Supplements for Investigating the impact of vascular risk factors on the progression of white matter hyperintensities

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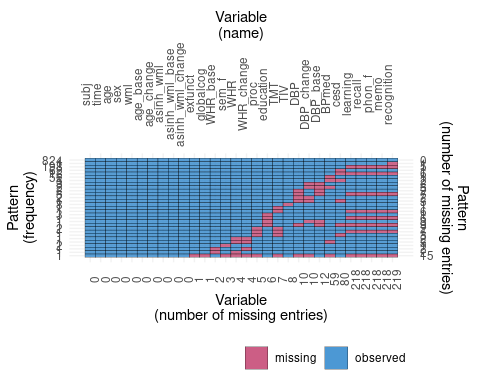
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# Missing data pattern



# Comparison to a change score model

We compared our results from the mixed effect model with the approach taken in Debette et al. ([2011](#ref-debette11)) using change in raw WMH volume or asinh-transformed WMH volume as outcome measure in a linear model (see Table 1). In the change score model with raw WMH volume as outcome, higher DBP at baseline was associated with WMH progression, this was attenuated when using asinh-transformed WMH as outcome. Comparing the model assumptions of the original model (Figure 1 with the change score models for raw and asinh-transformed WMH (Figures 2 and 3), we noticed that the assumptions are not well fulfilled for the change score model.

Table 1: Results for DBP baseline and change from linear models using change in raw WMH or asinh-transformed WMH as outcome

|  | Raw WMH: Estimate  [95 % CI] | Raw WMH: p-value | asinh WMH: Estimate  [95 % CI] | asinh WMH: p-value |
| --- | --- | --- | --- | --- |
| Age at baseline | 0.102 [0.081, 0.122] | <0.001 | 0.003 [0.002, 0.003] | <0.001 |
| Time between baseline and followup | -0.080 [-0.361, 0.201] | 0.576 | -0.002 [-0.009, 0.004] | 0.491 |
| DBP at baseline baseline | 0.056 [0.035, 0.076] | <0.001 | 0.001 [0.000, 0.001] | 0.030 |
| Change in DBP | 0.050 [0.030, 0.070] | <0.001 | 0.001 [0.001, 0.002] | <0.001 |

