Epidemiology/Population

Retinal Microvasculature Is Associated With Long-Term Survival in the General Adult Dutch Population

Unal Mutlu, M. Kamran Ikram, Frank J. Wolters, Albert Hofman, Caroline C.W. Klaver, M. Arfan Ikram

Abstract—Retinal vascular diameters are associated with (sub)clinical cardiovascular disease and short-term cardiovascular mortality, but their association with long-term mortality is uncertain. We studied the association of retinal vascular diameters with cause-specific mortality in the general adult Dutch population during 25 years of follow-up. From 1990 to 1993, arteriolar and venular diameters were measured semiautomatically on digitized images in 5674 persons (mean age 68.0 years, 59% women) from the population-based Rotterdam study. Follow-up for mortality was complete till March 2015. Associations between vascular diameters and mortality were examined using Cox proportional hazards models, adjusting for age, sex, cardiovascular risk factors, and the fellow vessel diameter. During 85 770 person-years (mean±SD: 15.1±6.67), 3794 (66.8%) persons died, of whom 1034 due to cardiovascular causes. We found that narrower arterioles and wider venules were associated with higher risk of mortality (adjusted hazard ratio [95% confidence interval] per SD decrease 1.04 [1.00–1.08] and increase 1.07 [1.03–1.12], respectively). For arterioles, these associations were strongest for cardiovascular mortality, whereas venules showed consistent associations for cardiovascular and noncardiovascular mortality. Importantly, these associations remained unchanged after excluding the first 10 years of follow-up as immortal person-time. We found evidence for effect modification with stronger associations in persons <70 years (venules only) and smokers (P value for interaction<0.01). We replicated our findings in another independent cohort from the Rotterdam Study of 3106 persons with 19 880 person-years of follow-up and 144 deaths (hazard ratio for venules 1.22 [1.00–1.49]). Markers of retinal microvasculature are associated with long-term mortality in the general adult Dutch population. (Hypertension. 2016;67:281-287. DOI: 10.1161/HYPERTENSIONAHA.115.06619.)

• Online Data Supplement

Key Words: arteriolosclerosis ■ cardiovascular disease ■ microcirculation ■ mortality ■ stroke

Cardiovascular diseases remain the most common cause of death worldwide, accounting for ≤23.1% of all deaths.¹ In addition, cardiovascular risk factors and subclinical cardiovascular pathology contribute to deaths that might not be formally classified as cardiovascular, such as due to chronic obstructive pulmonary disease, diabetes mellitus, dementia, or even cancer.²³ An important cornerstone in cardiovascular research has been the identification of early biomarkers that relate to subclinical and clinical disease as well as subsequent mortality. Such markers are not only important for understanding pathogenesis or disease monitoring, but—if feasible in community-dwelling individuals—can also serve as potential intervention targets for prevention or even used as risk predictors. For instance, coronary calcification and carotid plaques are strong predictors of myocardial infarction and stroke, and also associate with subsequent mortality.⁴⁻⁵ However, most population-based research on cardiovascular biomarkers has revolved around noninvasive imaging of the large or medium-sized vessels, for example, aorta, carotid arteries, and coronary arteries.⁶⁻⁷ Yet, it is increasingly recognized that the microvasculature is important for cardiovascular health as well.⁷⁻⁸ Retinal imaging provides a unique opportunity to visualize microvascular damage in vivo and indeed, there is now abundant literature demonstrating strong associations of retinal markers with cardiovascular diseases.⁹⁻¹¹ By extension, several studies have shown an association of retinal microvasculature with cardiovascular mortality, but these studies usually had a short follow-up.¹²⁻¹⁴ To really play a role as long-term biomarker, it is important to establish a link between retinal microvasculature with long-term mortality. This entails not only extending the follow-up time but also investigating long-term associations after accounting for the short-term increased risk.

Moreover, it is interesting to study the role of microvasculature in noncardiovascular mortality, especially given the
established link between small vessels and diseases, such as diabetes mellitus, dementia, and chronic obstructive pulmonary disease. Therefore, we studied the association between retinal microvasculature and long-term cause-specific mortality in the general adult Dutch population.

