# Long-Term Blood Pressure and Age-Related Macular Degeneration: The ALIENOR Study

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**Purpose.** To explore the association of AMD with long-term average blood pressure (BP) parameters, including pulse pressure (PP).

**Methods.** The ALIENOR study is a population-based study on age-related eye diseases in 963 residents of Bordeaux, France, aged 73 years or older. AMD was graded from nonmydriatic color retinal photographs, in three exclusive stages: no AMD (1015 eyes), large soft distinct drusen and/or large soft indistinct drusen and/or reticular drusen and/or pigmentary abnormalities (early AMD, 276 eyes), and late AMD (66 eyes). BP parameters were measured at four occasions over a 7-year period. PP was defined as systolic BP minus diastolic BP. Associations of AMD with BP parameters were estimated using generalized estimating equation logistic regressions. Statistical analyses included 702 subjects (1357 eyes) with complete data.

**Results.** After adjustment for age, sex, educational level, smoking, body mass index, plasma HDL and LDL cholesterol, CFH Y402H, ApoE2, ApoE4, and ARMS2 A69S polymorphisms, elevated PP was significantly associated with an increased risk of late AMD (odds ratio [OR] = 1.37 for a 10-mm Hg increase, 95% confidence interval [CI]: 1.03–1.82). Associations were similar for late atrophic and late neovascular AMD (OR = 1.39, 95% CI: 1.01–1.92, $P = 0.04$, and OR = 1.43, 95% CI: 0.90–2.23, $P = 0.13$, respectively). Association with early AMD was in the same direction but did not reach statistical significance (OR = 1.12, 95% CI: 0.98–1.28). Early and late AMD were not significantly associated with systolic or diastolic BP, hypertension, or use of antihypertensive medications.

**Conclusions.** This study suggests that high PP may be associated with increased risk for AMD. (*Invest Ophthalmol Vis Sci.* 2013;54:1905–1912) DOI:10.1167/iovs.12-10192

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in the elderly in North America and other Western countries.[1] The resulting loss of vision is associated with significant limitations in activities of daily living, while life expectancy is still increasing. AMD is a multifactorial disease, resulting from both nonmodifiable factors (age, sex, genetic susceptibility) and modifiable factors (smoking, nutrition). The control of these modifiable factors may represent a preventive means to reduce its incidence.[2] Among these factors, cardiovascular risk factors, including smoking,[3–9] abdominal obesity,[4,7,10,11] and blood pressure (BP),[12–18] have received much attention for their potential role in the development and progression of AMD. However, except for smoking, epidemiological studies have reported conflicting results, particularly for BP, as some studies[13–18] found associations between higher risk of AMD and elevated blood pressure, while others did not.[7,8,10,19–23]

Studies that explored the impact of BP on cardiovascular diseases have demonstrated that long-term average BP is a better determinant of risk for cardiovascular disease events,[24,25] as the effect of high BP seems to be cumulative. By contrast, most of the studies focusing on the association of cardiovascular risk factors with AMD used a single time point for BP measurement (at baseline). However, during their lifetime, individuals are exposed to varying levels of BP in relation to aging, antihypertensive treatment use, comorbidity, or behavioral modifications (diet, physical activity). In addition, BP may be influenced by intraindividual physiological fluctuations (fluctuation within a day or day to day) and measurement error.[26] Hence, long-term average BP appears to be a more stable representation of the true individual BP than measurement of BP at a single time point.

Some investigators who examined the relationships between AMD and BP used three components of BP: (1) the systolic BP (SBP), the highest pressure of the blood when the heart is pumping; (2) the diastolic BP (DBP), the BP when the heart is at rest; and (3) the pulse pressure (PP), an indirect measure of arterial stiffness, which is the difference between SBP and DBP. Commonly, PP ranges from 40 to 50 mm Hg in healthy adults.[27] When PP is greater than 50 mm Hg, the risk for cardiovascular events increases, especially in the elderly.[28] Indeed, after 60 years, SBP rises and DBP falls in both normotensive and untreated hypertensive individuals, resulting in a large increase of PP in older individuals.[29] Independently of SBP, DBP, and hypertension, PP has been reported to be a

