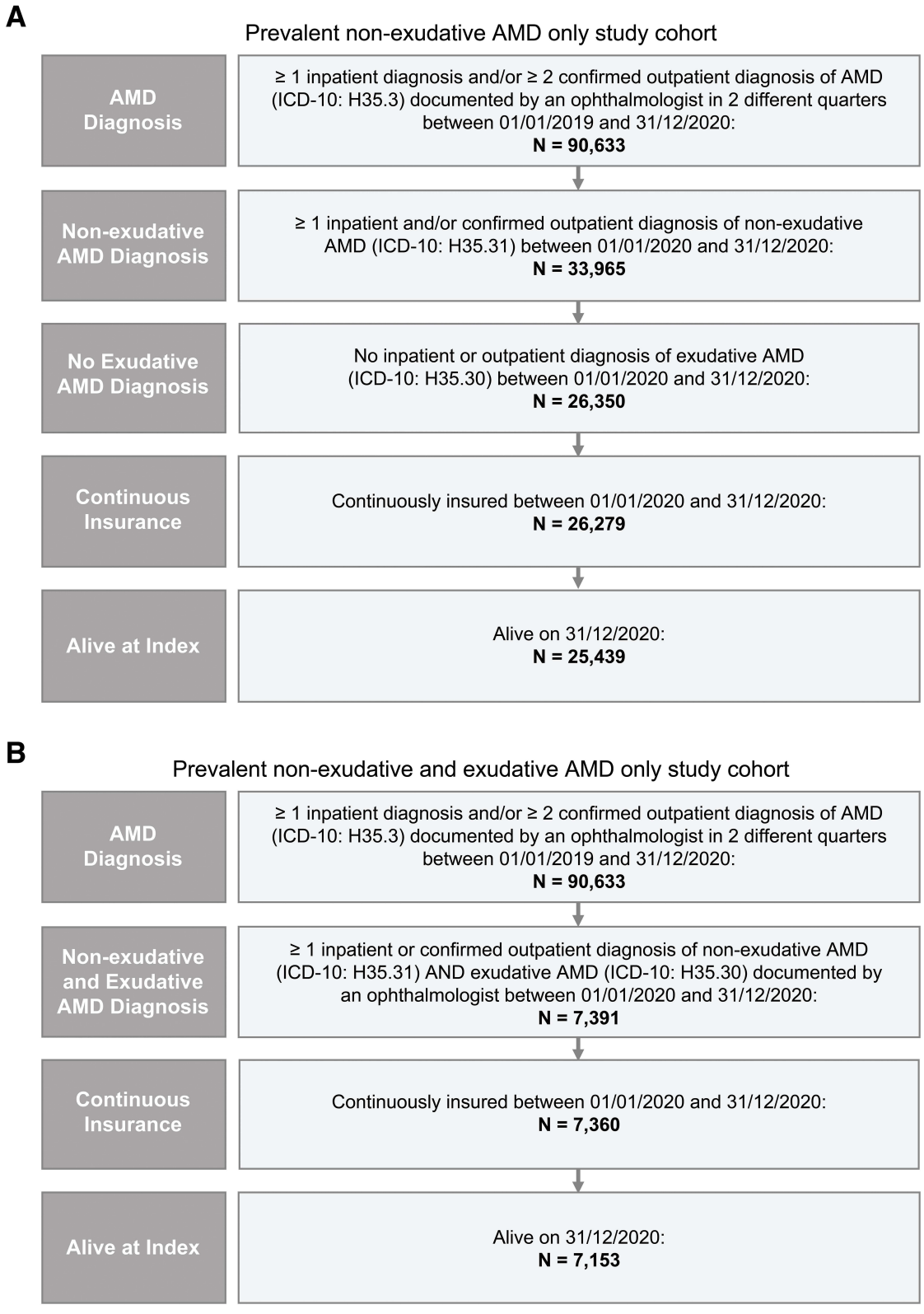

Figure 1 Selection of prevalent non-exudative AMD patients without (**A**) and with (**B**) concomitant exudative AMD. Sample sizes are in bold.