**Participants and Methods**

**Setting and Study Population**

This study was performed as part of the Rotterdam Study, a prospective population-based cohort study, details of which have been described previously. In brief, the initial cohort (RS-I) started in 1990 and there have been 2 expansion waves: in 2000 (RS-II) and 2005 (RS-III). Retinal vessel diameters were systematically quantified in RS-I and RS-III. For this study, the main analyses were carried out in RS-I, which was the largest sample with longest follow-up, whereas RS-III served as replication sample. For RS-I, all inhabitants of the Ommoord district in the city of Rotterdam, the Netherlands, aged ≥55 years were invited to the study, of whom 7983 participated (overall response 78%). Because the ophthalmic part became only operational after the study had started, a total of 6780 participants underwent the ophthalmic examination in RS-I. For RS-III, we invited all inhabitants who reached the age of 45 years or migrated into the study population because the start of RS-I, but were not part of RS-II. A total of 3932 (64.9%) were enrolled, and baseline data were collected from 2005 to 2009. The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. A written informed consent was obtained from all participants. Baseline home interviews and examinations were performed from 1990 to mid-1993. This study adhered to the principles of the declaration of Helsinki.

**Assessment of Retinal Vessels**

In both RS-I and RS-III, participants underwent a full eye examination at baseline including simultaneous stereoscopic fundus color photography of the optic disc (20° field, Topcon Optical Company, Tokyo, Japan) after pharmacological mydriasis. For each participant, the image of 1 eye with the best quality was analyzed with the Retinal Vessel Measurement System (Retinal Analysis, Optimate, WI; Department of Ophthalmology and Visual Science, University of Wisconsin-Madison). For each participant, one summary value was calculated for the arteriolar diameters (in μm) and one for the venular diameters of the blood column after correction for differences in magnification because of refractive status of the eye, enabling us to use the separate arteriolar and venular diameter sum values. We verified in a random subsample of 100 participants in RS-I that individual measurements in the left and right eye were similar. Measurements were performed by 4 (RS-I) and 2 (RS-III) trained raters, masked for participant characteristics, masked for the end points, and blinded to each other’s measurements. Pearson correlation coefficients for inter-rater agreement in RS-I (n=40) and RS-III (n=100) were for arteriolar diameters 0.67 to 0.80 and 0.85, and for venular diameters 0.91 to 0.94 and 0.87, respectively. For intrarater agreement, the correlation coefficients were 0.69 to 0.88 and 0.86 for arteriolar diameters, and 0.90 to 0.95 and 0.87 for venular diameters.

**Assessment of Cause-Specific and All-Cause Mortality**

For the entire cohort from baseline onwards, information on vital status was obtained for cause-specific mortality and all-cause mortality from the municipal health services in Rotterdam on a biweekly basis. Also, the general practitioners in the study area reported deaths on a continuous basis. Specially trained study personnel verified reported deaths by checking the medical records. Research physicians reviewed all available information and independently coded the events according to the International Classification of Diseases, Tenth Revision. Cases on which they disagreed were discussed to reach consensus in a separate session. If the cause of death was coded as I20–25, I46, I50, I61, I63, I64, I66, I68–70, or R96, the cause of death was labeled as cardiovascular. The following codes (label) were all labeled as noncardiovascular mortality: A32-B99 (infectious disease), C00-C97 (cancer), F00-F03 (dementia), J15-J19 (pneumonia), J30-J98 (chronic respiratory disease), S12.1, S32-72 or T90.2 (fracture), and the remaining codes (other). A consensus panel of medical specialists in cardiovascular disease and internal medicine, adjudicated the final cause of death according to International Classification of Diseases, Tenth Revision codes using standardized definitions, as described in detail previously. This panel consisted of a cardiologist, 2 geriatricians, and a general practitioner experienced in cardiac disease, and their judgment was considered decisive. All participants were followed up from date of study entry until date of death, up till 15 March 2015 (for all-cause mortality) or 1 January 2013 (for cause-specific mortality). A flow diagram of the study population is depicted in Figure S1 in the online-only Data Supplement. Data on vital status was complete.

