**Associated factors of white matter hyperintensity volume - a machine learning approach**

**Supplemental Material**

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**Targeted literature search on associations with WMH:**

Literature search was performed on the Pubmed search engine from January 1st, 2015 to August 7th, 2020, run on August 8th, 2020, restricted to human studies published in English using the search terms listed below in order to evaluate publications on factors associated with WMH. Literature search conducted in this manner yielded 448 hits. The machine learning based Pubmed search algorithm "Best Match" was used to select the 100/448 most relevant publications on WMH for further analysis 1.

WMH search terms (filters applied: humans):

((White matter hyperintens\*) OR (white matter lesion\*) OR (white matter disease\*) OR (white matter change\*) OR (leukoaraiosis)) AND ((leukoaraiosis) OR (cerebral small vessel disease) OR (vascular dementia)) AND (MRI) AND (risk factor\*)

Our targeted literature search identified N=45 different factors potentially associated with WMH, which are listed in Supplementary Table 1 in descending order:

**Supplementary Table I:**

|  |
| --- |
| hypertension (N=11) 2-12 |
| age (N=10) 4,5,10,13-19 |
| cognitive impairment (N=6) 6,20-24 |
| diabetes (N=5) 3,7,25-27 |
| dyslipidaemia (N=5) 12,17,19,28,29 |
| gait impairment (N=5) 6,30-33 |
| dementia (N=4) 22,24,30,34 |
| renal impairment (N=4) 23,35-37 |
| stroke (N=4) 6,13,21,38 |
| Alzheimer's disease (N=3) 30,39,40 |
| depression (N=3) 6,22,30 |
| genetic influences (N=3) 41-43 |
| smoking (N=3) 6,7,12 |
| arterial stiffness (N=2) 44,45 |
| β-amyloid (Aβ) cerebral burden (N=2) 44,46 |
| bradykinesia (N=2) 47 |
| body mass index (N=2) 3,7 |
| cardiovascular disease (N=2) 4,48 |
| dietary salt consumption (N=2) 11,49 |
| functional outcome after stroke poor (N=2) 50,51 |
| intracranial atherosclerosis (N=2) 6,52 |
| retinal microvasculopathy (N=2) 42,53 |
| systemic lupus erythematosus (N=2) 54,55 |
| α-Klotho (anti-aging protein) reduced blood levels 56 |
| ANCA-associated vasculitis 57 |
| blood-brain barrier permeability 58 |
| cerebral microbleeds 59 |
| copper serum levels 26 |
| dialysis 21 |
| early life factors (lower age-11 IQ) 60 |
| fabry disease 61 |
| functional decline (Barthel Index) 62 |
| hearing loss sudden sensorineural 63 |
| hemoglobin level 64 |
| homocysteine level 65 |
| hemorrhage intracerebral 66 |
| inflammation serum parameters 7 |
| metabolic syndrome 17 |
| n-3 polyunsaturated fatty acids 67 |
| obese waist circumference 68 |
| obstructive sleep apnea 69 |
| prediabetes 25 |
| rigidity 47 |
| stress 17 |
| telomere length reduction 18 |

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**Study Design/Subject selection:**

KORA MRI comprises 400 participants and is a sub-study of the population-based KORA FF4 study (2013-2014, 2279 subjects). The FF4 study is the second follow-up of the baseline study KORA S4 (1999-2001, 4261 subjects), which is a large sample from the general population in the region of Augsburg, Germany. Exclusion criteria for the MRI sub-study were: age >74 years, validated/self-reported stroke, myocardial infarction, peripheral artery disease (PAD), type 1 diabetes mellitus, poor overall health condition, missing oral glucose tolerance test result (OGTT) or contraindications to MRI [1].

The MRI-data was originally acquired as a nested case-control study to investigate differences in subclinical cardiovascular disease between persons with diabetes, prediabetes and non-diabetic controls. Consequently, the MRI sub-study was enriched with prediabetic and diabetic individuals. However, additional analyses for dissimilarities between the aforementioned MRI sub-study and the whole KORA-cohort did not reveal any differences [2].

SHIP-TREND-0 is a population-based cohort sampled from the population of West Pomerania in North Eastern Germany [3]. Participants in the age range of 20 to 79 years were recruited by a random cluster sample, and 4 420 individuals were included in SHIP-TREND-0. Standardized interviews and examinations were conducted between 2008 and 2012. Individuals eligible and willing to undergo whole-body MRI participated in the MRI substudy**.**