Table 1 Baseline Demographics and Clinical Characteristics of Prevalent Non-Exudative AMD Patients Without and with Concomitant Exudative AMD

	Non-exudative AMD Only N = 25,439	Non-exudative and Exudative AMD N = 7,153
Sex, female – n (%)	16,358 (64.3)	4,573 (63.9)
Age, at index – Mean (SD)	79 (9.0)	81 (7.7)
Insurance status – n (%)		
Pensioner	23,949 (94.1)	6,866 (96.0)
Employed	896 (3.5)	109 (1.5)
Other	594 (2.3)	178 (2.5)
Long-term care level – n (%)		
LTCL 1	1,070 (4.2)	388 (5.4)
LTCL 2	3,665 (14.4)	1,285 (18.0)
LTCL 3	2,088 (8.2)	661 (9.2)
LTCL 4	595 (2.3)	124 (1.7)
LTCL 5	177 (0.7)	26 (0.4)
No LTCL	17,844 (70.1)	4,669 (65.3)
Charlson Comorbidity Index – Mean (SD)	3.5 (2.8)	3.7 (2.9)
Top-10 diagnoses (ICD-10 code) – n (%)		
Primary hypertension (I10)	21,393 (84.1)	6,228 (87.1)
Disorders of lipoprotein metabolism and other lipidemias (E78)	12,923 (50.8)	3,766 (52.6)
Disorders of refraction and accommodation (H52)	11,008 (43.3)	4,440 (62.1)
Type 2 diabetes mellitus (E11)	10,487 (41.2)	2,938 (41.1)
Dorsalgia (M54)	8,884 (34.9)	2,506 (35.0)
Glaucoma (H40)	7,659 (30.1)	1,955 (27.3)
Osteoarthritis of knee (M17)	7,491 (29.4)	2,222 (31.1)
Age-related cataract (H25)	7,398 (29.1)	2,882 (40.3)
Chronic ischemic heart diseases (I25)	7,189 (28.3)	2,300 (32.2)
Other cataract (H26)	7,033 (27.6)	2,670 (37.3)
Non-exudative AMD location – n (%)		
Monocular	3,211 (12.6)	2,972 (41.6)
Binocular	12,407 (48.8)	2,713 (37.9)
Not reported[a]	9,821 (38.6)	1,468 (20.5)
AMD-related risk factors – n (%)		
Nicotine dependence	665 (2.6)	252 (3.5)
Obesity	4,423 (17.4)	1,361 (19.0)
Eye procedures based on EBM or OPS codes[b] – n (%)		
OCT for diagnostics (EBM)	2,297 (9.0)	3,029 (42.3)
OCT for therapy monitoring (EBM)	-	3,193 (44.6)
Fluorescence angiography (EBM)	437 (1.7)	1,392 (19.5)
Intravitreal administration of medication (EBM)	-	3,604 (50.4)
Other surgeries of the retina (OPS)	271 (1.1)	3,728 (52.1)
OCT for diagnostics and monitoring (OPS)	82 (0.3)	37 (0.5)
Angiography of the eye (OPS)	-	22 (0.3)
Destruction of unhealthy tissue of retina and choroidea (OPS)	130 (0.5)	58 (0.8)

Notes: Dashes indicate that the procedure was not ranked among the top-20 most frequent for this cohort, hence no value is provided. [a] Reporting of a location associated with this ICD-10 diagnosis is not required for insurance claims. [b] Patients with ocular comorbidities were not excluded from analysis; hence, results may not exclusively be related to AMD. In Germany, intravitreal injections can also be refunded through the coding of "other surgeries of the retina" (OPS code: 5-156.9)

partner eye was not differentiated. In contrast, not a single ocular diagnosis was detected among the top-10 most common diagnoses for the age/sex-matched non-AMD control (Table S2), probably because these patients were less likely to visit an ophthalmologist and hence less likely to receive an ocular diagnosis of any kind (Table S3). Of note, disorders of

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refraction and accommodation as well as both cataract forms were the most common ocular comorbidities among the study cohorts, affecting more patients diagnosed with both AMD forms than with non-exudative AMD only (disorders of refraction and accommodation: 43.3% (non-exudative only) vs 62.1% (non-exudative and exudative); age-related cataract: 29.1% (non-exudative only) vs 40.3% (non-exudative and exudative); other cataract: 27.6% (non-exudative only) vs 37.3% (non-exudative and exudative); Table 1). Glaucoma, on the other hand, was slightly more frequent in non-exudative AMD only (30.1%) compared to non-exudative and exudative AMD patients (27.3%; Table 1). The other six non-ocular comorbidities from the top-10 list of the non-exudative AMD only study cohort were also represented among the top-10 most frequent comorbidities of the non-AMD controls (Table 1; Table S2). These comorbidities included primary hypertension, disorders of lipoprotein metabolism and other lipidemias, diabetes mellitus type 2, dorsalgia, osteoarthritis of the knee, and chronic ischemic heart disease (Table 1; Table S2).