**Assessment of Covariates**

In both cohorts, baseline blood pressure was measured twice in sitting position at the right brachial artery with a random-zero sphygmomanometer. We used the average of 2 readings for analysis. Body mass index was computed as weight divided by height squared. Nonfasting serum total and high-density lipoprotein cholesterol concentrations were determined by an automated enzymatic procedure. Diabetes mellitus was considered present if participants reported the use of antidiabetic medication or when random or postload serum glucose level was >11 mmol/L (RS-I), or if participants reported the use of antidiabetic medication or when fasting glucose level in serum was >7 mmol/L (RS-III). Serum levels of C-reactive protein were determined by the Rate Near Infrared Particle Immunoassay method (Immage high-sensitive C-reactive protein, Beckman Coulter, Brea, CA). Atherosclerotic plaques were assessed by ultrasound at the carotid artery bifurcation, common carotid artery, and internal carotid artery on both sides. Plaques were defined as focal thickening of the vessel wall of at least 1.5x the average intima-media thickness for RS-I, or at least 2-mm thickening of the intima-media...
thickness for RS-III, relative to adjacent segments with or without calcified components. The carotid artery plaque score (range, 0–6) reflected the number of these locations with plaques. Information on smoking (categorized as current, former or never) and antihypertensive medication use was obtained during the home interview by a computerized questionnaire.

Statistical Analysis
Analysis included all participants who underwent ophthalmological examination at the study center. We used analysis of covariance, adjusted for age and sex, to assess differences in baseline characteristics between participants and nonparticipants from the eligibility cohort. We determined associations between baseline retinal vessel diameter (arteriolar and venular) and all-cause and cause-specific mortality, using Cox proportional hazards models. Adjusted hazard ratios (HR) with corresponding 95% confidence intervals for mortality were calculated per SD increase or decrease and per quartile of vessel diameter, adjusted for age and sex, the other vessel diameter measurements and additionally for systolic and diastolic blood pressure, antihypertensive medication, body mass index, serum total and high-density lipoprotein cholesterol, diabetes mellitus, C-reactive protein, carotid artery plaque score, and baseline history of smoking. We subsequently determined HR after excluding 10-year immortal person-time to investigate whether retinal vessel diameters were specifically associated with mortality in the long term. We also explored the effect size for venular diameter, although it remained attenuated with retinal vessel diameters, both continuously and in quartiles. Both narrower arterioles and wider venules were associated with an increased risk of mortality (HR [95% confidence intervals] for arterioles per SD decrease 1.07 [1.03–1.12], and HR for venules per SD increase 1.11 [1.07–1.16]). Adjustments for cardiovascular risk factors had no effect of arterioles (HR per SD decrease 1.04 [1.00–1.08]), but attenuated the effect size for venular diameter, although it remained statistically significant (per SD increase 1.07 [1.03–1.12]).

In RS-III, similar models were constructed, but we only considered all-cause mortality because the numbers of cause-specific mortality were too small. We explored the possibility of collinearity, given the Pearson correlation coefficient between arteriolar and venular diameter (r = 0.59), using the variance inflation factor, but none was identified (variance inflation factor <1.1). Analyses were performed using SPSS 21.0 for Windows (IBM Corp., Armonk, New York).

Results
Of 6780 participants undergoing ophthalmic examination in RS-I, 6436 persons underwent optic disc photography. From these, fundus transparencies of 762 (11.2%) persons could not be rated on either eye, leaving 5674 participants for analysis. Compared with participants, nonparticipants were significantly older, and more often had diabetes mellitus and hypertension, a lower body mass index, higher diastolic blood pressure, and higher serum levels of C-reactive protein (Table 1).

During a total follow-up of 85 770 person-years (mean±SD: 15.1±6.67), 3794 (66.8%) participants died. Cause of death was cardiovascular in 1079 participants (19.0%) predominantly due to cardiac arrest (n=183), heart failure (n=230), stroke (n=264), and myocardial infarction (n=183). Noncardiovascular cause of death in 2379 participants (41.9%) was due to infectious disease (n=56), cancer (n=910), dementia (n=348), pneumonia (n=103), chronic respiratory disease (n=123), fracture (n=65), and other remaining causes (n=774).

Figure 1 shows the hazard of all-cause mortality associated with retinal vessel diameters, both continuously and in quartiles. Both narrower arterioles and wider venules were associated with an increased risk of mortality (HR [95% confidence intervals] for arterioles per SD decrease 1.05 [1.01–1.09], and HR for venules per SD increase 1.11 [1.07–1.16]). Adjustments for cardiovascular risk factors had no effect of arterioles (HR per SD decrease 1.04 [1.00–1.08]), but attenuated the effect size for venular diameter, although it remained statistically significant (per SD increase 1.07 [1.03–1.12]).