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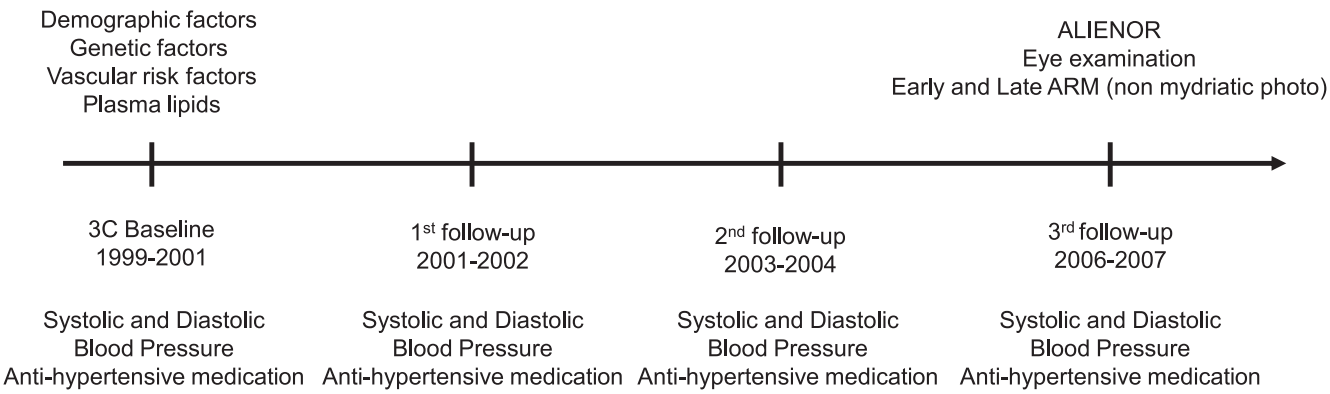


**Figure.** Design of the ALIENOR study.

major predictor of cardiovascular disease and mortality in both hypertensive and normotensive elderly.[29] A high PP tends to accelerate the aging of body organs, particularly the heart, the brain, and kidneys. Since Klein et al.,[30] several studies that investigated the relationships between AMD and BP have used PP as an indicator of BP risk in addition to SBP, DBP, and hypertension.[18,20,30–33] Most of these studies reported a significant relationship between elevated PP and a higher risk of early and/or late AMD.[18,30,31,33]

Accordingly, the aim of this study was to explore the association of AMD with long-term average BP parameters, including PP, in the framework of a population-based cohort.

## Subjects and Methods

### Study Purpose

The ALIENOR (Antioxydants, LIpids Essentiels, Nutrition et maladies OculaiRes) study is a population-based prospective study aimed at assessing the associations of age-related eye diseases (AMD, glaucoma, cataract, dry eye syndrome) with nutritional factors (in particular antioxidants, macular pigment, and fatty acids), determined from plasma measurements and estimations of dietary intake.[34] It also takes into account other major determinants of eye disease, including gene polymorphisms, lifestyle, and vascular factors.

### Study Sample

Subjects of the ALIENOR study were recruited from an ongoing population-based study (Three-City [3C] study) on the vascular risk factors for dementia.[35] The 3C study included 9294 subjects aged 65 years and older from three French cities (Bordeaux, Dijon, Montpellier), among whom 2104 were recruited in Bordeaux (response rate 43.2%). Subjects were contacted individually from the electoral rolls. They were initially recruited from 1999 to 2001 and were followed-up approximately every 2 years since baseline (Figure). Data collected at each examination included cognitive testing with diagnoses of dementia and assessment of vascular risk factors. In addition, fasting blood and DNA samples were collected at baseline and kept frozen at −80°C.

The ALIENOR study consisted of an eye examination, which was proposed to all participants of the third follow-up (2006–2008) of the 3C cohort in Bordeaux. Among the 1450 alive participants reexamined in 2006 to 2008, 963 (66.4%) participated in the ALIENOR study, and 487 (33.5%) declined participation. Detailed characteristics of participants and nonparticipants have been published elsewhere.[34]

This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for participation in the study. The design of the ALIENOR study was approved by the Ethical Committee of Bordeaux (Comite de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006.

### Eye Examination

The eye examination took place in the Department of Ophthalmology of the University Hospital of Bordeaux, France. It included a recording of ophthalmological history, measures of visual acuity, refraction, two 45° nonmydriatic color retinal photographs (one centered on the macula, the other centered on the optic disc), measures of IOP and central corneal thickness, and break-up time test. A self-completed questionnaire on risk factors specific to the eye and dry eye symptoms was completed at home and brought back on the day of the eye examination.

Retinal photographs were taken using a nonmydriatic retinograph (TRC NW6S; Topcon, Tokyo, Japan) and were interpreted in duplicate by two specially trained technicians. Inconsistencies between the two interpretations were adjudicated by a retina specialist for classification of AMD and other retinal diseases and by a glaucoma specialist for classification of glaucoma. All cases of late AMD, other retinal diseases, and glaucoma were reviewed and confirmed by specialists.