Documentation of visual disturbance was detected in both study cohorts at a comparable rate (non-exudative AMD only: 14.4%, 3,664/25,439; non-exudative and exudative AMD: 17.6%, 1,259/7,153; Table S4). The non-AMD control cohort showed significantly less reporting of visual disturbances (age/sex-matched to non-exudative AMD: 4.8%, 1,217/25,439; $p < 0.0005$; Table S4), this again may be attributed to different frequencies in ophthalmologist visits (Table S3). Degrees of visual impairment (mild, moderate, severe or a high-grade) were reported for only a small proportion of the study cohorts: 5.4% (1,374/25,439) of the non-exudative AMD only patients and almost double as many (10.4%, 746/7,153) of the non-exudative and exudative AMD patients, with the biggest proportion of reported levels being high-grade visual impairment including blindness (non-exudative AMD only: 2.9%, 737/25,439; non-exudative and exudative AMD: 6.7%, 482/7,153; Table S4). The percentages of reported visual impairment levels were lower for the non-AMD controls (age/sex-matched to non-exudative AMD: 1.6%, 410/25,439), with the same tendency towards high-grade visual impairment (Table S4).

Lastly, risk factors, like smoking and obesity, were evaluated. Only 2.6% (665/25,439) of non-exudative AMD only patients were reported as nicotine dependent (Table 1). For non-exudative AMD patients with a concomitant exudative AMD diagnosis, it was 3.5% (252/7,153; Table 1). 17.4% (4,423/25,439) of non-exudative AMD only patients were obese, comparable to the 19.0% (1,361/7,153) of patients with non-exudative and exudative AMD diagnoses (Table 1). Also disorders of lipoprotein metabolism and other lipidemias were detected at similar frequencies in both cohorts (non-exudative AMD only: 12,923/25,439, 50.8%; non-exudative and concomitant exudative AMD: 3,766/7,153, 52.6%; Table 1).

Eye-Related Diagnostic and Monitoring Procedures at Baseline

Eye-related healthcare was primarily conducted in the outpatient setting, as indicated by the higher percentages of documented EBM codes (Table S5) compared to OPS codes (Table S6). According to the detected EBM codes, OCT for diagnostics was received by both study cohorts, but predominantly by non-exudative AMD patients with a concomitant exudative AMD diagnosis (non-exudative AMD only: 9.0%, 2,297/25,439; non-exudative and exudative AMD: 42.3%, 3,029/7,153; Table 1; Table S5). In line with an exudative AMD therapy, OCT for therapy monitoring purposes was subjected only to patients with a concomitant exudative AMD diagnosis (non-exudative and exudative AMD: 44.6%, 3,193/7,153; Table 1; Table S5). Also, only non-exudative and exudative AMD patients received intravitreal administration of medication (non-exudative and exudative AMD: 50.4%, 3,604/7,153; Table 1; Table S5). Fluorescence angiography was performed on both study cohorts, again predominantly on non-exudative AMD patients with a concomitant exudative AMD diagnosis (non-exudative AMD only: 1.7%, 437/25,439; non-exudative and exudative AMD: 19.5%, 1,392/7,153; Table 1; Table S5). Also, more non-exudative and exudative AMD patients compared to non-exudative AMD only patients experienced another form of optical examination, the so-called binocular examinations of the back of the eye, which is unrelated to the procedures mentioned above (non-exudative AMD only: 65.6%, 16,696/25,439; non-exudative and exudative AMD: 84.5%, 6,044/7,153; Table S5). Perimetry was performed to a similar extent in both study cohorts (non-exudative AMD only: 30.9%, 7,865/25,439; non-exudative and exudative AMD: 25.7%, 1,835/7,153; Table S5). Furthermore, among the three most frequently documented OPS codes, we identified the extracapsular extraction of the lens, the capsulotomy of the lens, and so-called "other surgeries of the retina" (Table S6). The latter covers the procedure called injection of any medication into the back of the eye, which is used for coding anti-VEGF therapies indicated for exudative AMD (Table S1). Hence, the documentation of this code was strongly pronounced in the non-exudative AMD

patients with a concomitant diagnosis for exudative AMD (non-exudative AMD only: 1.1%, 271/25,439; non-exudative and exudative AMD: 52.1%, 3,728/7,153; Table 1; Table S6). Both lens procedures were most likely employed for the treatment of cataract, a common comorbidity of both study cohorts (Table 1). In contrast to the EBM codes, OCT and angiography of the eye were hardly coded by OPS codes (Table 1; Table S6). Lastly, the OPS code for destruction of unhealthy tissue of the retina and choroidea includes photodynamic therapy as a subcode. It was detected only at a very low percentage, in both study cohorts (non-exudative AMD only: 0.5%, 130/25,439; non-exudative and exudative AMD: 0.8%, 58/7,153; Table 1; Table S6).