Table 2 shows the hazard of cause-specific mortality in relation to vessel diameters. We found that the increased risk

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants</th>
<th>Nonparticipants</th>
<th>Mean Differences (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>5674</td>
<td>2309</td>
<td>NA</td>
</tr>
<tr>
<td>Age (y)</td>
<td>68.0 (8.2)</td>
<td>77.1 (10.3)</td>
<td>−8.90 (−9.3 to −8.5)†</td>
</tr>
<tr>
<td>Female (%)</td>
<td>59</td>
<td>67</td>
<td>−2.4 (−5.0 to 0.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138.6 (22.0)</td>
<td>143.2 (23.2)</td>
<td>0.56 (−0.79 to 1.91)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73.7 (11.3)</td>
<td>73.7 (12.8)</td>
<td>−1.19 (−1.91 to −0.47)†</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3 (3.7)</td>
<td>26.1 (3.9)</td>
<td>0.31 (0.07 to 0.54)†</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>6.64 (1.21)</td>
<td>6.46 (1.28)</td>
<td>0.05 (−0.03 to 0.12)</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/L)</td>
<td>1.35 (0.37)</td>
<td>1.32 (0.39)</td>
<td>0.02 (−0.01 to 0.04)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>7</td>
<td>17</td>
<td>−7.0 (−8.9 to −5.2)†</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>3.20 (6.02)</td>
<td>4.32 (9.18)</td>
<td>−0.57 (−1.00 to −0.14)†</td>
</tr>
<tr>
<td>No. of carotid artery plaques ≥4 (%)</td>
<td>11</td>
<td>21</td>
<td>−5.3 (−7.7 to −3.0)†</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>23</td>
<td>17</td>
<td>−1.1 (−3.2 to 1.1)</td>
</tr>
<tr>
<td>Arteriolar diameter (µm)</td>
<td>146.9 (14.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Venular diameter (µm)</td>
<td>222.0 (20.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Values are presented as mean (SD) or percentages. CI indicates confidence interval; HDL, high-density lipoprotein; and NA, not applicable.
†Age and sex adjusted if applicable.
‡Significant (P<0.05).
of mortality associated with arterioles was primarily driven by cardiovascular mortality. In contrast, the effect sizes of cardiovascular and noncardiovascular mortality were similar for venules (HR per SD increase 1.07 [0.99–1.15] versus 1.08 [1.02–1.13]). Further investigating specific causes, we found large effect sizes of wider venules on infectious diseases, dementia, pneumonia, and chronic obstructive pulmonary disease. Interestingly, arteriolar narrowing was only associated with pneumonia.

When excluding the first 10 years of follow-up as immortal person-time, the association of arterioles to be associated with cardiovascular mortality during long-term follow-up. Importantly, we further expanded on the role of small vessels by also investigating venular diameters. We found that wider venules were associated with cardiovascular, as well as noncardiovascular mortality. The finding that wider venules are detrimental to health is in line with previous studies, but the underlying mechanism remains uncertain. Wider venules have been shown to reflect microvascular damage because of smoking, inflammation, hypoxia, and metabolic disturbances.8,24 In our study, adjusting for markers of these mechanisms did attenuate the associations of venules with mortality, indeed pointing toward some

**Table 2. Hazard Ratios (95% CI) of Cause-Specific Mortality per SD Difference in Baseline Retinal Vessel Diameters**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Arteriolar Diameter</th>
<th>Venular Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (n=3794 deaths)</td>
<td>1.04 (1.00–1.08)</td>
<td>1.07 (1.03–1.12)</td>
</tr>
<tr>
<td>CVD mortality (n=1079 deaths)</td>
<td>1.07 (0.99–1.15)</td>
<td>1.07 (0.99–1.15)</td>
</tr>
<tr>
<td>Non-CVD mortality (n=2379 deaths)</td>
<td>1.03 (0.98–1.08)</td>
<td>1.08 (1.02–1.13)</td>
</tr>
<tr>
<td>Infectious disease (n=56 deaths)</td>
<td>0.95 (0.68–1.32)</td>
<td>1.31 (0.95–1.81)</td>
</tr>
<tr>
<td>Cancer (n=910 deaths)</td>
<td>1.02 (0.94–1.11)</td>
<td>1.00 (0.92–1.09)</td>
</tr>
<tr>
<td>Dementia (n=348 deaths)</td>
<td>0.99 (0.86–1.14)</td>
<td>1.08 (0.94–1.23)</td>
</tr>
<tr>
<td>Pneumonia (n=103 deaths)</td>
<td>1.54 (1.19–1.99)</td>
<td>1.64 (1.30–2.06)</td>
</tr>
<tr>
<td>Chronic respiratory disease (n=123 deaths)</td>
<td>0.92 (0.74–1.14)</td>
<td>1.18 (0.95–1.47)</td>
</tr>
<tr>
<td>Fracture (n=65 deaths)</td>
<td>0.98 (0.71–1.34)</td>
<td>0.83 (0.60–1.14)</td>
</tr>
<tr>
<td>Other (n=774 deaths)</td>
<td>1.03 (0.94–1.13)</td>
<td>1.09 (1.00–1.19)</td>
</tr>
</tbody>
</table>