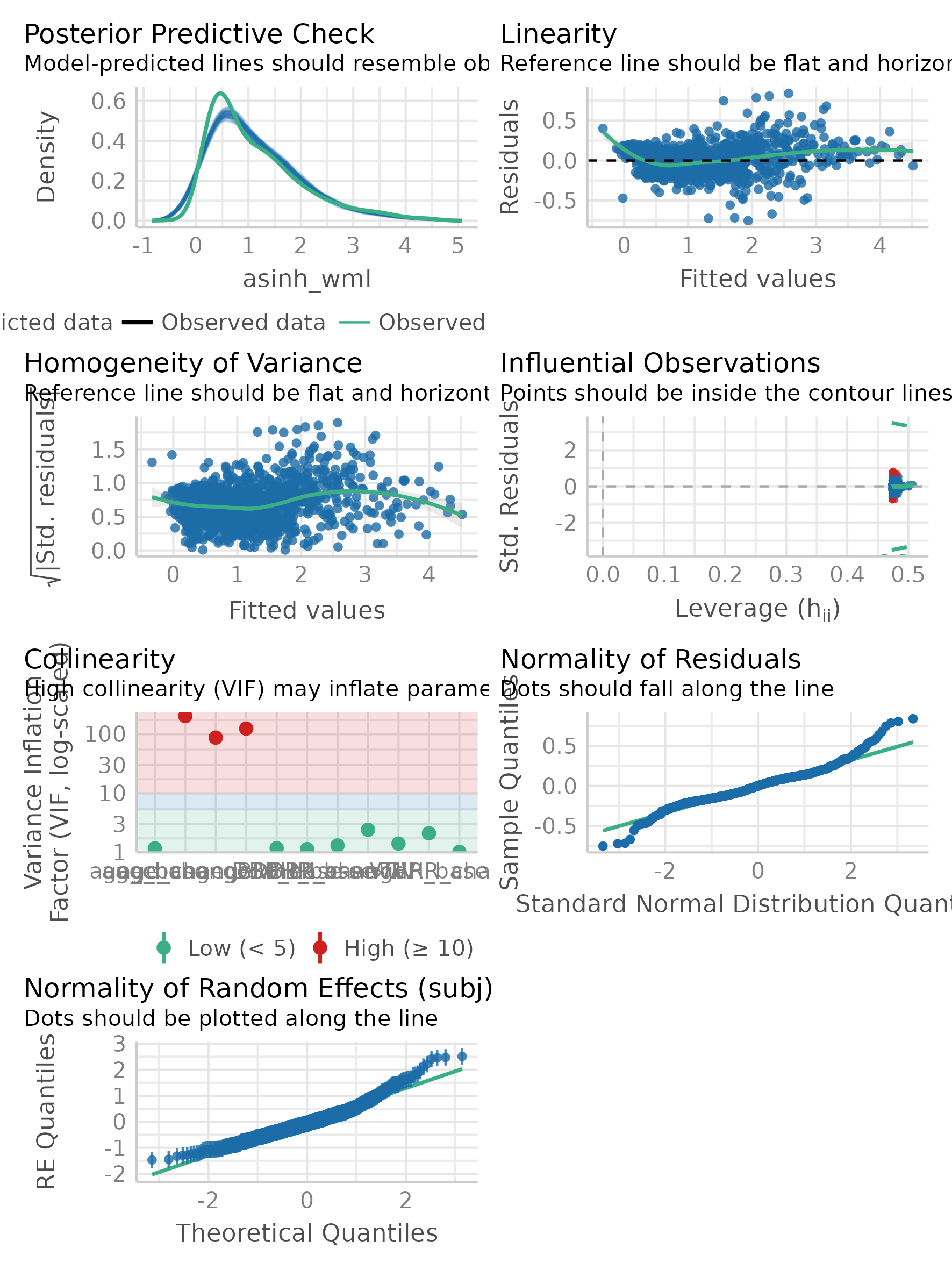


Figure 1: Assumptions of linear model for the original model M1 (from the package check\_model)