### Classification of AMD

Retinal photographs were interpreted according to the international classification[36] and to a modification of the grading scheme used in the Multi-Ethnic Study of Atherosclerosis for drusen size, location, and area.[37] Late AMD was defined by the presence of neovascular AMD or geographic atrophy within the grid (3000 μm from the foveola). Neovascular AMD included serous or hemorrhagic detachment of the RPE or sensory retina, subretinal or sub-RPE hemorrhages, and fibrous scar tissue. Geographic atrophy was defined as a discrete area of retinal depigmentation, 175 μm in diameter or larger, characterized by a sharp border and the presence of visible choroidal vessels. Five cases of late AMD had no gradable photographs and were classified by ophthalmological history of AMD and AMD therapy (in particular, antiangiogenic agents and photodynamic therapy) and confirmed by their treating ophthalmologist. Because etiologies of neovascular and atrophic AMD may be different,[38] we separated two groups: subjects with neovascular AMD (with or without geographic atrophy) and subjects with late atrophic AMD (geographic atrophy without neovascular AMD).

Early AMD was defined by the presence of soft distinct drusen and/or soft indistinct drusen and/or reticular drusen and/or pigmentary abnormalities. Soft distinct and soft indistinct drusen were larger than 125 μm in diameter and had, respectively, uniform density and sharp edges or decreasing density from the center outward and fuzzy edges. Pigmentary abnormalities were defined as areas of hyperpigmentation and/or hypopigmentation (without visibility of choroidal vessels). Eyes were classified according to three exclusive groups: no AMD, early AMD, and late AMD.

### BP Parameters

The clinical baseline (from 1999–2001) and follow-up examinations (first follow-up examination from 2001–2002, second follow-up

examination from 2003–2004, and third follow-up examination from 2006–2007) included several measurements of SBP and DBP (Figure). At each examination, two separate measures in a seated position were performed in all participants, the first one before and the second one during the interview, using a digital electronic tensiometer (OMRON M4; Omron Sante France Sas, Rosny-Sous-Bois Cedex, France).

With regard to use of antihypertensive medications, baseline and follow-up examinations included an inventory of all drugs used during the preceding month. Medical prescriptions and, where feasible, the medications themselves, were seen by the interviewer. The name of the medication was recorded, and all drugs were subsequently coded according to the French translation of the World Health Organization Anatomical Therapeutic Chemical (ATC) classification.[39] Five classes of antihypertensive medication were defined according to the ATC classification: (1) diuretic (ATC codes: C03A, C03B, C03C, C03E, C03X, C02LA, C02LB, C02LC, C02LE, C02LF, C02LG, C02LK, C02LL, C02LN, C07CA, C07CB, C07CG, C07DA, C07DB, C08GA, C09BA, C09DA), (2) beta-blocker (ATC codes: C07A, C07B, C07C, C07D, C07E, C07F), (3) calcium-channel blocker (ATC codes: C08C, C08D, C08E, C08GA, C09BB, C09DB), (4) angiotensin II receptor antagonist (ATC codes: C09C, C09D), and (5) angiotensin-converting enzyme (ATC codes: C09A, C09B). Antihypertensive medication use was defined as the use of at least one of the preceding classes of antihypertensive medication between the baseline and the last follow-up.

## Other Variables

Potential confounders were selected, based on literature results reporting significant associations of AMD or BP with age, sex, educational level, smoking, body mass index (BMI), plasma high-density lipoprotein (HDL) cholesterol, plasma LDL cholesterol, antihypertensive medication use, and the polymorphisms Complement Factor H (CFH) Y402H, Age-Related Maculopathy Susceptibility 2 (ARMS2) A69S, and apolipoprotein E2 (ApoE2) and E4 (ApoE4).

Data were collected during a face-to-face interview using a standardized questionnaire administered by a trained psychologist or nurse. At baseline, general data included demographic characteristics, educational level, and smoking. BMI (kg/m$^2$) was calculated as weight/height$^2$ using weight and height measured at baseline. Plasma lipids were measured at the Biochemistry Laboratory of the University Hospital of Dijon from baseline fasting blood samples.