Values are hazard ratios (95% CI) per SD decrease (for arterioles) or increase (for venules), adjusted for age, sex, other retinal vessel, systolic and diastolic pressure, antihypertensive medication, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, C-reactive protein, carotid artery plaque score, and smoking. CI indicates confidence interval; and CVD, cardiovascular disease.
effect of these mechanisms. Still, the association remained statistically significant, indicating that other processes probably also play a role. Similarly, the associations remained significant in persons without diabetes mellitus or low plaque score, again pointing to other contributing factors. The notion that wider venules reflect more diverse pathways than merely arteriolar or atherosclerotic disease also fits with the observation that venules associated with noncardiovascular disease. At the same time, we note that some of the diseases that drive the association with noncardiovascular disease, that is, chronic obstructive pulmonary disease and dementia, have been shown to have a partly vascular pathogenesis. It is therefore also possible that cardiovascular damage contributed to deaths due to those diseases, which formally get classified as noncardiovascular. Taken together, we suspect that our findings are explained by both wider venules reflecting more diverse pathways and cardiovascular damage contributing to deaths formally classified as noncardiovascular.

A major novelty of our study is that excluding the first 10 years of follow-up did not alter the associations; if anything, these became stronger. Many biomarkers for cardiovascular disease and subsequent mortality have been identified, but usually these associate with outcome only in the short term. Examples include N-terminal pro b-type natriuretic peptide and troponin T in clinical and nonclinical populations. There is a dearth of markers that indicate an increased risk in the long term. This is on the one hand caused by single measurements of the biomarker that can vary considerably over time, leading to measurement error and noise. On the other hand, reverse causality, that is, biomarker changes because of accumulation of preclinical damage, can restrict significant associations with clinical outcome to the short term. Apart from a few genetic factors, such as APOE, that remain stable throughout life, not many long-term predictors of mortality have been identified. Our findings that microvascular damage, both arteriolar and venular, associate with mortality beyond a 10-year horizon might open the way for further risk prediction and prognostic research incorporating these markers. Given the semiautomated and noninvasive nature of measuring retinal vessels, there might thus be an opportunity for translation to clinical practice and public health. Future studies should focus on the clinical applications of retinal vascular imaging in patients with cardiovascular risk factors. It may help to noninvasively stratify cardiovascular risk of patients with consequent optimization of treatment. For instance, patients with wide venular calibers might benefit from aggressive management of cardiovascular risk factors.

Table 3. Hazard Ratios (95% CI) per SD Difference in Baseline Retinal Vessel Diameters, Excluding 10-Year as Immortal Person-Time

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Arteriolar Diameter</th>
<th>Venular Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1*</td>
<td>Model 2†</td>
</tr>
<tr>
<td>All-cause mortality (n=2212 deaths)</td>
<td>1.04 (0.98–1.09)</td>
<td>1.02 (0.97–1.08)</td>
</tr>
<tr>
<td>CVD mortality (n=560 deaths)</td>
<td>1.15 (1.02–1.28)</td>
<td>1.13 (1.01–1.26)</td>
</tr>
<tr>
<td>Non-CVD mortality (n=1435 deaths)</td>
<td>1.00 (0.93–1.08)</td>
<td>0.98 (0.92–1.05)</td>
</tr>
</tbody>
</table>

Values are hazard ratios (95% CI) per SD decrease (for arterioles) or increase (for venules). CI indicates confidence interval; and CVD, cardiovascular disease.