Healthcare Resource Use

The utilization of healthcare resources was determined for the year 2021 for non-exudative AMD only patients and compared to patients with a concomitant exudative AMD diagnosis as well as to non-AMD controls.

Most AMD patients went at least once to the general practitioner in 2021 (non-exudative AMD only: 96.4%, 24,521/25,439; non-exudative and exudative AMD: 97.1%, 6,948/7,153; Table 2), with a frequency of 4.3 times per PY for both study cohorts. Most patients also went at least once to the ophthalmologist in 2021 (non-exudative AMD only: 82.5%, 20,981/25,439; non-exudative and exudative AMD: 89.4%, 6,394/7,153; Table 2). Yet, non-exudative AMD patients with a concomitant exudative AMD diagnosis visited the ophthalmologist twice as often as non-exudative AMD only patients (non-exudative AMD only: 2.0 times per PY; non-exudative and exudative AMD: 4.1 times per PY; Table 2), meaning that patients with only the non-exudative form of AMD received ophthalmological care about every half a year and patients with non-exudative and exudative AMD about every quarter.

Compared to prevalent patients with non-exudative AMD only, a significantly smaller proportion (38.5%, 9,802/25,439) of age- and sex-matched non-AMD individuals visited the ophthalmologist in 2021, with a frequency of even less than once a year (0.8 times per PY; $p < 0.001$; Table S3). The age/sex-based matching does not account for prominent differences in baseline characteristics between non-exudative AMD only patients and non-AMD individuals,

Table 2 Healthcare Resource Utilization During 2021 for Prevalent Non-Exudative AMD Patients Without and with Concomitant Exudative AMD

	Non-exudative AMD only	**Non-exudative and exudative AMD**
Total number of patients	25,439	7,153
Total number of observed person-years (PY)	23,905.6	6,915.0
Outpatient visits		
GP visits		
Patients with ≥1 GP visit, n (%)	24,521 (96.4)	6,948 (97.1)
Frequency per PY	4.3	4.3
Ophthalmologist visits[a]		
Patients with ≥1 ophthalmologist visit, n (%)	20,981 (82.5)	6,394 (89.4)
Frequency per PY	2.0	4.1
Inpatient stays		
All-cause hospitalizations		
Patients with ≥1 hospitalization, n (%)	7,715 (30.3)	2,448 (34.2)
Frequency per PY	0.56	0.62
Days per PY	4.1	4.5
AMD-related hospitalizations		
Patients with ≥1 hospitalization, n (%)	153 (0.6)	151 (2.1)
Rehabilitation stays		
Patients with ≥1 rehabilitation, n (%)	729 (2.9)	226 (3.2)

Notes: [a] Patients with ocular comorbidities were not excluded from analysis. Hence, results may not exclusively be related to AMD.

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like the ocular comorbidities for example (Table 1; Table S2). For this reason, an additional non-AMD control cohort ("extended non-AMD control") was generated. 60% (15,252/25,438) of the extended non-AMD controls showed at least one visit at the ophthalmologist compared to 82.5% (20,980/25,438) for non-exudative AMD only patients ($p < 0.001$), with a frequency of 1.5 times per PY for non-AMD controls versus 2.0 times per PY for non-exudative AMD only patients ($p < 0.001$) (Table S3). These additional findings indicate that a part of the difference in ophthalmological visits between non-exudative AMD only and age/sex-matched non-AMD patients can be attributed to ocular comorbidities (age/sex-matched control versus extended match control). Yet, for a proportion of patients, the non-exudative AMD diagnosis itself was a sufficient driving force to receive regular ocular examinations (non-exudative AMD only versus extended match control).