Genetic polymorphisms were determined by the Lille Génopôle, from the DNA samples collected at baseline (1999–2001). The included genetic factors have been shown to be very strong predictors of risk for AMD and/or cardiovascular disease in previous studies, including the ALIENOR study.[40–43]

## Statistical Analyses

For the comparison of subjects included or not included in the statistical analyses because of missing data, we performed $\chi^2$ and Student's *t*-tests, as appropriate. We then estimated age- and sex-adjusted *P* values using logistic regression. The average SBP was the average of the eight SBP measures (two measures in sitting position at each examination). The same calculation was made for the average DBP. Hypertension was defined as average SBP of 140 mm Hg or higher and/or average DBP of 90 mm Hg or higher. For each measurement, PP was defined as SBP minus DBP. Average PP was the average of all calculations of PP made for the eight measurements. An abnormal PP was defined as a PP higher than 50 mm Hg.[28]

We studied the potential change over time of BP parameters, using linear mixed models,[44] with BP parameters as the dependent variable, time (in years) as the independent variable, with fixed and/or random effects. The linear mixed models included an intercept, representing the baseline mean level of BP parameters, and a slope, representing the annual change over time from baseline.

Associations of early and late AMD with each of the BP variables were estimated using logistic generalized estimating equation (GEE) models, taking into account the data from both eyes and their intraindividual correlation.[45] In all analyses, subjects without any AMD were considered as the reference group.

GEE models were adjusted at first for age and sex, and second for age, sex, educational level (no education or primary school or short secondary school versus long secondary school or high school or university), smoking (never, 1 to less than 20 pack-years, 20 pack-years or more), baseline BMI (kg/m$^2$), plasma HDL cholesterol (mmol/L), plasma LDL cholesterol (mmol/L), and genetic risk factors (CFH Y402H, ARMS2 A69S, and ApoE2 and ApoE4 polymorphisms). The associations are presented as odds ratios (ORs), with 95% confidence intervals (CIs). For the associations between AMD and average SBP, DBP, and PP, the ORs were expressed per 10-mm Hg increase. Potential interactions of antihypertensive medication and of the major genetic polymorphisms (ApoE2, ApoE4, CFH, and ARMS2) with SBP, DBP, PP, and hypertension were introduced in the models. We withdrew interaction terms when they were not statistically significant ($P > 0.05$). All statistical analyses were performed using statistical software (SAS, version 9.1; SAS Institute, Inc., Cary, NC).

# Results

Among the 963 subjects of the ALIENOR study, 84 (8.7%) subjects had ungradable photographs in both eyes and 177 (18.4%) had missing data for BP measurement and/or potential confounders. Thus, the statistical analyses were conducted on 702 subjects (73.9%). Although participants without missing data were very similar to participants with missing data (except for use of angiotensin II antagonist), participants without missing data showed some differences in demographic status and cardiovascular risk factors by comparison with nonparticipants. They were younger, more often males, had higher educational levels and a lower BMI, and were less often affected by hypertension and users of antihypertensive medications (Table 1). However, after adjustment for age and sex, we detected no significant differences for average SBP, average DBP, average PP, hypertension, and the frequency of use of antihypertensive medication, although the distribution of subtypes of antihypertensive medications remained different between participants and nonparticipants, with less frequent use of diuretics and angiotensin-converting enzymes and more frequent use of beta-blockers in participants without missing data. Length of follow-up of all participants, from baseline of the 3C study to eye examination, was on average 7.2 years, with a range of 6.4 to 9.0 years. Regarding the baseline demographic characteristics, approximately 60% were females, more than half had low educational level, and approximately two-thirds of subjects had never smoked.

Table 2 presents the clinical characteristics of participants of the ALIENOR study according to AMD status. AMD was diagnosed in more than one of three individuals, most of whom had early AMD (195, 81.9%) and 43 (18.1%) had late AMD (8.4% atrophic and 9.7% neovascular). AMD subjects tended to have slightly higher HDL cholesterol, but similar LDL cholesterol and BMI.

Nearly half of the subjects with AMD had suffered from hypertension. Among people suffering from hypertension, more than three-quarters were treated by an antihypertensive medication at one examination or more ($n = 258$, 76.8%), whether they presented AMD (78.9%) or not (75.6%). Regarding the whole population, more than two of three subjects used at least one antihypertensive medication during follow-up. Diuretics and beta-blockers were the two classes of antihypertensive medications most commonly used overall. For the whole population, and whatever the AMD status, the average SBP was relatively high (>139 mm Hg) and the average PP was abnormal (>62 mm Hg).

