nature medicine

Article

https://doi.org/10.1038/s41591-023-02476-4

Cerebrospinal fluid proteomics define the natural history of autosomal dominant Alzheimer's disease

In the format provided by the authors and unedited

Category 1 – *Aβ plaque/matrisome*: this category is defined by the Aβ42/40 ratio—a recognized marker of brain amyloid deposition[1]—and two proteins that map to the M42 matrisome brain module, SPON1 and SMOC1.

Category 2 – *Synapse Changes, Glycolytic Metabolism, Stress Response*: these categories are again derived from brain co-expression, where a majority of the proteins fall into either the M1 synapse/neuron, M4 synapse/neuron, M7 MAPK/metabolism, M25 sugar metabolism, or M14 protein folding and M24 ubiquitination modules. We interpret the M14 protein folding module to reflect a stress response. We also interpret the early elevation in PGRN levels to reflect a stress response, although PRGN is not measured in our brain proteomic studies and therefore does not map to a brain module. GOT1 maps to the ubiquitination module. Because GOT1 acts as a scavenger of excess glutamate in the brain and is involved in redox metabolism and the regulation of hydrogen sulfide production important for neuroprotection[2-4], we interpret this protein to be involved in stress response as well. As we note at the beginning of the results section, other protein and non-protein biomarkers measured in DIAN are incorporated into the analysis to serve as benchmarks for the proteomic measures. pTau217, pTau181, and PIB-PET happen to fall into Category 2 based on the time of change, although we are not able to use brain co-expression to map pTau changes directly to the ontologies that describe Category 2 because pTau was not measured in our brain proteomics studies. PIB-PET reflects Aβ plaques, but is a less sensitive measure than the Aβ42/40 ratio for plaques[5,6], and therefore ends up falling into Category 2 based on time of change.

Category 3 – *White Matter, Axonal Integrity*: this category is bounded by t-Tau and NEFL. NEFL consistently maps in our studies to the oligo/myelination module in brain, as it likely reflects loss of myelinated axonal integrity along with pTau205[7,8]. The other markers do not have a cognate brain module because they were not measured in our brain proteomic studies. CSF t-Tau, along with the pTau measurements, was measured as described by Barthelemy *et al*.[9], and was not mapped to MAPT in brain because the brain MAPT mass spec protein measurement is strongly confounded by truncated tau isoforms and does not show a strong increase in AD. This stands in contrast to the MTBR region itself, which shows a strong increase in AD brain by mass spec, but the MTBR is not represented as a canonical protein in the protein search database. Tau binds to microtubules and is considered to be an axonal marker[10], which is why it is included in this category. The cognitive composite measure is another benchmark biomarker in DIAN that falls into this category based on its relative time of change. MDH1 and PKM2 are both involved in glycolysis, although PKM2 does not map to a brain co-expression module. One could plausibly extend Category 2 to include PKM2, which would consequently encompass t-Tau as well into Category 2. However, we decided instead to use t-Tau as the cutpoint for Category 3 based on its relationship to axonal biology.

Category 4 – *Immune Activation, Metabolic Failure, Cognitive Decline*: this category is where we first see proteins associated with the M21 MHC/Immune brain module, SPP1 and CHI3L1. SPP1, or osteopontin, is a multifunctional protein that has been associated with T-lymphocyte and microglial activation[11,12], whereas CHI3L1 is associated with astrocyte activation in brain and is considered to reflect an inflammatory response[13,14]. The metabolic failure term comes from the decrease in the FDG-PET signal. PPIA maps to the M25 sugar metabolism module and may also reflect this metabolic change. The cognitive decline term comes from the decrease in the cognitive composite measure at the same time as the inflammatory changes and change in FDG-PET signal.