Around one third of patients from both study cohorts experienced at least one all-cause hospitalization in 2021 (non-exudative AMD only: 30.3%, 7,715/25,439; non-exudative and exudative AMD: 34.2%, 2,448/7,153; Table 2). These values were very similar to both non-AMD controls that were matched to the non-exudative AMD only study cohort (age/sex-matched: 29.4%, 7,482/25,439; extended match: 29.9%, 7,611/25,438; Table S3). For only 0.6% (153/25,439) of the prevalent non-exudative AMD only patients and for 2.1% (151/7,153) of the prevalent non-exudative and exudative AMD patients, these hospitalizations were related to AMD (Table 2). All-cause hospitalization stays amounted to 4.1 days per PY for non-exudative AMD only patients and 4.5 days per PY for non-exudative and exudative AMD patients and occurred at a frequency of 0.56 (non-exudative AMD only) and 0.62 (non-exudative and exudative AMD) per PY, respectively (Table 2). Likewise, these values were also comparable to the non-AMD controls (age/sex-matched: 4.0 days per PY hospitalized and 0.53 hospitalizations per PY; extended match: 3.9 days per PY hospitalized and 0.54 hospitalizations per PY; Table S3). Moreover, fracture- or burn-related hospitalizations were assessed for the non-exudative AMD only cohort and compared to non-AMD controls. No difference was found for these endpoints either (patients with at least one fracture-related hospitalization: 6.7% for non-exudative AMD only, 6.5% for age/sex-matched non-AMD, 6.3% for extended match non-AMD controls; patients with at least one burn-related hospitalization: 0.02% for non-exudative AMD only, 0.04% for age/sex-matched non-AMD, 0.03% for extended match non-AMD controls; Table S3). The inpatient rehabilitation stays documented in claims data were not common – only around 3% of the study cohort patients showed at least one rehabilitation stay in 2021 (non-exudative AMD only: 2.9%, 729/25,439; non-exudative and exudative AMD: 3.2%, 226/7,153; Table 2).

Health Insurance Costs

The economic burden of disease was assessed based on direct medical costs from the perspective of the German SHI system. The absolute total cost of a non-exudative AMD only patient was determined at 6,497 € per PY and at 10,046 € per PY for a non-exudative and exudative AMD patient, showing a substantial difference of 3,549 € per PY (Figure 2; Table 3). This difference mainly resulted from the higher costs of outpatient prescriptions for patients with a concomitant exudative AMD diagnosis (non-exudative AMD only: 1,805 €/PY; non-exudative and exudative AMD: 4,880 €/PY; Table 3). However, also the costs for outpatient visits at any physician (997 €/PY vs 1,172 €/PY), for visits at the ophthalmologist (149 €/PY vs 307 €/PY), and for AMD-related hospitalizations (29 €/PY vs 94 €/PY) were higher for the non-exudative and exudative AMD cohort (Table 3). Overall, for the non-exudative AMD only patients, the biggest contribution to costs arose from all-cause hospitalizations (42.0%); for the non-exudative and exudative AMD cohort, it was the outpatient prescriptions (48.6%; Figure 2). The percentage distribution of all other costs was similar between the two cohorts (Figure 2).

Compared to non-AMD controls, non-exudative AMD only patients were more costly in terms of total cost, with a calculated difference of 523 € per PY (age/sex-matched control) and of 465 € per PY (extended control), respectively (Figure S2). Of note, the difference in total costs between the age/sex-matched and the extended match non-AMD controls was marginal, even though the age/sex-matched controls were not adjusted for the most common comorbidities (including four ocular diagnoses) of the non-exudative AMD only study cohort. As for the individual cost components of the total costs, all were higher in the non-exudative AMD only patients compared to the non-AMD controls (Table S7), yet their percentual contribution to the total cost was very similar (Figure S2). The main drivers for the higher total costs were the outpatient visits and the outpatient prescriptions (Table S7). The costs for medical aids and remedies were also increased (Table S7).

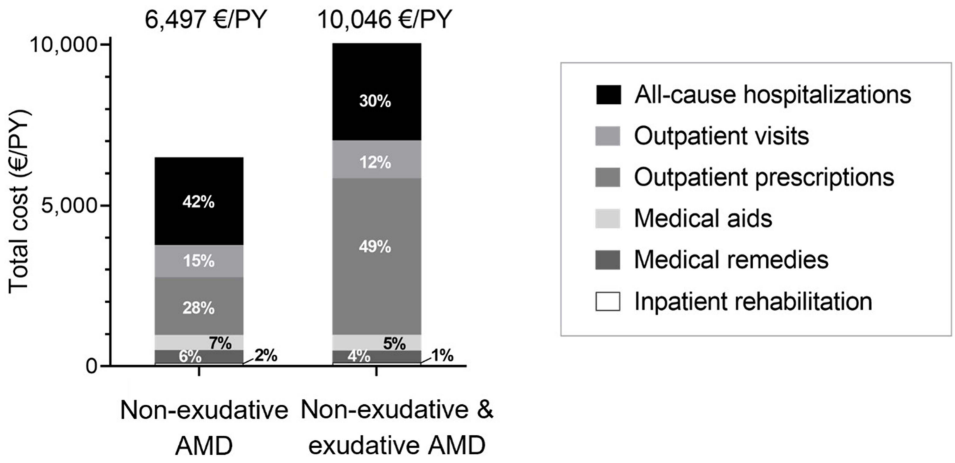

Figure 2 Composition and absolute amounts of the total direct healthcare costs in 2021 for prevalent non-exudative AMD patients without and with concomitant exudative AMD.