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**Supplementary Table II:**

|  |  |
| --- | --- |
|  | Description |
| **Sociodemographics** | **Further reference: [1-4]** |
| Age, years | Self-reported in standardized interview |
| Family status | Self-reported in standardized interview |
| Schooling | Self-reported in standardized interview |
| Schooling, years | calculated based on self-report in standardized interview |
| Highest professional degree | Self-reported in standardized interview |
| Per-capita income, Euro | calculated based on self-report in standardized interview |
| Equivalence income, Euro | calculated based on per-capita income, weighted according to number and age of all household members. Weights are derived according to cost of living, following Bundessozialhilfegesetz (BSHG) |
| Social stratum, Helmert scale | numeric score based on schooling, degree, job position and equivalence income |
| **Anthropometric measurements** | **Further reference: [5]** |
| Weight, kg | measured in standardized examination by calibrated steelyards or digital scales (SECA 635 or SECA 877 or SECA measuring station 285, Seca GmbH & Co, KG, Hamburg, Germany) |
| Height, cm | measured in standardized examination by calibrated levelling bar (SECA 242, Seca GmbH & Co, KG, Hamburg, Germany) |
| BMI, kg/m2 | calculated as weight in kg divided by squared height in m |
| Waist circumference, cm | measured in standardized examination with an inelastic tape at the level midway between the lower rib margin and the iliac crest |
| Hip circumference, cm | measured in standardized examination with an inelastic tape at the level of maximal gluteal protrusion |
| Waist-To-Hip Ratio | calculated as waist circumference in cm divided by hip circumference in cm |
| right-handed | Self-reported in standardized interview |
| **Other metabolic measurements** | **Further reference: [6-8]** |
| Hepatic Fat, % | MRI measurement: proton density fat fraction by multiecho single-voxel 1H spectroscopy |
| Visceral Fat, l | MRI measurement: calculated semiautomatically from volume-interpolated three-dimensional in/opposed-phase volumetric interpolated Dixon sequence from femoral head to the diaphragm |
| **Diabetes related measurements** | **Further reference: [4, 9, 10]** |
| Glycemic Status | determined as either established type-2 diabetes (validated by physician) or after OGTT according to WHO criteria. OGTT was based on 300ml of liquid containing 75g of carbohydrates. |
| normal | fasting glucose < 110 mg/dL and 2h glucose < 140 mg/dL |
| prediabetes | 110 mg/dL <= fasting glucose <= 125 mg/dL and/or 140 mg/dL <= 2-h glucose <= 200 mg/dL |
| diabetes | fasting glucose > 140 mg/dL and/or 2-h glucose > 200 mg/dL |
| Duration of diabetes, years | calculated based on self report |
| Fasting glucose, mg/dL (Serum) | UV test using enzymatic reference method with hexokinase (Vista, Siemens or Cobas, Roche) |
| Fasting insulin, mg/dL (Serum) | Elecsys Insulin immunoassay with two monoclonal antibodies (Vista, Siemens or Cobas, Roche) |
| HbA1c, % (hemolyzed whole blood) | cation-exchange high performance liquid chromatographic, photometric assay (VARIANT II TURBO Hemoglobon Testing System, Bio-Rad Laboratories Inc, Hercules, US) |
| **Behavioural factors** | **Further reference: [11-13]** |
| Alcohol consumption, categorical or g/day | calculated based on self-reported amount and type of alcoholic beverages consumed |
| Smoking | Self-reported in standardized interview |
| Packyears | calculated based on self-reported number of cigarettes smoked |
| Physically active | Self-reported in standardized interview |
| Physical activity | calculated based on self-report in standardized interview |
| **Somatic and Depressive Symptoms** | **Further references: [14-16]** |
| Angina Pectoris | determined based on self-reported symptoms in standardized interview |
| Sf-12 Somatic Scale | determined based on standardized questionnaire |
| Depressive Symptoms: PHQ-9 | assessed using the 9-item Patient Health Questionnaire (PHQ-9) in standardized interview |
| Depressed mood/Exhaustion: DEEX scale | Assessed using the Depression and Exhaustion (DEEX) scale consisting of eight items with a 4-point scale |
| **Medication intake** | **Further reference: [17]** |
| Antidiabetic | based on standardized interview. Participants were asked to bring packages of every medication that they had taken in the 7 days before the interview. Additionally, medication intake was assessed by interview.  ATC Codes A10 |
| Antihypertensive | compounds from ATC Codes C02, C03, C07, C08, C09 when German guidelines classify the compound as anti-hypertensive |
| Anticoagulant | ATC Codes B01AA, B01AB, B01AE, B01AF, B01AX |
| Antiplatelet | ATC Codes B01AC |
| Thyroidal | ATC Codes H03 (but not H03PB, H03BP, H03CA) |
| NSAID | ATC Codes N02B or M01A (but not M01AX), R05XA, N02AA59, N02AA69, N02AX62 |
| ASS 100/300 | ATC Codes B01AC06 |
| **Blood pressure** | **Further reference: [18]** |
| Systolic BP, mmHg | 3 measurements with an oscillometric digital device (OMRON HEM-705CP). Average of 2nd and 3rd measurements. |
| Diastolic BP, mmHg | 3 measurements with an oscillometric digital device (OMRON HEM-705CP). Average of 2nd and 3rd measurements. |
| Pulse Pressure | 3 measurements with an oscillometric digital device (OMRON HEM-705CP). Average of 2nd and 3rd measurements. |
| Hypertension | defined as systolic/diastolic blood pressure above 140/90 mmHg or intake of antihypertensive medication, given that the participant was aware of being hypertensive. |
| Control and awareness of hypertension | based on blood pressure measurements as detailed above, self-reported diagnosis of hypertension by a physician and intake of antihypertensive medication |
| Hypertension, controlled | Participant is normotensive due to hypertension treatment, and aware of having hypertension |
| Hypertension, uncontrolled | Participant is hypertensive, treated for hypertension, and aware of having hypertension |
| Hypertension, untreated | Participant is hypertensive, not treated for hypertension, and aware of having hypertension |
| Hypertension, unknown | Participant is hypertensive and unaware of having hypertension |
| **Sleep** | **Further reference: [19]** |
| Sleep, h/day | Self-reported in standardized interview |
| Problems falling asleep | Self-reported in standardized interview |
| Problems keeping asleep | Self-reported in standardized interview |
| Feeling tired and exhausted because of sleep problems | Self-reported in standardized interview |
| **Laboratory values** | **Further reference: [10, 20]** |
| Glomerular Filtration Rate | sex-specific calculation based on serum creatinine according to CKD-EPI |
| Total cholesterol, mg/dL (Serum) | Enzymatic, colorimetric CHOL Flex assay (Vista, Siemens or Cobas, Roche) |
| HDL cholesterol, mg/dL (Serum) | Enzymatic, colorimetric LDLC Flex assay (Vista, Siemens or Cobas, Roche) |
| LDL cholesterol, mg/dL (Serum) | Enzymatic, colorimetric HDLC Flex assay (Vista, Siemens or Cobas, Roche) |
| Triglycerides, mg/dL (Serum) | Enzymatic, colorimetric TRIG Flex assay (Vista, Siemens or Cobas, Roche) |
| Uric Acid, mg/dL (Serum) | Enzymatic colorimetric UA Flex assay (Vista, Siemens or Cobas, Roche) |
| Creatinine, mg/dL (Serum) | Kinetic colorimetric CREJ assay based on Jaffé method |

**Supplementary Table II:** Description of extracranial parameters including measures of diabetes, blood pressure, adipose tissue, medication intake, sociodemographics, anthropometrics, behaviour, somatic and depressive symptoms and sleep. Extracranial parameters were collected in a standardized method as part of the KORA study design. Please note that although the reference might not pertain to KORA FF4 but to one of the other KORA surveys, the described procedure was also applicable in FF4.

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**Handling of missing values:**

In the KORA sample T2w 3D-FLAIR cMRI images were not assessable in 12 participants. In 16 cases hepatic or visceral fat measurements were missing. Visible lesions with other aetiology were reported in 2 cases (1 participant with lesions suspicious for multiple sclerosis; 1 participant with not WMH-like FLAIR-hyperintense lesion in the left parietal lobe).