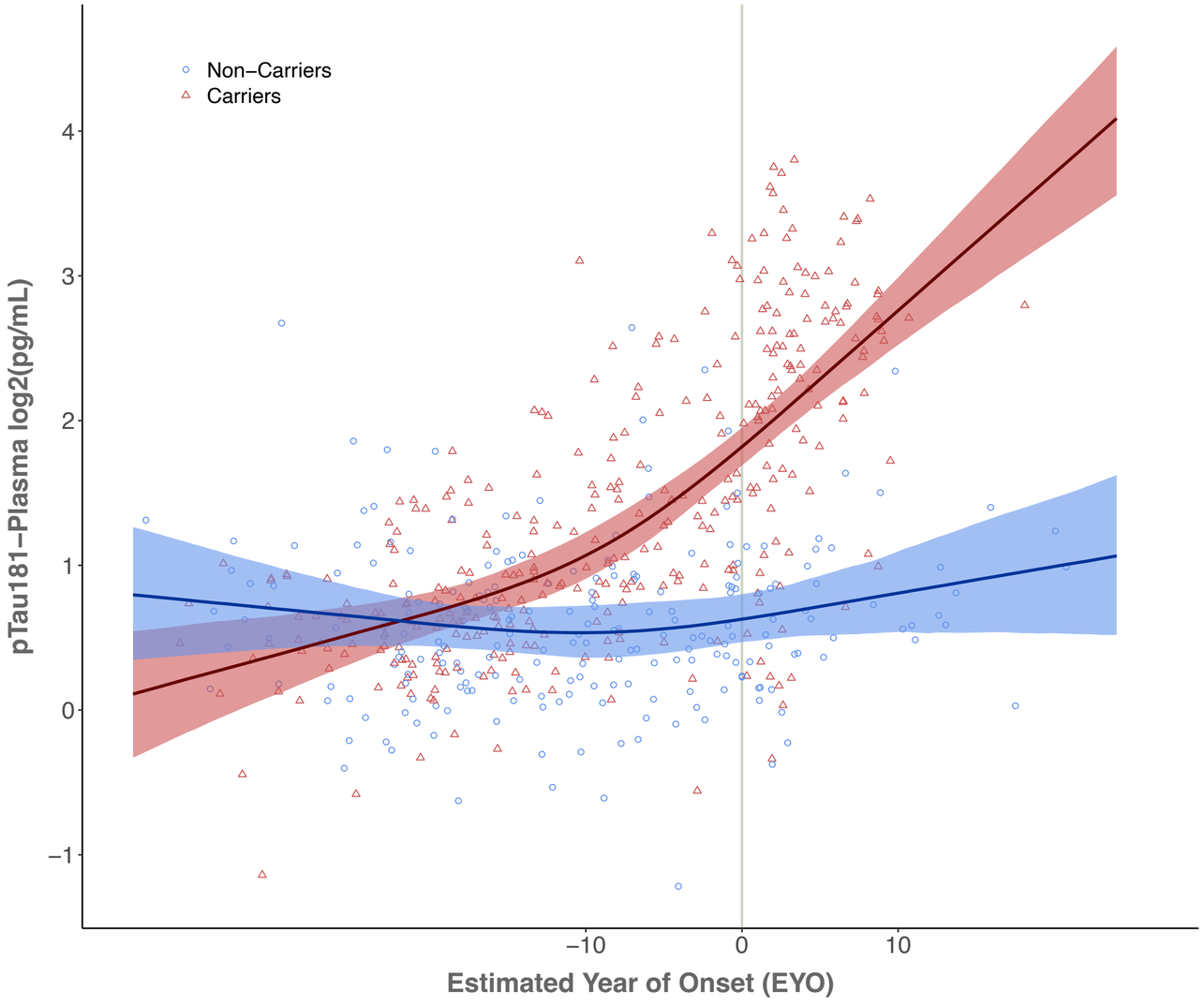
Category 5 – *Cortical Atrophy, Synaptic/Neuronal Loss, Glycolytic Metabolism, Functional Decline*: the cortical atrophy term comes from the decrease in precuneus thickness in this