Lastly, the healthcare associated costs were assessed for non-exudative AMD only patients in subgroups based on the reported level of visual impairment, as specified by ICD-10 code H54 (Figure S3, Tables S4 and S8). Interestingly, the total costs per PY increased with a progressively impaired vision: while non-exudative AMD only patients with a visual

Table 3 Direct Medical Costs Estimated Based on Claims Data From 2021 for Prevalent Non-Exudative AMD Patients Without and with Concomitant Exudative AMD

	Non-exudative AMD Only	**Non-exudative and Exudative AMD**
Total number of patients	25,439	7,153
Total number of observed person-years (PY)	23,905.6	6,915.0
All-cause hospitalizations		
€ per PY	2,725.74	3,019.52
AMD-related hospitalizations		
€ per PY	29.36	93.52
Outpatient visits		
€ per PY	997.25	1,171.83
General practitioner visits		
€ per PY	287.17	285.22
Ophthalmologist visits[a]		
€ per PY	149.24	307.37
Outpatient prescriptions		
€ per PY	1,805.38	4,880.08
Medical aids		
€ per PY	465.71	488.30
Remedies		
€ per PY	388.96	366.90
Inpatient rehabilitation		
€ per PY	113.74	119.74
Total all-cause costs		
€ per PY	6,496.76	10,046.36

Notes: [a]Patients with ocular comorbidities were not excluded from analysis. Hence, results may not exclusively be related to AMD.

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impairment level 1 costed 6,377 € per PY, patients with a visual impairment level 2 amounted to 7,253 € per PY, and with a visual impairment level 3 to even 8,050 € per PY (Figure S3). These differences were mainly attributed to differences in costs for all-cause hospitalizations, for outpatient prescriptions, and for medical aids (Figure S3). Yet, it must be noted that the vast majority (94.6%, 24,065/25,439) of non-exudative AMD only patients did not show a documented level of visual impairment. The total costs for these patients were calculated to be 6,445 € per PY (Figure S3).

Taken together, total health insurance costs for non-exudative AMD only patients were estimated to be around 3,500 € per PY lower than for non-exudative AMD patients with a concomitant exudative AMD diagnosis. This difference was mainly driven by outpatient prescriptions (potentially exudative AMD therapies). Moreover, compared to non-AMD controls, the costs presumably specific to non-exudative AMD amounted to about 500 € per PY, resulting in approximately 6,500 € per PY of overall costs. A subgroup analysis of the non-exudative AMD only patients per reported visual impairment level indicated an increase in total annual costs with a pronounced progression of visual impairment.

Discussion

To the best of our knowledge, this is the first real-world, retrospective study estimating the economic and medical burden of non-exudative AMD in a broad patient population from Germany using claims data.

As expected for an age-related disease, the vast majority (>94%) of the AMD patients in this study were pensioners with an average age of about 80 years. Interestingly, the most common ocular comorbidities of non-exudative AMD patients with or without concomitant exudative AMD diagnosis (disorders of refraction and accommodation, cataract, and glaucoma) were not detected in the age/sex-matched non-AMD controls. Medical reasoning for co-occurrence of these ocular comorbidities with non-exudative AMD is debatable. The reasons may be more of a practical nature: for one, patients with ocular diseases go to ophthalmologists more often, thereby increasing the chances of receiving the diagnosis of another ocular disease. On the other hand, glaucoma and cataract may be diagnosed first before the visual problems of the patients are recognized as non-exudative AMD. In fact, cataract and glaucoma were observed at similar rates also for patients with another, unrelated eye disease, the dry eye disease, in Germany.[24] Besides the most common ocular comorbidities, non-exudative only AMD patients also showed roughly three times more visual disturbance diagnoses as well as more frequent documentation of visual impairment levels. In terms of the most common non-ocular comorbidities, the AMD study cohorts were comparable to their non-AMD controls. Considering the progressive nature of AMD, reporting of visual impairment levels was low – only 5.4% of non-exudative AMD only patients showed a documented H54 subcode as well as 10.4% of the non-exudative and exudative AMD patients. This infrequent documentation may be attributed to the fact that this code is not used for reimbursement purposes in the German SHI system and hence little incentive is provided reporting it. Based on the available data, the documentation of visual impairment levels seems to happen mostly for patients with high-grade visual impairment (including blindness). Overall, our findings suggest that non-exudative AMD patients (whether with or without a concomitant exudative AMD diagnosis) are burdened with more ocular comorbidities than the age/sex-matched non-AMD population.