As missing values in the predictor variables of interest were rare, they were imputed by single imputation based on predictive mean matching using 5 cases in each match set for continuous variables and logistic regression based for dichotomous variables [4]. Variables used in the imputation model were all predictor variables of interest as well as the outcome. We used R package MICE for imputation.

In SHIP, all participants with any missing values were excluded from the analysis.

4 Morris TP, White IR, Royston P (2014) Tuning multiple imputation by predictive mean matching and local residual draws. BMC medical research methodology 14:75

**Supplementary Table III:**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **KORA sample** | |  | | **SHIP sample** | |
| **Variable** | | **N selected** | **mean beta** | **Variable** | | **N selected** | **mean beta** |
| 1 | Age (years) | 224 | 0.349 | 1 | Age | 1000 | 0.742 |
| 2 | Hypertension, controlled | 169 | 0.305 | 2 | Hypertension, controlled | 1000 | 0.616 |
| 3 | HbA1c | 148 | 0.045 | 3 | Physical activity: 2h/week | 978 | 0.238 |
| 4 | Widowed | 145 | 0.396 | 4 | Hypertension, unknown | 966 | 0.341 |
| 5 | Prediabetes | 135 | 0.148 | 5 | NSAID medication | 906 | -0.170 |
| 6 | Medication: Antiplatelet | 134 | 0.501 | 6 | separated or divorced | 877 | -0.162 |
| 7 | Hypertension, unknown | 106 | 0.726 | 7 | living alone | 800 | 0.169 |
| 8 | Medication: NSAID | 65 | 0.716 | 8 | Prediabetes | 656 | 0.039 |
| 9 | Physical activity: 2h/week | 46 | -0.097 | 9 | Alcohol consumption: 20-40 g/day | 615 | 0.050 |
| 10 | Alcohol consumption: 1-20g/day | 46 | 0.085 | 10 | Alcohol consumption: 1-20g/day | 576 | -0.031 |

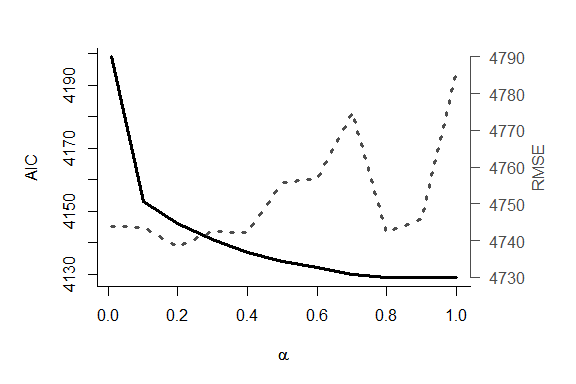
**Supplementary Table III:** Table to Figure 4. Top ten selected variables for α = 0.8 of the ZINB model based on elastic net regularization in KORA and α = 1 of the NB model in SHIP. Beta coefficient of the respective variable, averaged over all splits where the variable was selected.

**Supplementary Table IV:**

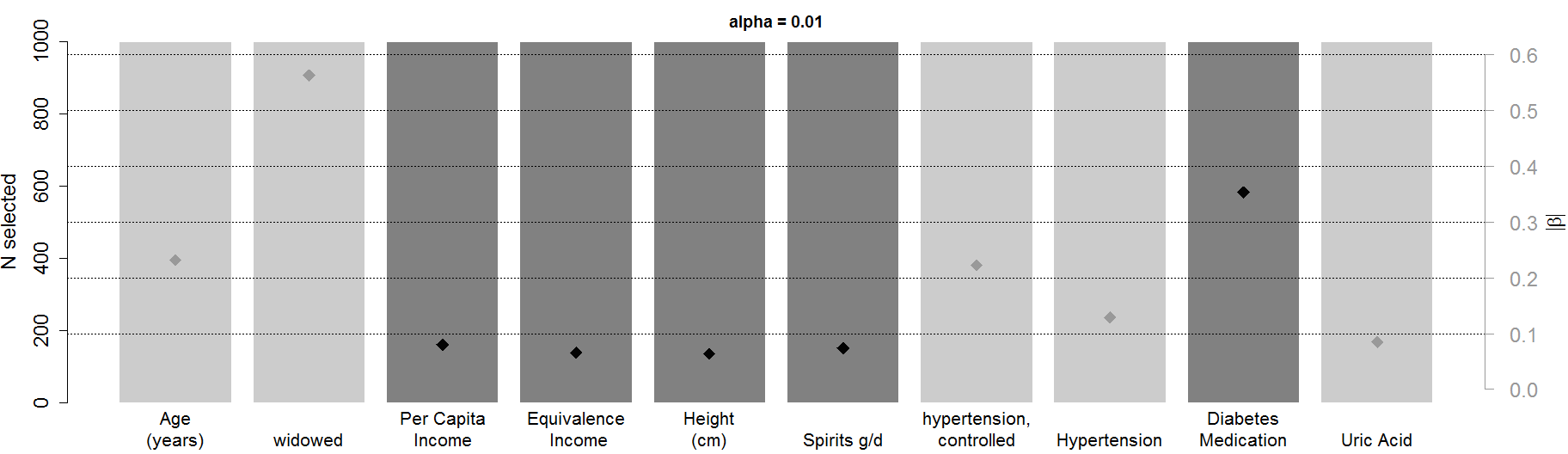
|  |  |  |
| --- | --- | --- |
| **Rank** | **Variable** | **N** |
| 1 | age | 212 |
| 2 | controlled hypertension | 198 |
| 3 | antiplatelet medication | 192 |
| 4 | alcohol consumption > 40 g/day | 182 |
| 5 | widowed | 176 |
| 6 | HbA1c | 165 |
| 7 | untreated hypertension | 154 |
| 8 | prediabetes | 143 |
| 9 | alcohol consumption | 110 |
| 10 | often problems keeping asleep | 96 |
| … | … | … |
| 23 | ICV | 18 |