category of changes. The synaptic/neuronal loss term comes from declines in SCG2 (https://www.uniprot.org/uniprotkb/P13521/entry) and VGF (https://www.uniprot.org/uniprotkb/O15240/entry), two well-known neurosecretory proteins, the neuropentraxin proteins NPTX2 and NPTXR that map to synapse/neuron and post-synaptic density modules in brain, and THY1. THY1 maps to the M1 Synapse/Neuron brain module. This conceptually makes sense, as THY1 is strongly expressed in brain (https://www.proteinatlas.org/ENSG00000154096-THY1/tissue) and is also used as a neuron-specific promoter in many transgenic mouse models. The glycolytic metabolism term comes from ENO2, PARK7, and GAPDH that map to the MAPK/metabolism module in brain. L-lactate dehydrogenase C chain (LDHC) could also be considered in this term, although it maps to the M8 protein transport brain module. The term "functional decline" comes from the observation that changes in this category coincide with onset and progression of clinical symptoms as reflected by increase in the Clinical Dementia Rating (CDR). This is shown in the Extended Data plot for CDR. We were not able to include the MMSE and CDR traits in the heatmap because they are ordinal, rather than continuous, traits, and could not be modeled in the same fashion as the other continuous measures.

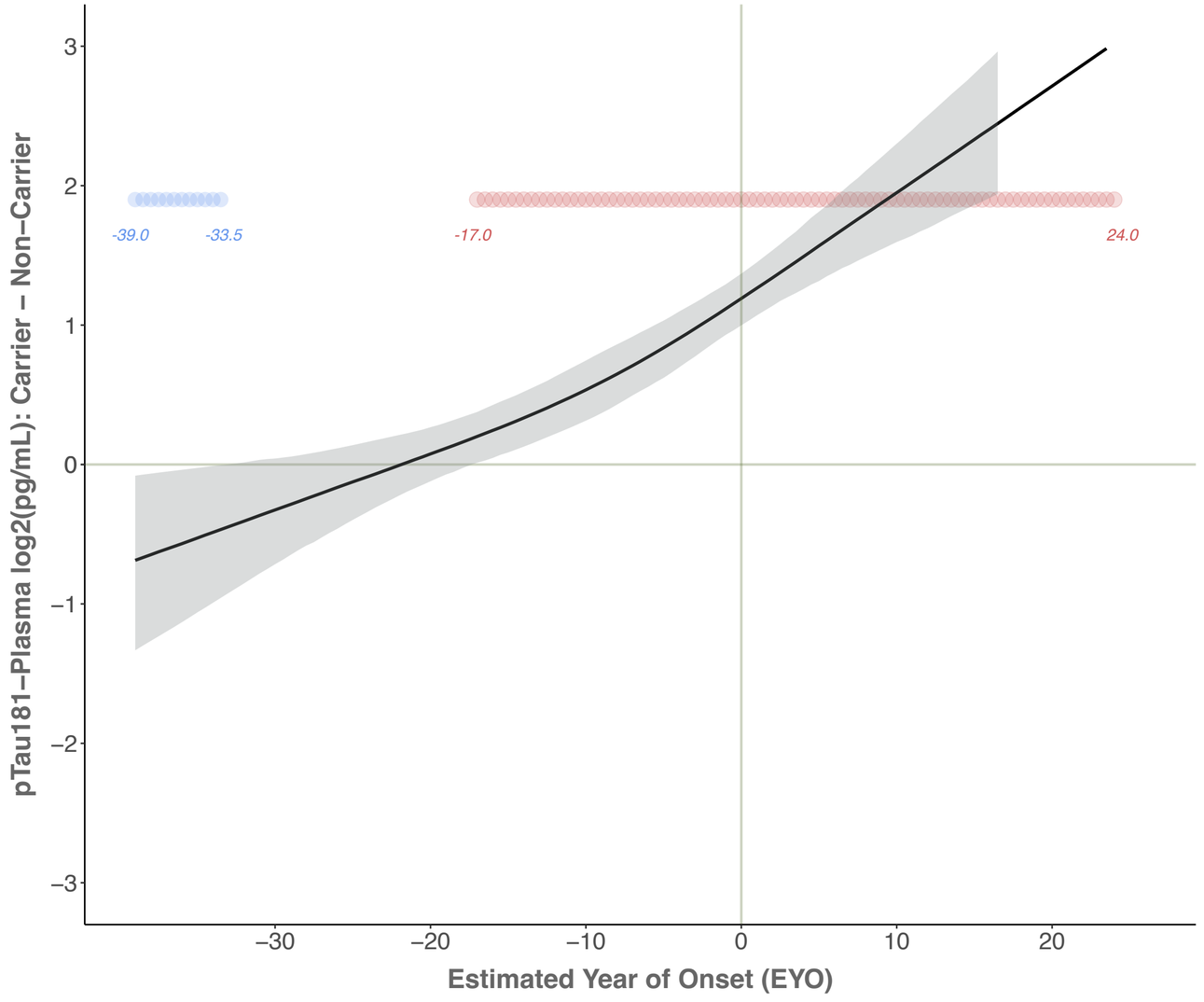
References

1. Janelidze, S.*, et al.* CSF Abeta42/Abeta40 and Abeta42/Abeta38 ratios: better diagnostic markers of Alzheimer disease. *Ann Clin Transl Neurol* **3**, 154-165 (2016).
2. Chen, W.L.*, et al.* Neuroprotective effects of hydrogen sulfide and the underlying signaling pathways. *Rev Neurosci* **26**, 129-142 (2015).
3. Dopico-Lopez, A.*, et al.* Inhibition of endogenous blood glutamate oxaloacetate transaminase enhances the ischemic damage. *Transl Res* **230**, 68-81 (2021).