*Model 1, hazard ratios (95% CI) were adjusted for age, sex, and for the fellow vessel diameter.
†Model 2, hazard ratios (95% CI) were adjusted for covariates in model 1 plus systolic and diastolic pressure, antihypertensive medication, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, C-reactive protein, carotid artery plaque score, and smoking.
further discussion on the use of retinal imaging, we refer the reader to the study by Rizzoni and Muijesan. 38

Limitations are the limited sample for further categorization of causes of death, as well as the use of a static measure of vascular diameter. Future studies should investigate more dynamic measurements of small vessels, including flowmetry and dynamic vessel assessments. Finally, the population of the Rotterdam Study is fairly homogeneous of middle-class white persons. Therefore, generalizability of our findings to other populations needs to be determined.

Perspectives

This study provides evidence that retinal microvascular abnormalities are predictive of cardiovascular and noncardiovascular mortality for 23 years and beyond in the general adult Dutch population. Wider venules in relatively young individuals and smokers are associated with higher risk of mortality compared with relatively old individuals and non-smokers.

There is an opportunity to use retinal vascular imaging in clinical settings as a noninvasive tool to help clinicians in identifying high-risk patients of future cardiovascular events. Given our findings, further study is warranted to understand the different pathogeneses of arterioles and venules in cardiovascular diseases, and in noncardiovascular diseases with vascular origins.

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Disclosures

None.

References


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**Novelty and Significance**

**What Is New?**

- This is the first study to report the association between retinal vessel diameters and cause-specific mortality in the long term, which persists after accounting for the short-term increased risk.
- The association between wider venules and noncardiovascular mortality is mainly attributable to diseases with vascular origins.

**What Is Relevant?**

- Retinal microvascular abnormalities can predict cardiovascular and noncardiovascular mortality, independent of traditional cardiovascular risk factors.

**Summary**

Retinal arteriolar and venular diameters are associated with long-term cardiovascular mortality. Moreover, venular diameters are also associated with noncardiovascular mortality.
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http://hyper.ahajournals.org/content/suppl/2015/11/30/HYPERTENSIONAHA.115.06619.DC1

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THE RETINAL MICROVASCULATURE IS ASSOCIATED WITH LONG-TERM SURVIVAL IN THE GENERAL ADULT DUTCH POPULATION

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Retinal microvasculature and long-term survival

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**Supplemental Material**

**Supplemental Table S1.** Baseline characteristics replication cohort (RS-III)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants</th>
<th>Non-participants</th>
<th>Mean differences (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>3106</td>
<td>826</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.8 (6.5)</td>
<td>58.5 (9.3)</td>
<td>-1.77 (-2.3;-1.2)†</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57</td>
<td>57</td>
<td>1.1 (-2.8;4.9)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.4 (19.0)</td>
<td>134.3 (17.2)</td>
<td>-0.75 (-2.13;0.63)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82.5 (11.0)</td>
<td>82.9 (9.6)</td>
<td>-0.49 (-1.31;0.34)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 (4.6)</td>
<td>28.3 (4.0)</td>
<td>0.51 (-0.86;-0.17)†</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/l)</td>
<td>5.56 (1.07)</td>
<td>5.57 (0.88)</td>
<td>-0.01 (-0.09;0.07)</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/l)</td>
<td>1.43 (0.44)</td>
<td>1.41 (0.37)</td>
<td>0.02 (-0.01;0.05)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>8</td>
<td>8</td>
<td>2.0 (-0.3;3.8)</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>2.65 (4.45)</td>
<td>4.00 (4.87)</td>
<td>-1.25 (-1.60;-0.90)†</td>
</tr>
<tr>
<td>Intima media thickness (%)</td>
<td>35</td>
<td>36</td>
<td>3.3 (-1.0;6.8)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>23</td>
<td>29</td>
<td>-7.4 (-10.6;-4.1)†</td>
</tr>
<tr>
<td>Arteriolar diameter (µm)</td>
<td>158.4 (15.5)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Venular diameter (µm)</td>
<td>239.6 (22.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are presented as means (standard deviation) or percentages.

*Age and gender adjusted if applicable
† Significant (p<0.05)
CI = Confidence Interval
HDL = high-density lipoprotein
NA = not applicable
Supplemental Figure S1. Flow diagram of the study population

Original participants in the Rotterdam Study (n= 7983)
- Not participated (n= 2309)
  - Did not underwent ophthalmic examination (n= 1203)
  - Did not underwent optic disc photography (n= 344)
  - Ungradable fundus transparencies (n= 762)

Participants included (n= 5674)
- Follow-up till 15 March 2015*
  - Alive/censored (n= 1880)

All-cause mortality (n= 3794)

*Follow-up for cause-specific mortality was till 1 January 2013 (alive/censored n=2216).