**Table 1.** Comparison of Characteristics of Subjects of the ALIENOR Study Included and Excluded for Missing Data and Subjects Not Included in the ALIENOR Study

| | ALIENOR Participants without Missing Data, $n = 702$ | ALIENOR Participants with Missing Data, $n = 261$ | ALIENOR Participants with Missing Data, *N* | ALIENOR Participants without versus with Missing Data | | ALIENOR Nonparticipants, $n = 487$ | ALIENOR Nonparticipants, *N* | ALIENOR Participants without Missing Data versus ALIENOR Nonparticipants | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *P** | *P*† | | | *P** | *P*† |
| Age, mean (SD), y | 80.1 (4.4) | 80.4 (4.5) | | 0.48 | 0.32 | 82.9 (5.1) | | 0.0002 | <0.0001 |
| Female sex, *n* (%) | 438 (62.4) | 158 (60.5) | | 0.60 | 0.54 | 334 (68.6) | | 0.03 | 0.14 |
| Educational level, *n* (%) | | | | | | | | | |
| No education or primary school or short secondary school | 407 (58.0) | 135 (51.9) | 260 | 0.09 | 0.10 | 345 (71.0) | 486 | 0.0001 | <0.0001 |
| Long secondary school or high school or university | 295 (42.0) | 125 (48.1) | | | | 141 (29.0) | | | |
| Smoking, *n* (%) | | | | | | | | | |
| Never | 459 (65.4) | 155 (62.2) | 249 | 0.38 | 0.31 | 345 (71.9) | 480 | 0.06 | 0.57 |
| 1 to 20 pack-years | 124 (17.7) | 54 (21.7) | | | | 70 (14.6) | | | |
| ≥20 pack-years | 119 (16.9) | 40 (16.1) | | | | 65 (13.5) | | | |
| Age-related maculopathy, *n* (%) | | | | | | | | | |
| None | 464 (66.1) | 116 (66.5) | 177 | 0.29 | 0.32 | | | | |
| Early AMD | 195 (27.8) | 55 (31.1) | | | | | | | |
| Late AMD | 43 (6.1) | 6 (3.4) | | | | | | | |
| BMI, mean (SD), kg/m$^2$ | 26.4 (3.8) | 26.2 (4.2) | 253 | 0.08 | 0.46 | 26.6 (4.6) | 471 | <0.0001 | 0.18 |
| HDL cholesterol, mean (SD), mM | 1.6 (0.4) | 1.6 (0.4) | 199 | 0.17 | 0.10 | 1.6 (0.4) | 405 | 0.33 | 0.04 |
| LDL cholesterol, mean (SD), mM, 64 MD | 3.6 (0.8) | 3.6 (0.8) | 197 | 0.99 | 0.86 | 3.6 (0.8) | 408 | 0.93 | 0.85 |
| Average SBP, mean (SD), mm Hg | 139.4 (16.4) | 141.7 (17.5) | | 0.17 | 0.08 | 142.0 (17.2) | 486 | 0.25 | 0.06 |
| Average DBP, mean (SD), mm Hg | 77.0 (8.3) | 77.7 (8.5) | | 0.61 | 0.17 | 76.7 (8.6) | 486 | 0.37 | 0.41 |
| Average PP,‡ mean (SD), mm Hg | 62.5 (12.6) | 64.0 (13.4) | | 0.22 | 0.15 | 65.3 (13.5) | 486 | 0.08 | 0.05 |
| Hypertension,§ *n* (%) | 336 (47.9) | 137 (52.5) | | 0.20 | 0.25 | 268 (55.1) | 486 | 0.01 | 0.05 |
| Antihypertensive medication use,‖ *n* (%) | 489 (69.7) | 180 (69.0) | | 0.84 | 0.73 | 366 (75.1) | | 0.04 | 0.26 |
| Diuretic use,‖ *n* (%) | 277 (39.5) | 102 (39.1) | | 0.91 | 0.84 | 248 (50.9) | | <0.0001 | 0.002 |
| Beta-blocker use,‖ *n* (%) | 257 (36.6) | 92 (35.2) | | 0.69 | 0.67 | 142 (29.2) | | 0.007 | 0.005 |
| Calcium-channel blocker use,‖ *n* (%) | 173 (24.6) | 67 (25.7) | | 0.74 | 0.87 | 146 (30.0) | | 0.04 | 0.17 |
| Angiotensin II receptor antagonist use,‖ *n* (%) | 177 (25.2) | 85 (32.6) | | 0.02 | 0.03 | 145 (29.8) | | 0.08 | 0.16 |
| Angiotensin-converting enzyme use,‖ *n* (%) | 148 (21.1) | 60 (23.0) | | 0.52 | 0.61 | 144 (29.6) | | 0.0008 | 0.002 |

* *P* values, $\chi^2$ for frequency comparison. Student's *t*-test for means comparison.
† Adjusted for age and sex using logistic regression.
‡ PP = average (SBP − DBP).
§ Average SBP ≥ 140 mm Hg and/or average DBP ≥ 90 mm Hg.
‖ Use of antihypertensive medication at one examination or more.