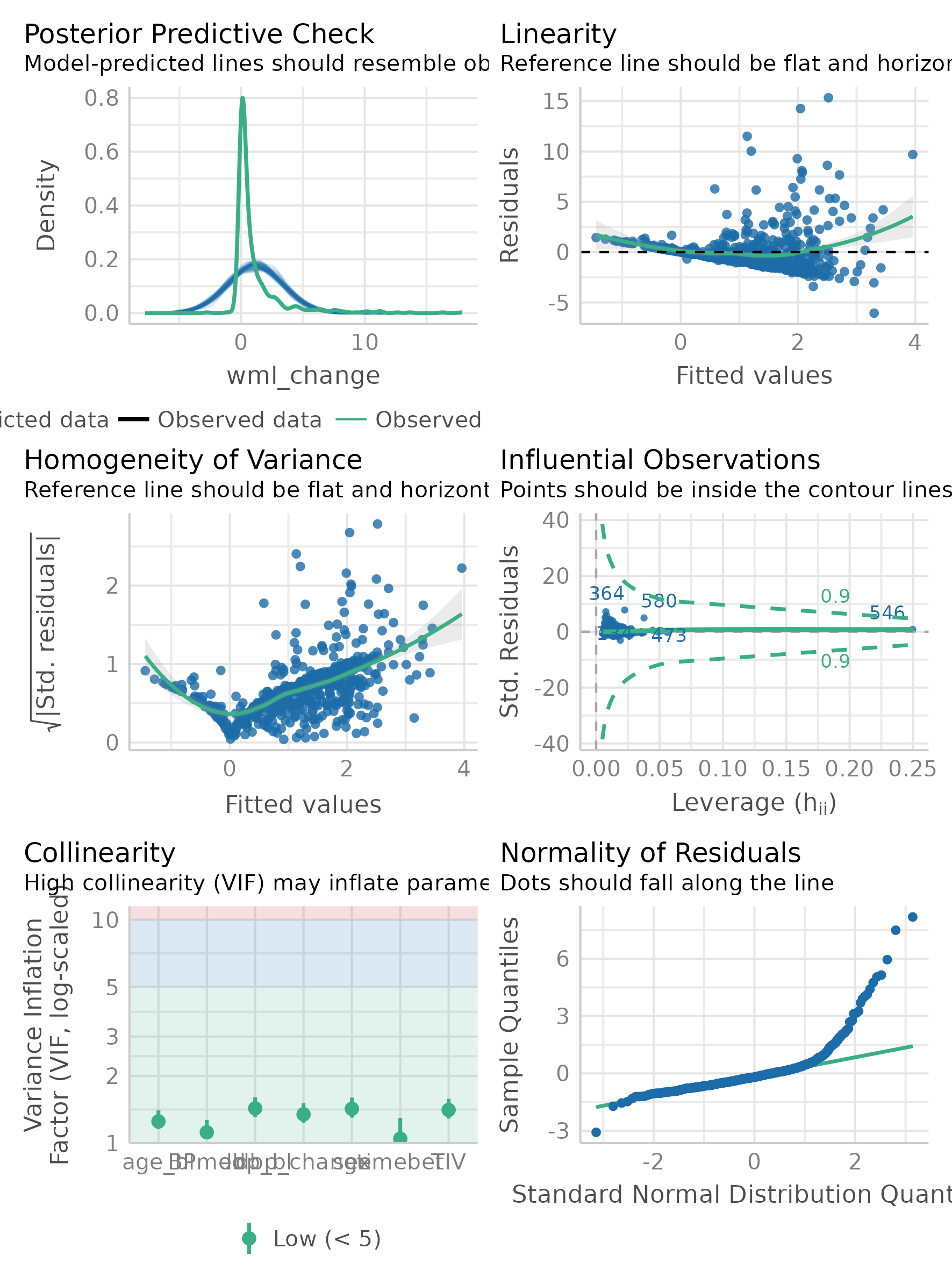


Figure 2: Assumptions of linear model for the change score model using raw WMH volume as outcome (from the package check\_model)

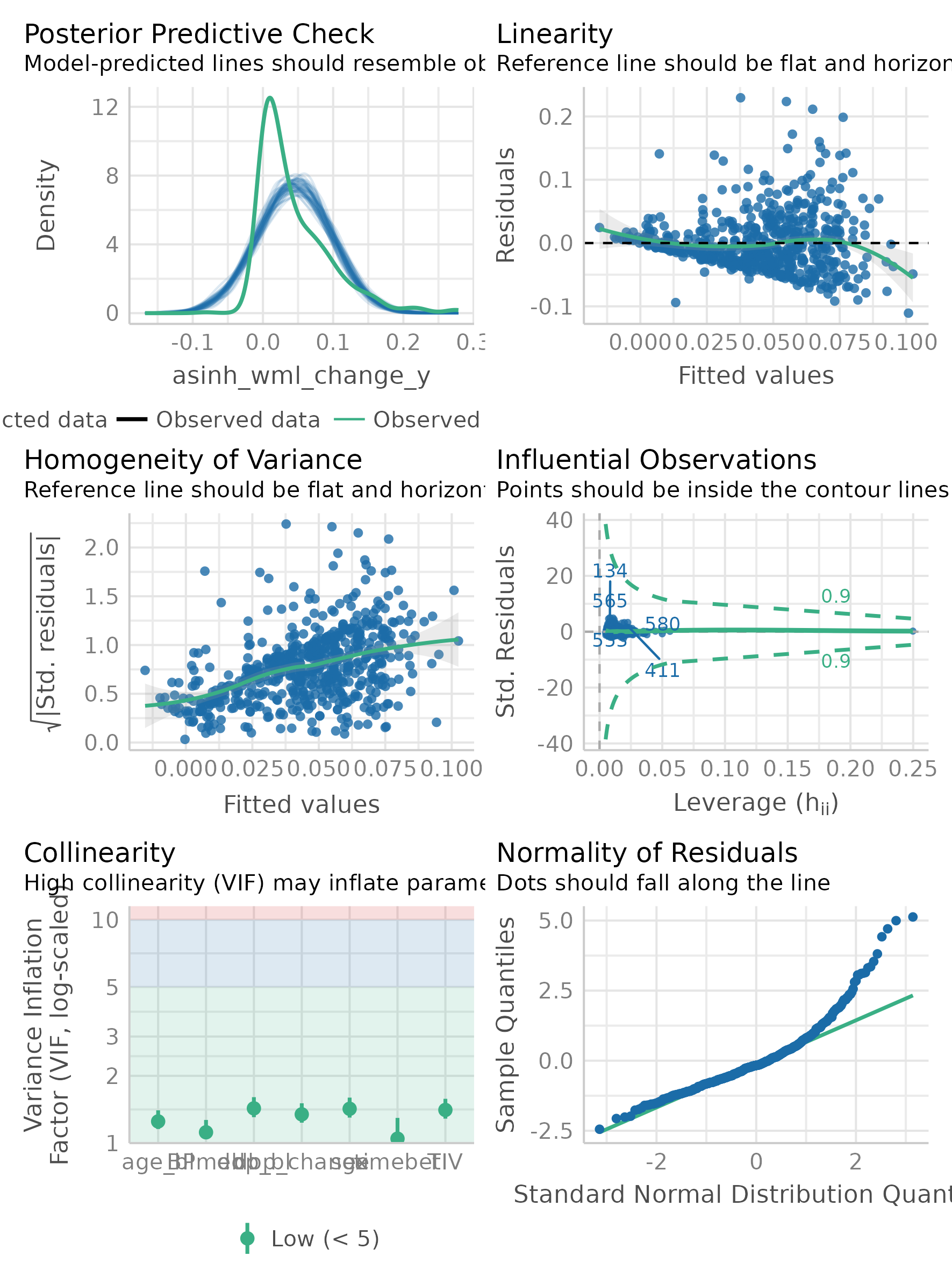


Figure 3: Assumptions of linear model for the change score model using asinh-transformed WMH volume as outcome (from the package check\_model)