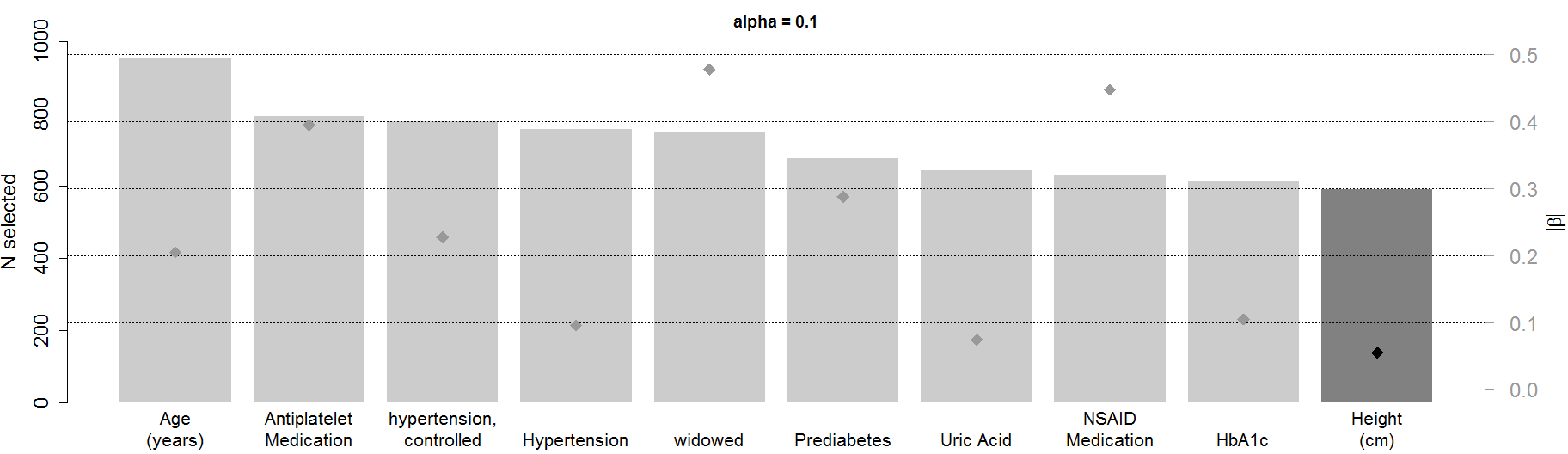
**Supplementary Table IV:** Results of the elastic net regression: Selection frequencies (N) when intracranial volume (ICV) is included as predictor variable in N=333 KORA participants.

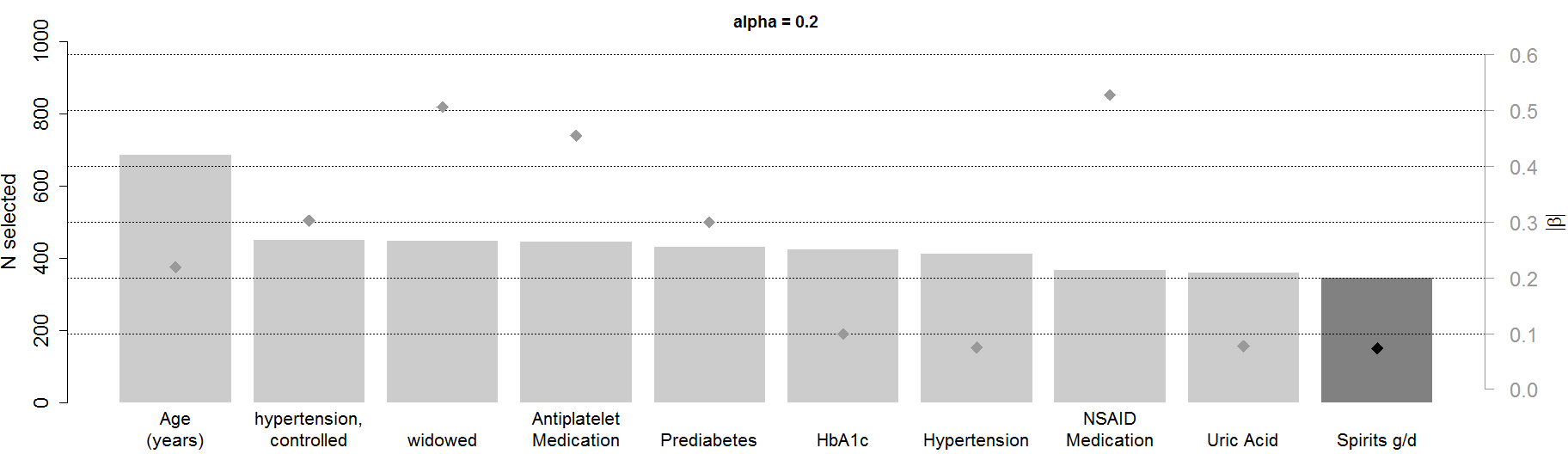
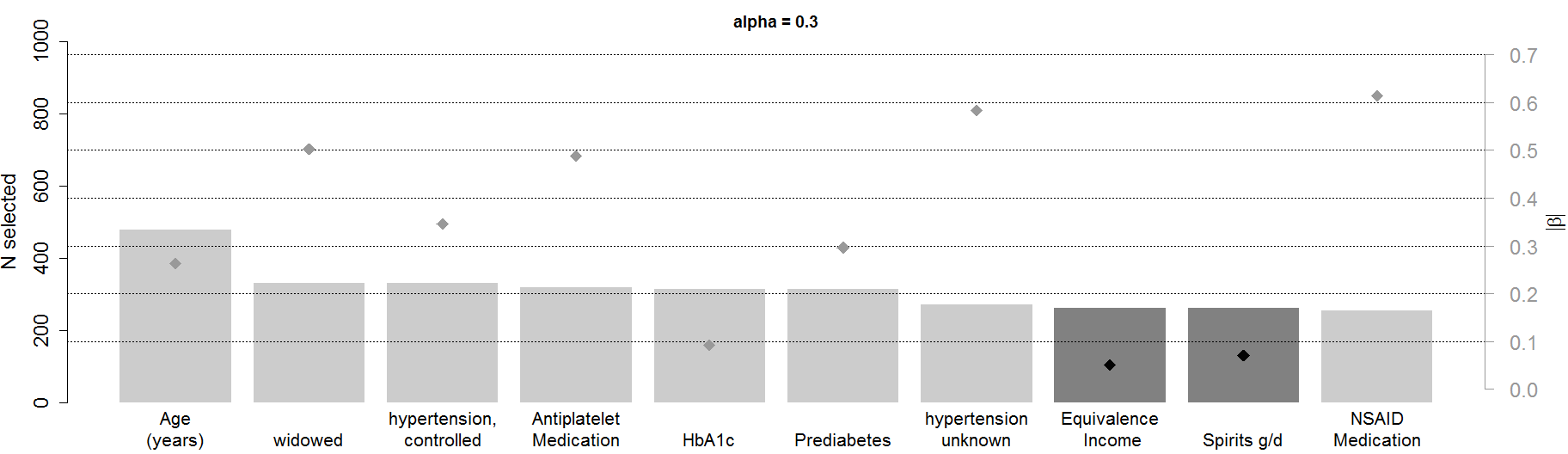
**Supplementary Figure I:**