**Table 2.** Demographic and Clinical Characteristics of Subjects of the ALIENOR Study according to AMD Status at Worse Eye ($N = 702$)

| | None, $n = 464$ | Early AMD, $n = 195$ | Late AMD, $n = 43$ |
|---|---|---|---|
| Baseline BMI, mean (SD), kg/m$^2$ | 26.6 (3.8) | 25.9 (3.9) | 26.3 (3.7) |
| Baseline HDL cholesterol, mean (SD), mM | 1.5 (0.4) | 1.7 (0.4) | 1.7 (0.4) |
| Baseline LDL cholesterol, mean (SD), mM | 3.7 (0.8) | 3.6 (0.8) | 3.5 (0.9) |
| Average SBP, mean (SD), mm Hg | 139 (16) | 141 (16) | 142 (17) |
| Average DBP, mean (SD), mm Hg | 77 (8) | 77 (8) | 75 (8) |
| Average PP,* mean (SD), mm Hg | 62 (13) | 63 (12) | 67 (13) |
| Hypertension,† *n* (%) | 213 (45.9) | 102 (52.3) | 21 (48.8) |
| Antihypertensive medication use,‡ *n* (%) | 319 (68.7) | 140 (71.8) | 30 (69.8) |
| Diuretic use,‡ *n* (%) | 178 (38.4) | 81 (41.5) | 18 (41.9) |
| Beta-blocker use,‡ *N* (%) | 171 (36.8) | 72 (36.9) | 14 (32.6) |
| Calcium-channel blocker use,‡ *n* (%) | 115 (24.8) | 46 (23.6) | 12 (27.9) |
| Angiotensin II receptor antagonist use,‡ *n* (%) | 111 (23.9) | 54 (27.7) | 12 (27.9) |
| Angiotensin-converting enzyme use,‡ *n* (%) | 96 (20.7) | 38 (19.5) | 14 (32.6) |

* PP = average (SBP − DBP).
† Average SBP ≥ 140 mm Hg and/or average DBP ≥ 90 mm Hg.
‡ Use of antihypertensive medication at one examination or more.

The evolution of BP parameters over time was described using linear mixed models. In models using fixed effect for time (estimating a unique slope for time for all subjects), and random intercept (individual intercepts for each subject), the effect of time was not significant, indicating that BP parameters were globally stable over time (beta = –0.04 mm Hg per year, $P = 0.98$ for SBP, beta = –0.18 mm Hg per year, $P = 0.79$ for DBP, and beta = 0.13 mm Hg per year, $P = 0.90$ for PP). In models using a fixed effect for time and random effects for both intercept and time (individual intercepts and slopes for time for each subject), the variance of slopes tended toward zero, indicating that BP parameters were also stable at the individual level (data not shown). We thus concluded that there was no major change of BP parameters over the 7 years of follow-up in the present study, and that the average of BP measurements at the different examinations constituted the most appropriate estimation of long-term BP status.

After adjusting for age and sex (Table 3, model 1), higher SBP tended to be associated with increased risk for early AMD, and higher PP tended to be associated with increased risk for early and late AMD, but none of these associated risks reached statistical significance (OR ranging from 1.09–1.26 per 10 mm Hg, *P* values ranging from 0.08–0.12). Associations of early and late AMD with DBP and hypertension were far from statistically significant. No associations were found for any stage of AMD with use of antihypertensive medication (Table 3), type of antihypertensive therapy (data not shown), or use of antihypertensive combined with elevated BP (hypertension and/or antihypertensive medication use) (data not shown).

After adjusting for age, sex, educational level, smoking, BMI, plasma HDL and LDL cholesterol, and genetic factors (CFH Y402H, ARMS2 A69S, and ApoE2 and E4 polymorphisms) (model 2, Table 3), elevated PP was significantly associated with an increased risk of late AMD (OR = 1.37, $P = 0.03$).