# Assumptions for models M2 and M3

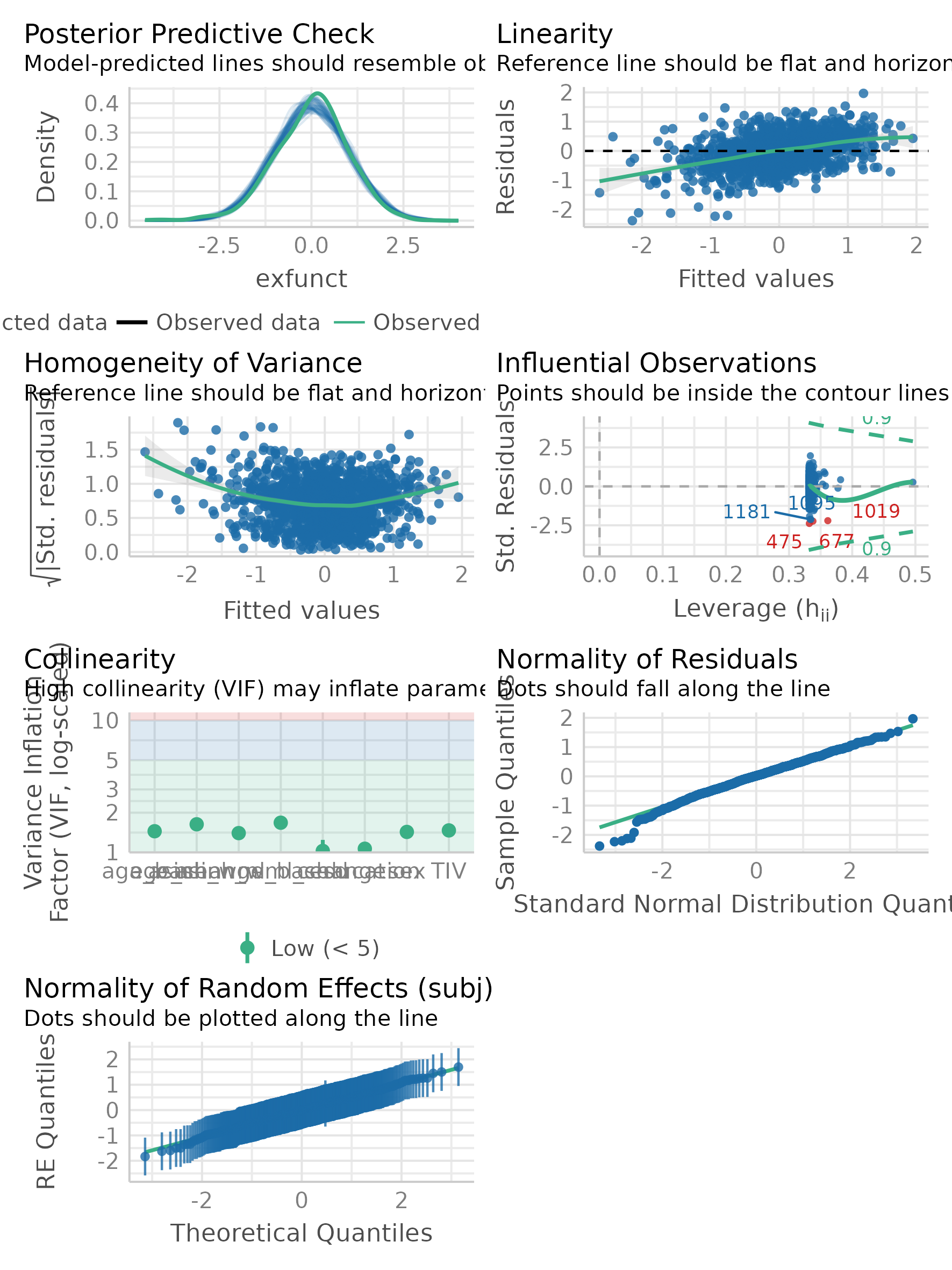


Figure 4: Assumptions of linear model for them model M2 (executive function)(from the package check\_model)