While most of the study patients visited an ophthalmologist at least once in 2021 (non-exudative AMD: 82.5%; non-exudative and exudative AMD: 89.4%), only 38.5% of the age/sex-matched non-AMD controls visited an ophthalmologist. The number increased to 60.0% for the extended non-AMD controls, once an adjustment for ocular comorbidities was performed. Also, the number of ophthalmologist visits per PY was higher for the study cohorts compared to the non-AMD controls, especially for non-exudative and exudative AMD patients (non-exudative AMD only: 2.0 times per PY; non-exudative and exudative AMD: 4.1 times per PY; extended non-AMD control: 1.53 times per PY). This trend is consistent with the findings of a retrospective cohort study of claims data from the National Health Insurance Service database of the Korean population, which found that the exudative AMD group had more outpatient visits compared with the non-AMD group.[25] Of note, non-exudative AMD patients without a concomitant exudative AMD diagnosis went to an ophthalmologist about half as often as non-exudative AMD patients with concomitant exudative AMD, which may be explained by the fact that in contrast to exudative AMD, non-exudative AMD treatments were unavailable in 2021. A study of patients with AMD in the UK-based National Health Service also found that patients with non-exudative AMD in one eye and exudative AMD in the other eye had more ophthalmology-related visits than patients with bilateral non-exudative AMD.[15] Additionally, patients with more severe disease may seek care more frequently, as evidenced by a US-based observed, retrospective cohort

study of data from 2015 to 2018 which found that patients with bilateral GA had more outpatient visits per year (2.57 and 2.63 visits in patients with bilateral GA without subfoveal involvement and in patients with bilateral GA with subfoveal involvement, respectively) than patients with early to intermediate AMD (1.98 visits).[26]

Regarding the inpatient setting, only about 30% of the AMD patients experienced at least one all-cause hospitalization per PY and the stays amounted to slightly more than 4 days per PY for non-exudative AMD as well as non-exudative and exudative AMD patients (4.1 and 4.5 days per PY, respectively), comparable to the non-AMD controls (age/sex-based match: 4.0 days per PY; extended match: 3.9 days per PY). A negligible proportion of these hospitalizations was caused by AMD.

For inpatient rehabilitation, only around 3% of the study patients showed at least one stay in 2021. This proportion may potentially be slightly underestimated because, for the German working population, the inpatient rehabilitation is covered by pension insurance and not by social health insurance. Consequently, the respective information is not documented in the claims data. However, since our study cohorts consisted mainly of pensioners (non-exudative AMD only: 94.1%; non-exudative and exudative AMD: 96.0%), the proportion of missing information was likely negligible.

The total annual costs, ie, the sum of costs associated with all-cause hospitalizations, outpatient visits, outpatient prescriptions, medical aids, medical remedies, and inpatient rehabilitations, were higher for non-exudative and exudative AMD patients than for non-exudative AMD only patients (10,046 € per PY vs 6,497 € per PY). This difference mainly resulted from the higher costs of outpatient prescriptions for patients with a concomitant exudative AMD diagnosis (non-exudative AMD only: 1,805 € per PY; non-exudative and exudative AMD: 4,880 € per PY), presumably due to exudative AMD therapy. The estimated total costs for non-exudative AMD only patients and patients with both non-exudative and exudative AMD were consistent with the individual financial costs, ie, the sum of direct medical, indirect medical, and productivity costs, published for German patients with non-exudative AMD (2,587 € per year) and exudative AMD (10,673 € per year).[16] These values are substantially lower than the published individual financial costs incurred in the US by patients with non-exudative AMD (27,303 € per year) and exudative AMD (35,172 € per year) that were estimated in the same study, potentially attributed to the higher productivity costs estimated for both patient groups in the US compared with those in Germany.[16] Notably, these US-based values were estimated based on online surveys completed from January 2021 to March 2022, which occurred before approval of the first FDA-approved treatment for GA, pegcetacoplan.[12,16] Based on data from the OAKS and DERBY trials, a recent study calculated the treatment cost of treating GA with pegcetacoplan monthly and every other month for 2 years to be $70,000 and $34,600, respectively.[27] Therefore, additional research is needed to determine how the availability and cost of pegcetacoplan will economically impact patients.