**Table 3.** Associations of AMD with Average BP and Hypertension in the ALIENOR Study (OR [95 % Confidence Interval] *P* Value)

| | None, $n = 1015$ Eyes | Early AMD, $n = 276$ Eyes | Late AMD, $n = 66$ Eyes | Any AMD, $n = 342$ Eyes |
|---|---|---|---|---|
| Average SBP, per 10-mm Hg increase | | | | |
| Model 1* | ref | 1.09 [0.99–1.20] 0.08 | 1.09 [0.88–1.37] 0.43 | 1.09 [0.99–1.19] 0.08 |
| Model 2† | ref | 1.10 [0.99–1.21] 0.07 | 1.15 [0.91–1.46] 0.23 | 1.09 [0.99–1.20] 0.07 |
| Average DBP, per 10-mm Hg increase | | | | |
| Model 1 | ref | 1.12 [0.93–1.36] 0.23 | 0.81 [0.53–1.25] 0.34 | 1.07 [0.89–1.29] 0.46 |
| Model 2 | ref | 1.13 [0.93–1.36] 0.21 | 0.81 [0.50–1.30] 0.39 | 1.07 [0.89–1.29] 0.46 |
| Average PP,‡ per 10-mm Hg increase | | | | |
| Model 1 | ref | 1.10 [0.97–1.25] 0.12 | 1.26 [0.95–1.66] 0.10 | 1.12 [0.99–1.26] 0.07 |
| Model 2 | ref | 1.12 [0.98–1.28] 0.10 | 1.37 [1.03–1.82] 0.03 | 1.13 [0.99–1.28] 0.06 |
| Hypertension§ | | | | |
| Model 1 | ref | 1.21 [0.89–1.66] 0.22 | 0.99 [0.51–1.92] 0.98 | 1.19 [0.88–1.61] 0.25 |
| Model 2 | ref | 1.22 [0.88–1.69] 0.24 | 1.07 [0.55–2.08] 0.85 | 1.19 [0.87–1.63] 0.28 |
| Antihypertensive medication use‖ | | | | |
| Model 1 | ref | 1.05 [0.74–1.45] 0.79 | 0.81 [0.40–1.66] 0.57 | 1.00 [0.72–1.40] 0.99 |
| Model 2 | ref | 1.06 [0.73–1.53] 0.77 | 0.87 [0.41–1.85] 0.72 | 1.03 [0.72–1.47] 0.87 |

ref, reference category.
* Model adjusted for age and sex.
† Model adjusted for age, sex, educational level, smoking, BMI, plasma HDL cholesterol, plasma LDL cholesterol, CFH Y402H, ApoE2, ApoE4, and ARMS2 A69S polymorphisms.
‡ PP = average (SBP − DBP).
§ Average SBP ≥ 140 mm Hg and/or average DBP ≥ 90 mm Hg.
‖ Use of antihypertensive medication at one examination or more.

Associations were similar for late atrophic and late neovascular AMD (OR = 1.39, 95% CI: 1.01–1.92, $P = 0.04$, and OR = 1.43, 95% CI: 0.90–2.23, $P = 0.13$, respectively). Association of PP with early AMD was in the same direction, but did not reach statistical significance (OR = 1.12, $P = 0.10$).

After full adjustment, no significant associations of early or late AMD were found with SBP or DBP, or hypertension, although the risk for AMD tended to be slightly higher with increasing SBP (Table 3). No associations were found of any stage of AMD with use of antihypertensive medication (Table 3) and type of antihypertensive therapy (data not shown).

No interactions were found between antihypertensive medication and SBP, DBP, or PP, suggesting that the relationship of AMD with BP parameters was similar whether subjects were treated with antihypertensive medications or not (data not shown). We also found no interaction of BP parameters with genetic polymorphisms, suggesting that genetic background does not modify the association of BP parameters with AMD.

## Discussion

In this population-based study, after multivariate adjustment, PP was associated with an increased risk for late AMD, whereas SBP and DBP, hypertension, and antihypertensive medication use were not significantly associated with AMD. Although some studies have reported a significant association of AMD with hypertension (or SBP and DBP),[13,15,17,30,46,47] this association was inconsistent in most studies.[4,7,9,10,20,21,31,32,48–50] Results from a recent meta-analysis[51] further confirmed the absence of significant association between systemic hypertension and AMD in population-based studies (six cross-sectional studies, four prospective studies), although data from three case-control studies showed an increased risk for AMD in hypertensive subjects. This suggests that some of the observed positive associations of hypertension with AMD might be due to selection bias, which remains of major concern in case-control studies.