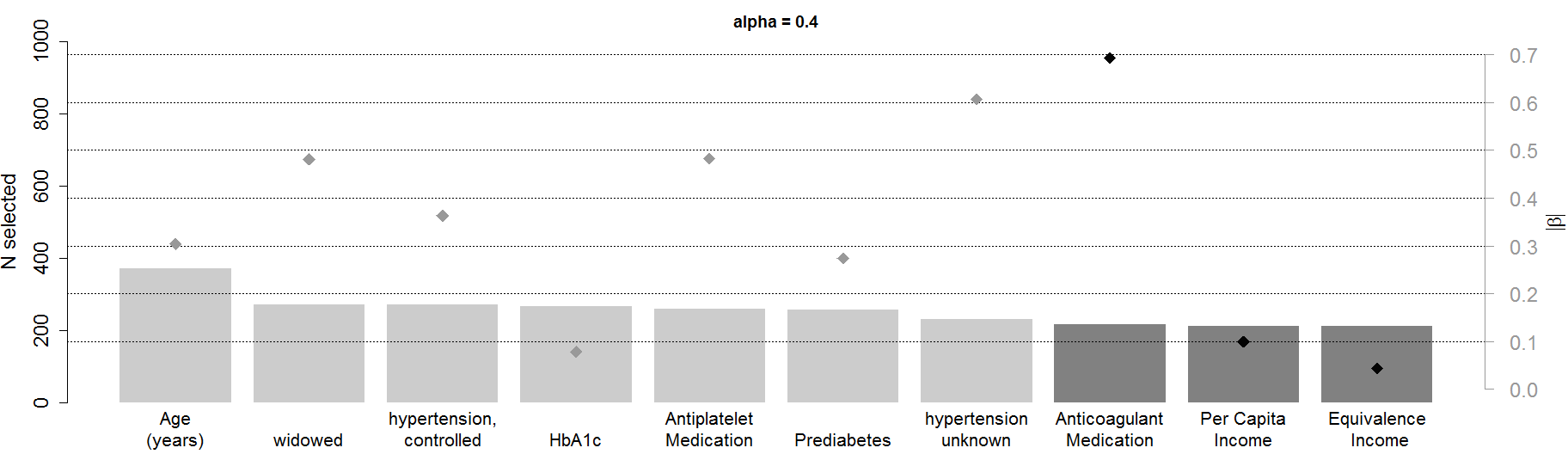
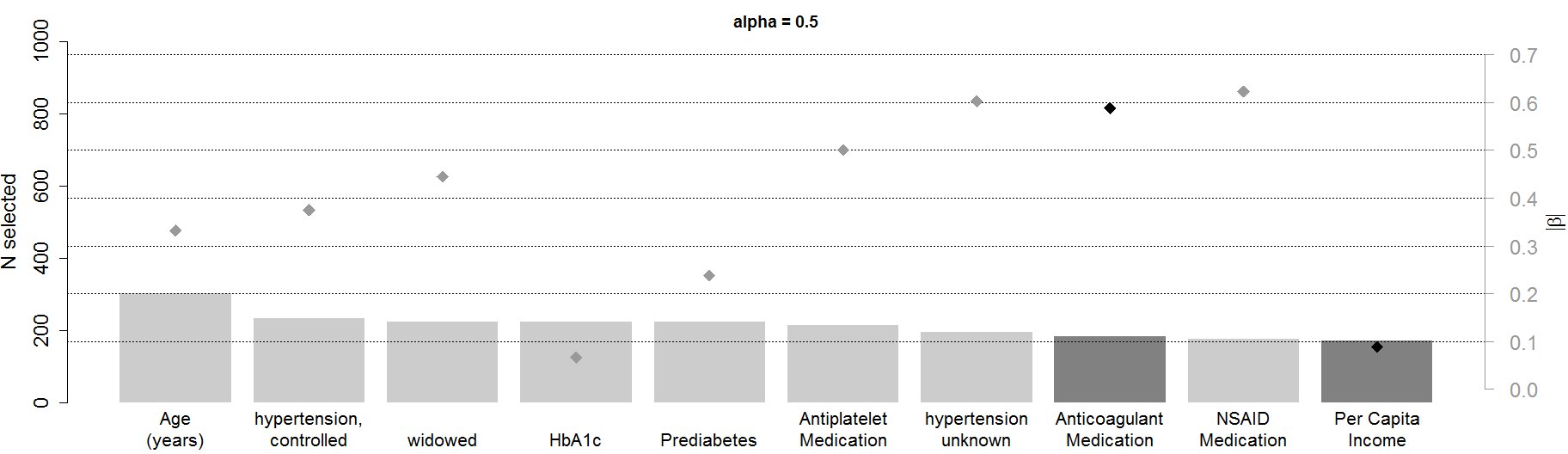