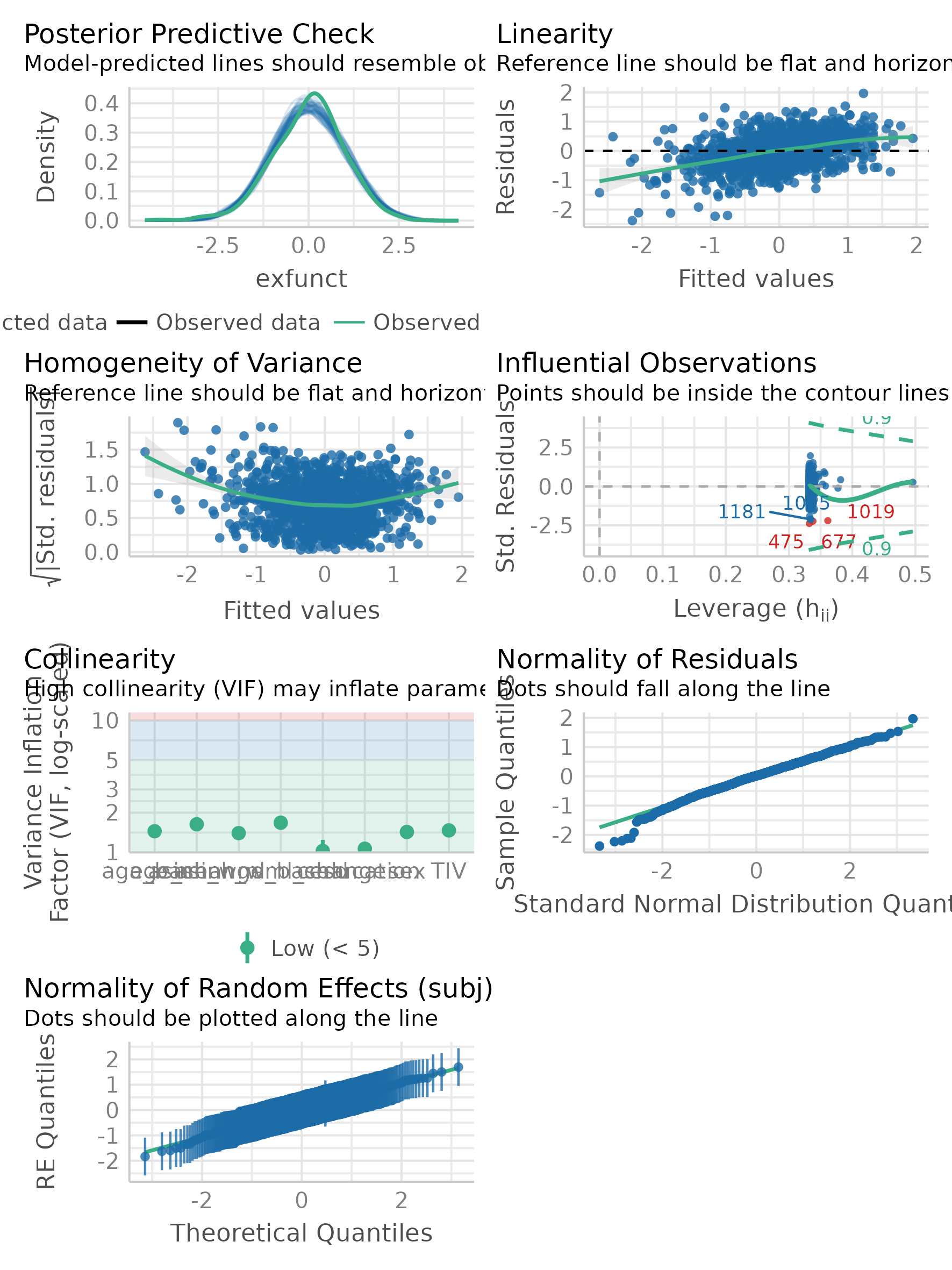


Figure 5: Assumptions of linear model for them model M3 (global cognitive function)(from the package check\_model)