By contrast, in the present study, high PP was significantly associated with late AMD. Only a few previous studies have reported the associations of PP with AMD. In the Rotterdam study, PP was significantly associated with incidence of any AMD (OR = 1.08 for a 10-mm Hg increase, 95% CI: 1.03–1.14).[18] This is very close to our estimate for the prevalence of any AMD (OR = 1.13, 95% CI: 0.99–1.28). Consistent with the present study, in the 10-year follow-up of the Beaver Dam Eye Study, PP was significantly associated with incident late AMD (relative risk [RR] = 1.19, 95% CI: 1.03–1.38) and tended to be associated with 10-year incidence of early AMD (RR = 1.07, 95% CI: 1.00–1.16).[13] In the Los Angeles Latinos Eye study, PP was significantly also associated with the 4-year incidence of any and early AMD.[33] However, no association of PP with early or late AMD was found in the 10-year follow-up of the Blue Mountains Study[32] or in the cross-sectional Singapore Malay Eye Study.[20]

Hence, PP may represent a better determinant of increased risk for AMD than other components of BP. With aging, there is gradual conduit vessel stiffness, resulting from elastin fragmentation and increased deposition of collagen.[52] This stiffness contributes to an increase of peak SBP and a reduction in DBP, and thereby to an increase in PP.[13,53] In Bruch's membrane, analogous age-related degenerative elastin and collagen changes have been described.[13,54] In addition to the systemic effects of high PP, it has been postulated that high PP may be a marker of such age-related degenerative changes in Bruch's membrane in eyes susceptible to develop AMD.[13] Systemic BP abnormalities may play a role in AMD by inducing choroidal perfusion abnormalities. Indeed, reduced choroidal blood flow has been reported in AMD,[55,56] and an association of low choroidal blood flow with history of hypertension was observed in AMD patients.[57]

The main strength of our study is the population based-sample with the repeated assessment of BP, measured at four occasions over a 7-year period. Because we found no major change of BP parameters over time, average of BP parameters across the different examinations seemed the most appropriate estimation of long-term BP status and allowed taking into account intraindividual variability. The lack of association found in some previous studies based on a single-time BP measurement may be explained by random intraindividual fluctuations of BP measurements, which would tend to bias the estimates toward the null.

Another strength is that major potential confounding factors were taken into account, including sociodemographic status, factors related to vascular disease, antihypertensive medication, and the major genetic polymorphisms CFH, ARMS2, Apoe2, and ApoE4. Although we observed no major confounding (less than 10% change in the ORs between models 1 and 2, performed on the same dataset), association of PP with late AMD was slightly stronger in model 2 and reached statistical significance only after full adjustment (OR = 1.26, $P = 0.10$ vs. OR = 1.37, $P = 0.04$ in models 1 and 2, respectively). This may be due to a better specification of the statistical models, in particular by taking into account CFH and ARMS2 polymorphisms, which have very strong associations with AMD in our sample.[41,58] This underlines the importance of taking into account all major known risk factors (including genetic polymorphisms) when studying potential new associations.

By contrast, one limitation of our study could come from the representativeness of the sample. The ALIENOR subsample tends to overrepresent younger subjects and high socioeconomic status, among subjects participating to the 3C study.[34] The individuals included in this study may consequently be healthier and have different lifestyles, particularly concerning their diet and physical activity, than the general population. These differences may have affected the distribution of vascular characteristics or the prevalence of eye diseases. However, participants from the 3C study who were included in the ALIENOR study were not different from those who were not included for most parameters of interest in our study, in particular BP.[34] Furthermore, as described previously,[34] the age- and sex-specific prevalence rates of AMD in the ALIENOR study were similar to those observed in other studies performed in Europe[59,60] and other industrialized countries.[61] Data collection was performed in the same way in all individuals regardless of their AMD stage and photograph graders had no access to BP data. Therefore, we can assume that the error was not differential and was unlikely to have biased the estimation of any of the associations of AMD with vascular parameters.

Another limitation of our study is the small number of cases of late AMD, which may have induced insufficient statistical power for detecting some associations with BP parameters (in particular for SBP, which showed a tendency toward an increased risk for early and late AMD in the present study, which did not reach statistical significance). Finally, a potential limitation of our study is the high number of comparisons performed. Therefore, we cannot exclude that some of the observed associations were due to chance finding, although our findings are generally consistent with previous studies in this field.

In summary, our results suggest that elderly patients with high SBP and high PP may be at increased risk for developing early or late AMD. If confirmed in future prospective studies, reduction of SBP and PP may represent an efficient preventive

means for AMD occurrence. Therefore, larger studies with longer follow-up are needed to provide a greater number of late AMD cases and long-term evaluation of BP status, and thus to clarify the associations of AMD with BP, particularly for the neovascular form of the disease. Randomized controlled trials are also further required to examine whether lowering BP, and in particular SBP, is associated with a reduction in the incidence and progression of AMD.

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