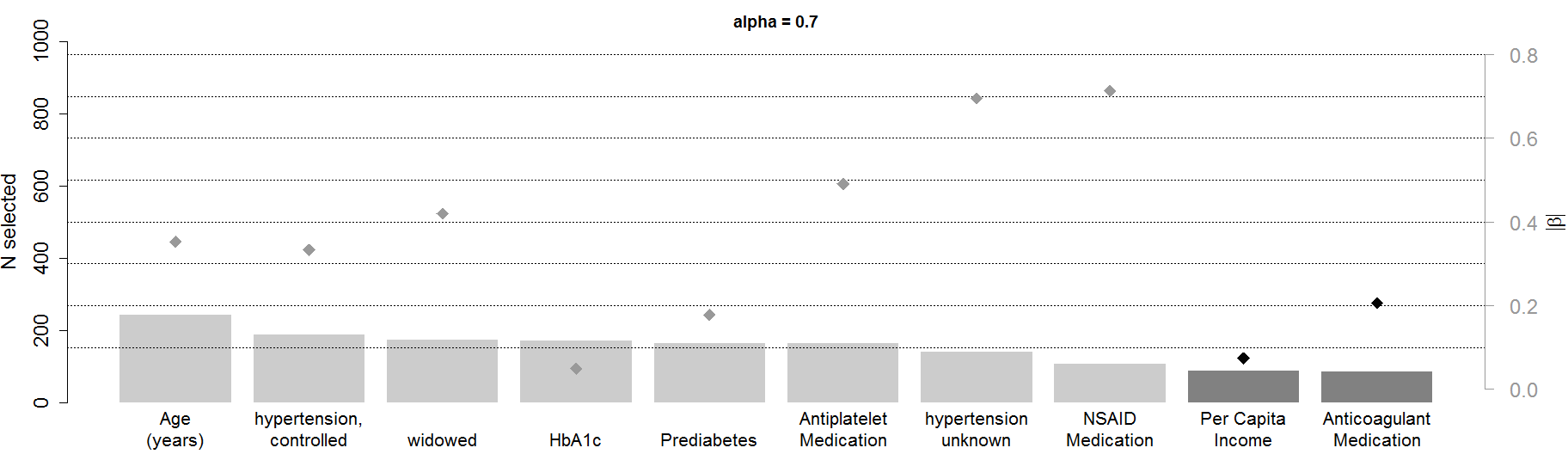
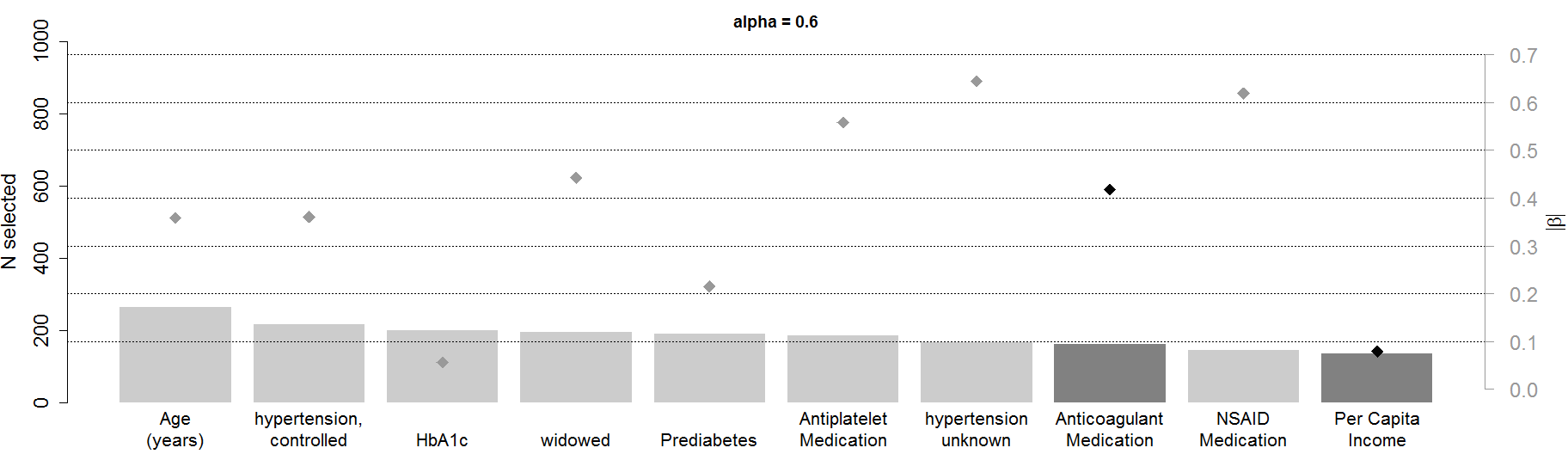
**Supplementary Figure I:** Model properties according to the grid of α-values. On the x-axis: α-value. On the left y-axis (solid line): Akaikes Information Criterion (AIC) values, averaged over 1000 splits. On the right y-axis (dotted line): Root Mean Squared Error (RMSE), averaged over 1000 splits. As both AIC and RMSE should be minimized, α=0.8 provided the best trade-off. Note that AIC of the Null Model (AIC = 1396092) and RMSE of the Null Model (RMSE = 4829) are not plotted, as they exceed the y-axes.