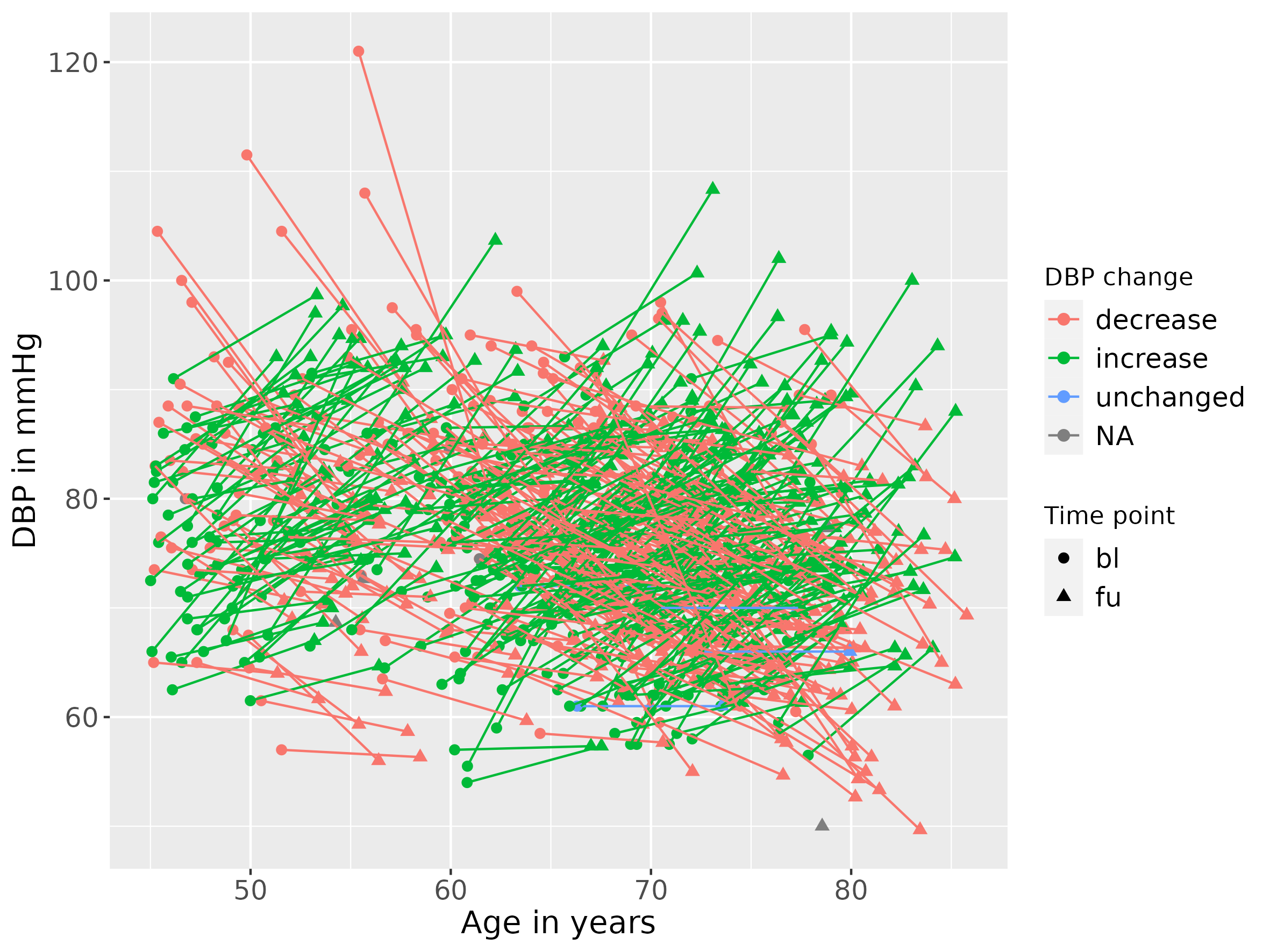


Figure 6: Age and DBP in Life-Adult. Colors indicate increase/stable/decrease in DBP over time.