There are certain limitations in this study. The early stages of AMD (including early and intermediate AMD) are mostly asymptomatic and may therefore not be diagnosed, leading to an underrepresentation of these patients and all their associated characteristics in this claims data analysis. Some limitations of this study are typical of claims data studies in general. For instance, clinical characteristics in the patient profile as well as preferences of the patient and physician, which contribute to treatment pathway(s), are often unobservable within claims data. Additionally, claims data may not reflect all potential medical interventions administered to a patient, which could include participation in clinical trials as well as interventions which do not qualify for medical claims. Information on disease progression was not directly available from the claims data, so diagnoses of visual impairment and/or blindness (ICD-10-GM code: H54) were used as proxy variables. Also, coding of insurance claims in Germany does not discriminate between the different subtypes of non-exudative AMD, limiting the insights from this claims data analysis. Furthermore, patients with ocular comorbidities have not been excluded from any analyses. Hence, any results associated with procedures or diagnoses on the eye may not exclusively be related to AMD. Moreover, in Germany, outpatient diagnoses and costs are not linked to single visits but are reported once per quarter of each calendar year as individual cases per physician. The total number of outpatient visits and related costs may therefore be misestimated. Furthermore, AOK PLUS patients represent approximately 4.1% of the German population and are geographically restricted to two administrative regions in Germany. Therefore, the generalizability of the findings of this study may be limited because patients insured by AOK PLUS may not be fully representative of all German patients. However, the demographic distribution in terms of age and sex differs only slightly between the AOK PLUS population and the general population of Germany, notably that the AOK PLUS population is slightly older.[28] Moreover, due to uniform healthcare

regulations, data entry requirements and access to healthcare resources and treatments are not expected to be significantly different from other regions. Yet, there may be potentially existing barriers regarding accessing specialized outpatient care in rural areas of Saxony and Thuringia, which may be attributable to the lower availability of ophthalmic practices in these regions compared to Germany overall. Visits to ophthalmic practices may also require assistance due to driving incapacity, consequently leading to less regular visits to the doctors. Lastly, the AOK PLUS database contains data from routine practices. Thus, it may contain missing data and coding errors (e.g., related to diagnoses that are irrelevant to reimbursement such as the visual impairment levels). It must also be noted that the proportion of severe visual impairment levels amongst H54 codes may potentially be overrepresented relative to lower visual impairment levels and therefore not representative of the overall non-exudative AMD population. Due to the lack of coding of visual impairment levels, reported percentages also do not allow for any conclusions to be made for geographic atrophy patients, i.e., for patients with late-stage non-exudative AMD. It can only be hypothesized that GA patients may be associated with higher degrees of visual impairment and thus higher treatment costs.

Overall, the coding of the AOK PLUS database is of high quality and has been used for a multitude of claims data studies in Germany. Taken together, due to the large and unselected sample of patients serviced by a multitude of healthcare providers, this health insurance dataset represents a robust and valid source for evidence on disease burden in any disease area codable by the ICD-10-GM system.

Conclusion

In conclusion, non-exudative AMD only patients were associated with an increased medical and economic burden compared to non-AMD individuals living in Germany, especially due to higher costs in outpatient visits and prescriptions. Higher visual impairment in non-exudative AMD only patients goes along with higher costs, underscoring the need for disease-delaying therapies.

Compliance with Ethics Guidelines

Research and analysis were conducted on anonymized data provided by AOK PLUS under formal agreement, and in accordance with the Helsinki Declaration of 1964, and its later amendments. No research was conducted on human subjects. In accordance with German laws (§ 75 of Book 10 of the German Code of Social Law [SGB X]), the use of such data is not subject to ethics committee approval because conclusions about individual patients are excluded, and only aggregated results are presented. No patient authorization was required because deidentified data was analyzed.

Data Sharing Statement

All aggregated results data relevant to this study are included in the article or as supporting information. The primary data source for this study was claims data obtained from AOK PLUS. Due to privacy, contractual obligations, and local data protection laws, both the raw claims data and anonymized derived datasets cannot be publicly shared. However, we are committed to data transparency. Requests for access to the study protocol or aggregated results data from the study should be addressed to MedicalResearch@apellis.com. The study protocol will be available with no end date. All proposals requesting aggregated results access will need to specify how the data will be used, and all proposals will need the approval of the investigator team before aggregated data release.

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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