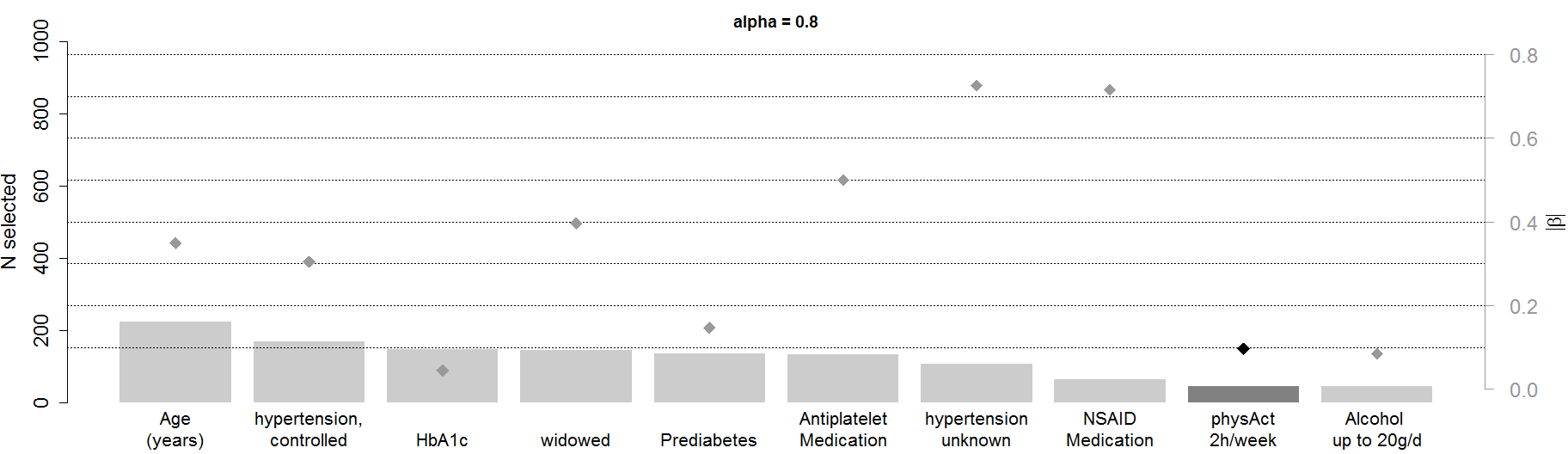
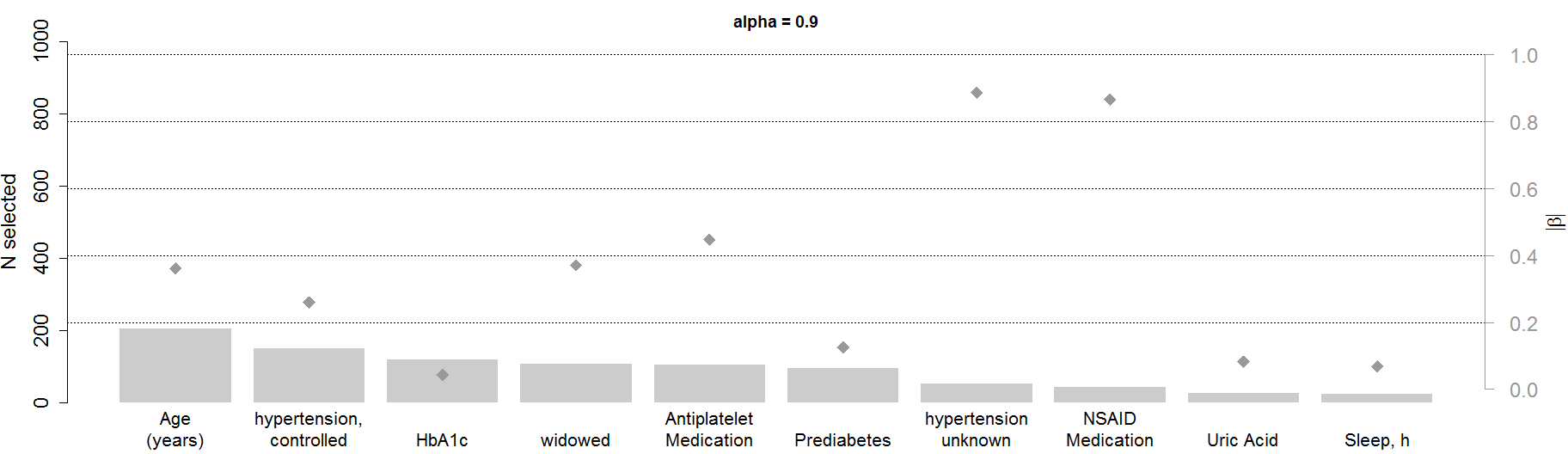
**Supplementary Figure II:**