4. Kremer, D.M.*, et al.* GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis. *Nat Commun* **12**, 4860 (2021).
5. Palmqvist, S., Mattsson, N., Hansson, O. & Alzheimer's Disease Neuroimaging, I. Cerebrospinal fluid analysis detects cerebral amyloid-beta accumulation earlier than positron emission tomography. *Brain* **139**, 1226-1236 (2016).
6. Palmqvist, S.*, et al.* Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. *Neurology* **85**, 1240-1249 (2015).
7. Schultz, S.A.*, et al.* Serum neurofilament light chain levels are associated with white matter integrity in autosomal dominant Alzheimer's disease. *Neurobiol Dis* **142**, 104960 (2020).
8. Strain, J.F.*, et al.* CSF Tau phosphorylation at Thr205 is associated with loss of white matter integrity in autosomal dominant Alzheimer disease. *Neurobiol Dis* **168**, 105714 (2022).
9. Barthelemy, N.R.*, et al.* A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat Med* **26**, 398-407 (2020).
10. Higuchi, M., Lee, V.M. & Trojanowski, J.Q. Tau and axonopathy in neurodegenerative disorders. *Neuromolecular Med* **2**, 131-150 (2002).
11. Cantor, H. & Shinohara, M.L. Regulation of T-helper-cell lineage development by osteopontin: the inside story. *Nature reviews. Immunology* **9**, 137-141 (2009).
12. Rosmus, D.D., Lange, C., Ludwig, F., Ajami, B. & Wieghofer, P. The Role of Osteopontin in Microglia Biology: Current Concepts and Future Perspectives. *Biomedicines* **10**(2022).
13. Connolly, K.*, et al.* Potential role of chitinase-3-like protein 1 (CHI3L1/YKL-40) in neurodegeneration and Alzheimer's disease. *Alzheimers Dement* (2022).
14. Craig-Schapiro, R.*, et al.* YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. *Biol Psychiatry* **68**, 903-912 (2010).