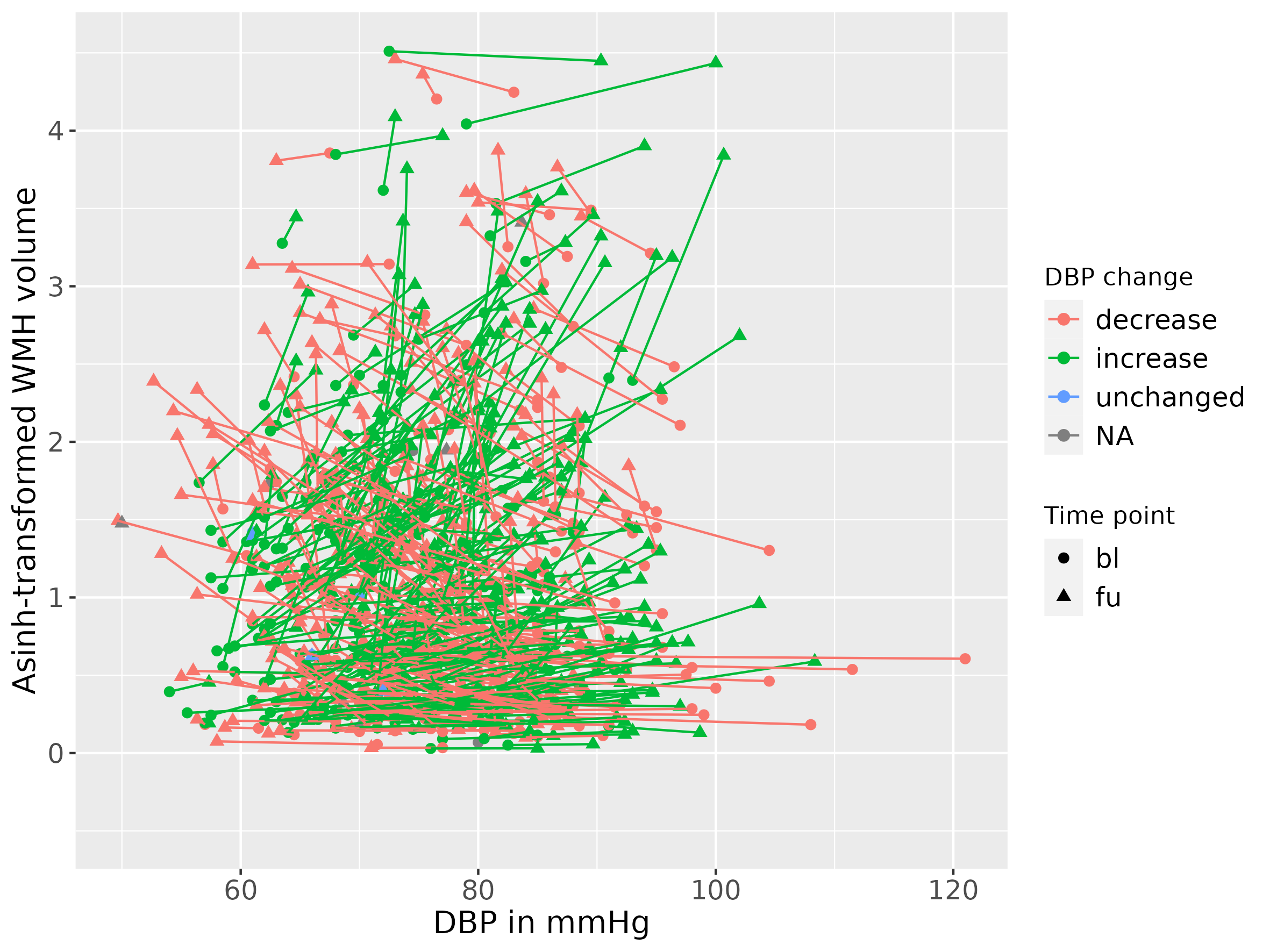


Figure 7: DBP and asinh-transformed WMH in Life-Adult. Colors indicate increase/stable/decrease in DBP over time.

# Interaction Models

Table 2: Interaction of gender and WMH progression

|  | Estimate [95 % CI] | p-value |
| --- | --- | --- |
| Age at baseline | 0.056 [0.049, 0.062] | <0.001 |
| Time between baseline and followup | 0.025 [-0.045, 0.094] | 0.486 |
| Diastolic BP at baseline | 0.012 [0.005, 0.018] | <0.001 |
| Change in diastolic BP | 0.006 [0.003, 0.009] | <0.001 |
| Waist-to-hip ratio at baseline | 0.836 [-0.134, 1.807] | 0.091 |
| Change in WHR | -0.078 [-0.693, 0.536] | 0.803 |
| Gender (males=1) | -0.281 [-0.462, -0.101] | 0.002 |
| Interaction of time and gender | 0.000 [-0.012, 0.011] | 0.936 |
| Interaction of time and DBP at baseline | 0.000 [-0.001, 0.000] | 0.616 |
| Interaction of time and WHR at baseline | 0.031 [-0.035, 0.098] | 0.356 |

#### E2aa: Gender and DBP change interaction (new exploratory analysis)

Table 3: Interaction of DBP change and gender on WMH progression

|  | Estimate [95 % CI] | p-value |
| --- | --- | --- |
| Age at baseline | 0.056 [0.049, 0.062] | <0.001 |
| Time between baseline and followup | 0.026 [-0.030, 0.083] | 0.359 |
| Diastolic BP at baseline | 0.012 [0.005, 0.018] | <0.001 |
| Change in diastolic BP | 0.008 [0.003, 0.013] | 0.002 |
| Waist-to-hip ratio at baseline | 0.843 [-0.116, 1.802] | 0.085 |
| Change in WHR | -0.074 [-0.674, 0.526] | 0.809 |
| Gender (males=1) | -0.282 [-0.459, -0.105] | 0.002 |
| Interaction of DBP change and gender | -0.003 [-0.009, 0.003] | 0.372 |
| Interaction of time and DBP at baseline | 0.000 [-0.001, 0.000] | 0.586 |