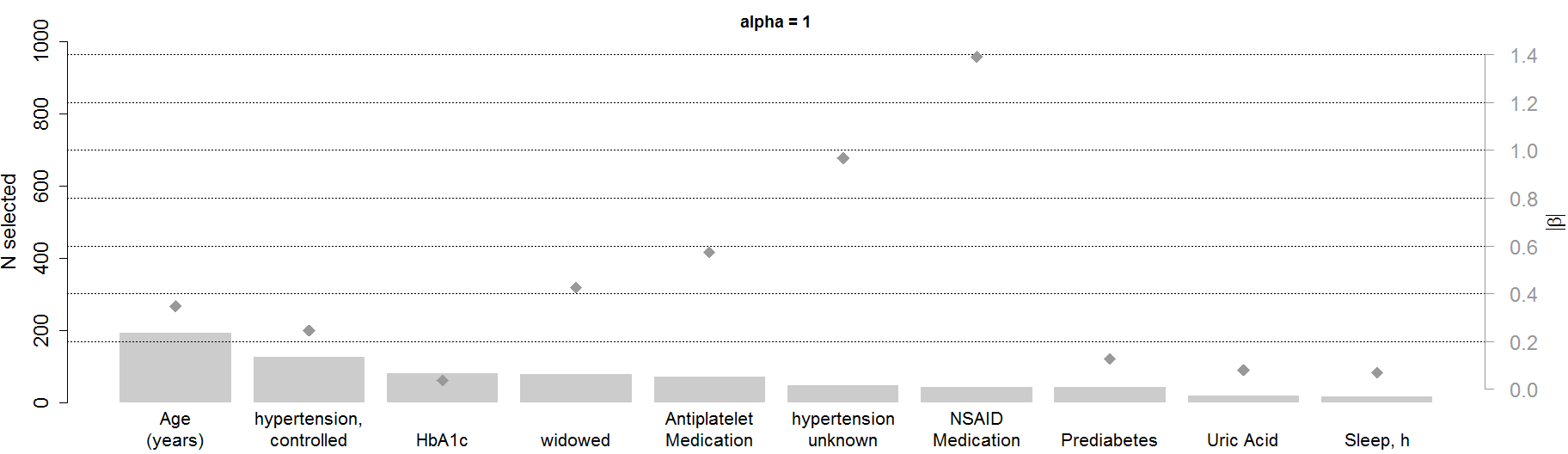






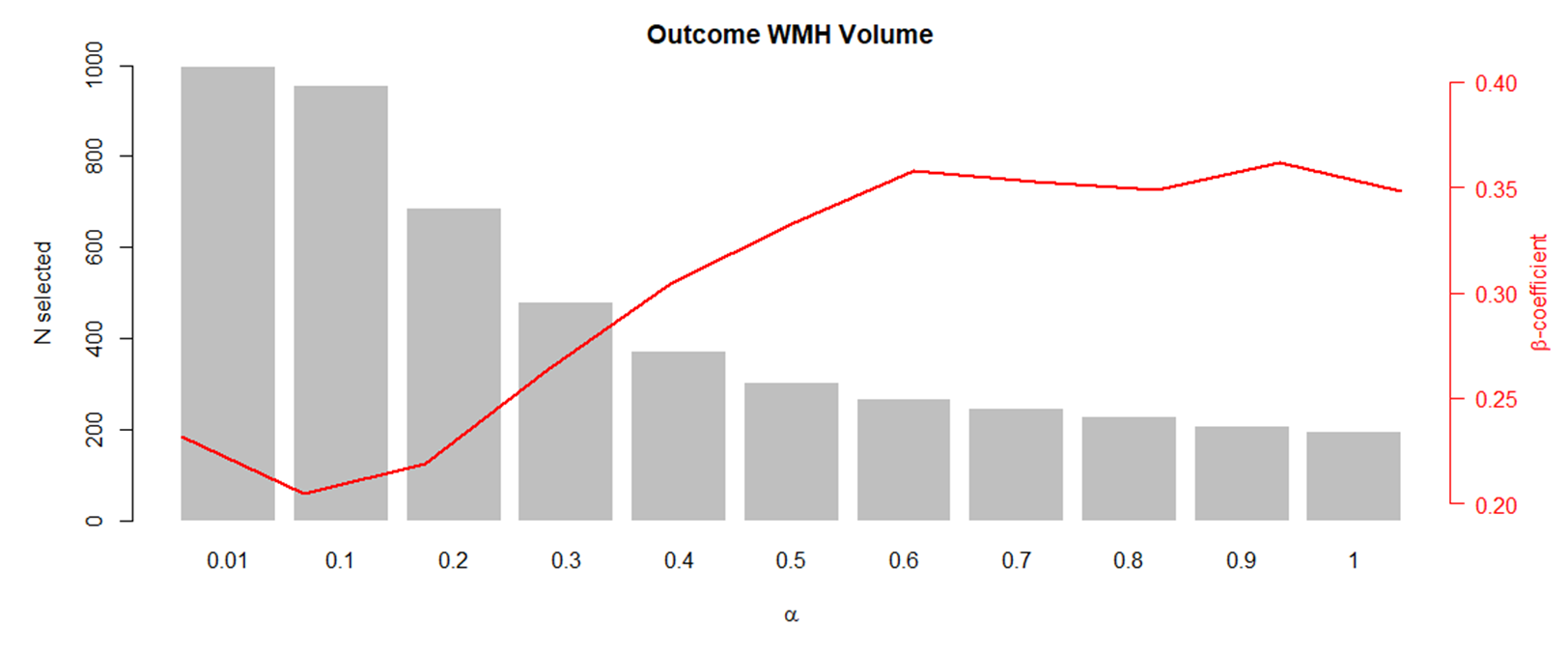




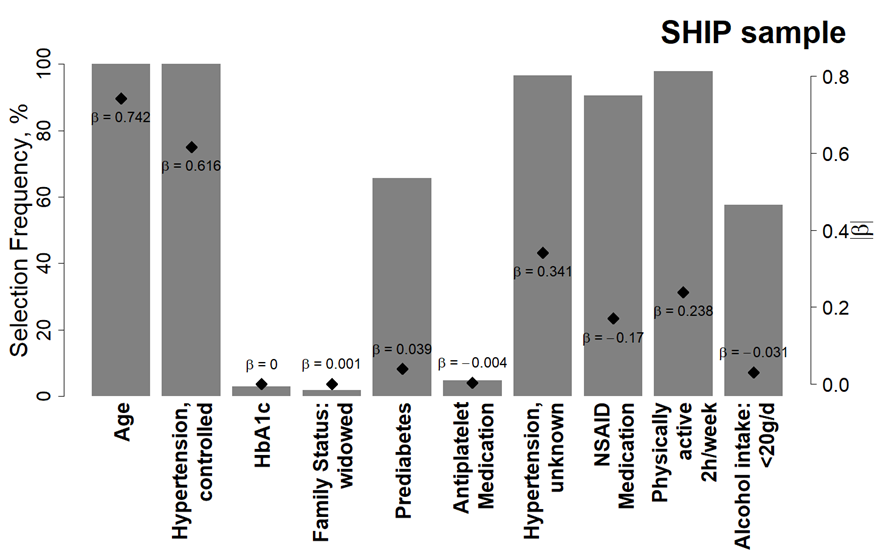


**Supplementary Figure II:** Top ten selected variables for α = 0.01 – 1.0 of the ZINB model based on elastic net regularization. On the x-axis: Predictor variable. Transparent grey bars indicate the number of data splits (of 1000) where the respective variable was selected (scale according to the left y-axis). Filled grey diamonds indicate the size of the beta coefficient of the respective variable, averaged over all splits where the variable was selected (scale according to the right y-axis). Light grey indicates a beta coefficient > 0. Dark grey indicates a beta coefficient < 0.

**Supplementary Figure III:**



**Supplementary Figure III:** Exemplary graph how number of selected splits and β-coefficients evolve on the grid of α-values. This figure shows results for the variable age. On the x-axis: α-value. On the left y-axis (grey bars): Number of splits where variable age was selected. On the right y-axis (red lines): estimated β-coefficients of variable age.

**Supplementary Figure IV:**

**Supplementary Figure IV:** Selection frequencies in the SHIP sample. Results are based on a negative binomial regression model with elastic net regularization for α=1. Shown are the top ten variables that were determined in the KORA sample ranked according to selection frequency in the KORA sample. On the x-axis: Predictor variable. Grey bars indicate the selection frequency (%) of the respective variable in 1000 data splits (scale according to the left y-axis). Diamonds indicate the size of the β coefficient of the respective variable, averaged over all splits where the variable was selected (scale according to the right y-axis).

**Supplementary Figure V:**

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**Supplementary Figure V:** On the x-axis: log-transformed predicted values from the model including the top 10 variables. On the y-axis: log-transformed true WMH volumes (>0). The correlation between log-transformed predicted and log-transformed true values as measured by Spearman‘s rho was 0.48 in SHIP and 0.41 in KORA.. For log-transformed values, the RMSE amounts to 1.61 and 1.41 for the Top 10 model in SHIP and KORA, respectively, and 2.00 and 1.60 for the Null model in SHIP and KORA, respectively.

**WMH volume:**

The median WMH volumes in both samples of this study (KORA sample: median WMH volume 997 mm3 (mean age 56 years); SHIP sample: median WMH volume 135 mm3 (mean age 54 years)) are in keeping with current literature, particularly with regard to age. Van Agtmaal et al. reported in a comparable population-based cohort study of 2,228 participants a median WMH volume of 238 mm3 (mean age 59 years) [1]. For comparison, Schneider et al. reported a noticeably higher median WMH volume of 10,320 mm3 in 1,713 participants of a community-based cohort study with a markedly higher mean age of 75 years [2]. Further studies reported median WMH volumes of 1,500 mm3 (mean age 63 years) [3], 1,700 mm3 (mean age 75 years) [4], 5,600 mm3 (mean age 72 years) [5], and 13,300 mm3 (mean age 74 years) [6].

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6 Teodorczuk A, Firbank MJ, Pantoni L et al (2010) Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-year results from the LADIS study. Psychological Medicine 40:603-610