#### E2a: Gender and baseline DBP interaction on WML progression

Table 4: Interaction of DBP baseline, age and gender on WML progression

|  | Estimate [95 % CI] | p-value |
| --- | --- | --- |
| Age at baseline | 0.055 [0.049, 0.062] | <0.001 |
| Time between baseline and followup | 0.014 [-0.064, 0.091] | 0.730 |
| Diastolic BP at baseline | 0.015 [0.006, 0.025] | 0.002 |
| Change in diastolic BP | 0.006 [0.003, 0.009] | <0.001 |
| Waist-to-hip ratio at baseline | 0.837 [-0.128, 1.802] | 0.089 |
| Change in WHR | -0.092 [-0.704, 0.520] | 0.767 |
| Gender (males=1) | 0.208 [-0.768, 1.184] | 0.676 |
| Interaction of DBP and gender | -0.006 [-0.019, 0.006] | 0.318 |
| Interaction of time and gender | 0.021 [-0.046, 0.089] | 0.534 |
| Interaction of time and DBP at baseline | 0.000 [-0.001, 0.001] | 0.932 |
| Interaction of time and WHR at baseline | 0.031 [-0.035, 0.097] | 0.361 |
| Gender differences of time x DBP at baseline | 0.000 [-0.001, 0.001] | 0.519 |

#### E2c: Interaction of gender and baseline WHR on WMH progression

Table 5: Interaction of gender and baseline WHR on WMH progression

|  | Estimate [95 % CI] | p-value |
| --- | --- | --- |
| Age at baseline | 0.056 [0.049, 0.062] | <0.001 |
| Time between baseline and followup | 0.052 [-0.045, 0.148] | 0.295 |
| Diastolic BP at baseline | 0.012 [0.005, 0.018] | <0.001 |
| Change in diastolic BP | 0.006 [0.003, 0.009] | <0.001 |
| Waist-to-hip ratio at baseline | 0.705 [-0.745, 2.155] | 0.340 |
| Change in WHR | -0.118 [-0.736, 0.500] | 0.708 |
| Gender (males=1) | -0.493 [-2.254, 1.268] | 0.583 |
| Interaction of WHR and gender | 0.228 [-1.662, 2.119] | 0.813 |
| Interaction of time and gender | -0.049 [-0.171, 0.073] | 0.433 |
| Interaction of time and DBP at baseline | 0.000 [-0.001, 0.000] | 0.618 |
| Interaction of time and WHR at baseline | 0.000 [-0.102, 0.102] | 0.994 |
| Gender differences of time x WHR at baseline | 0.052 [-0.079, 0.184] | 0.436 |

#### E3a: Interaction of gender and WMH progression on executive cognitive function

Table 6: Interaction of WMH progression and gender on executive function

|  | Estimate [95 % CI] | p-value |
| --- | --- | --- |
| Age at baseline | -0.017 [-0.026, -0.008] | <0.001 |
| Time between baseline and followup | -0.047 [-0.061, -0.033] | <0.001 |
| Asinh-transformed WMH volume baseline | -0.017 [-0.116, 0.082] | 0.735 |
| Change in Asinh-transformed WMH volume | -0.097 [-0.370, 0.175] | 0.483 |
| Gender (males=1) | -0.229 [-0.392, -0.066] | 0.006 |
| Interaction of gender and Asinh-transformed WMH change | -0.104 [-0.417, 0.209] | 0.513 |

Table 7: Interaction of gender and WMH progression on general cognitive function

|  | Estimate [95 % CI] | p-value |
| --- | --- | --- |
| Age at baseline | -0.045 [-0.053, -0.037] | <0.001 |
| Time between baseline and followup | -0.040 [-0.052, -0.028] | <0.001 |
| Asinh-transformed WMH volume baseline | -0.044 [-0.135, 0.046] | 0.337 |
| Change in Asinh-transformed WMH volume | -0.231 [-0.463, 0.002] | 0.052 |
| Gender (males=1) | -0.273 [-0.422, -0.125] | <0.001 |
| Interaction of gender and Asinh-transformed WMH change | -0.160 [-0.427, 0.107] | 0.239 |

# References

Debette, S., S. Seshadri, A. Beiser, R. Au, J. J. Himali, C. Palumbo, P. A. Wolf, and C. DeCarli. 2011. “Midlife Vascular Risk Factor Exposure Accelerates Structural Brain Aging and Cognitive Decline.” *Neurology* 77 (5): 461–68. <https://doi.org/10.1212/WNL.0b013e318227b227>.