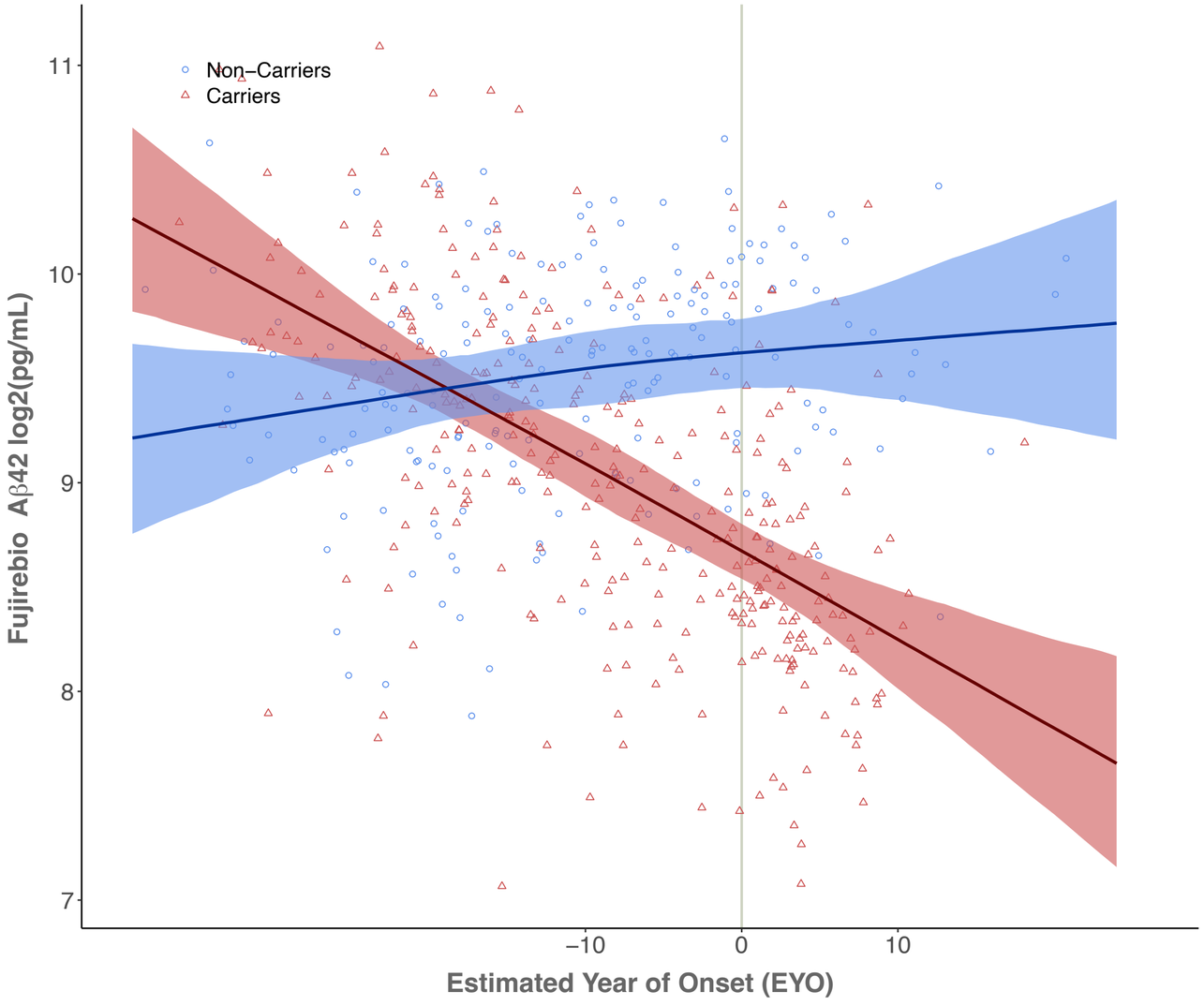
pTau181–Plasma level in mutation carriers and non–carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



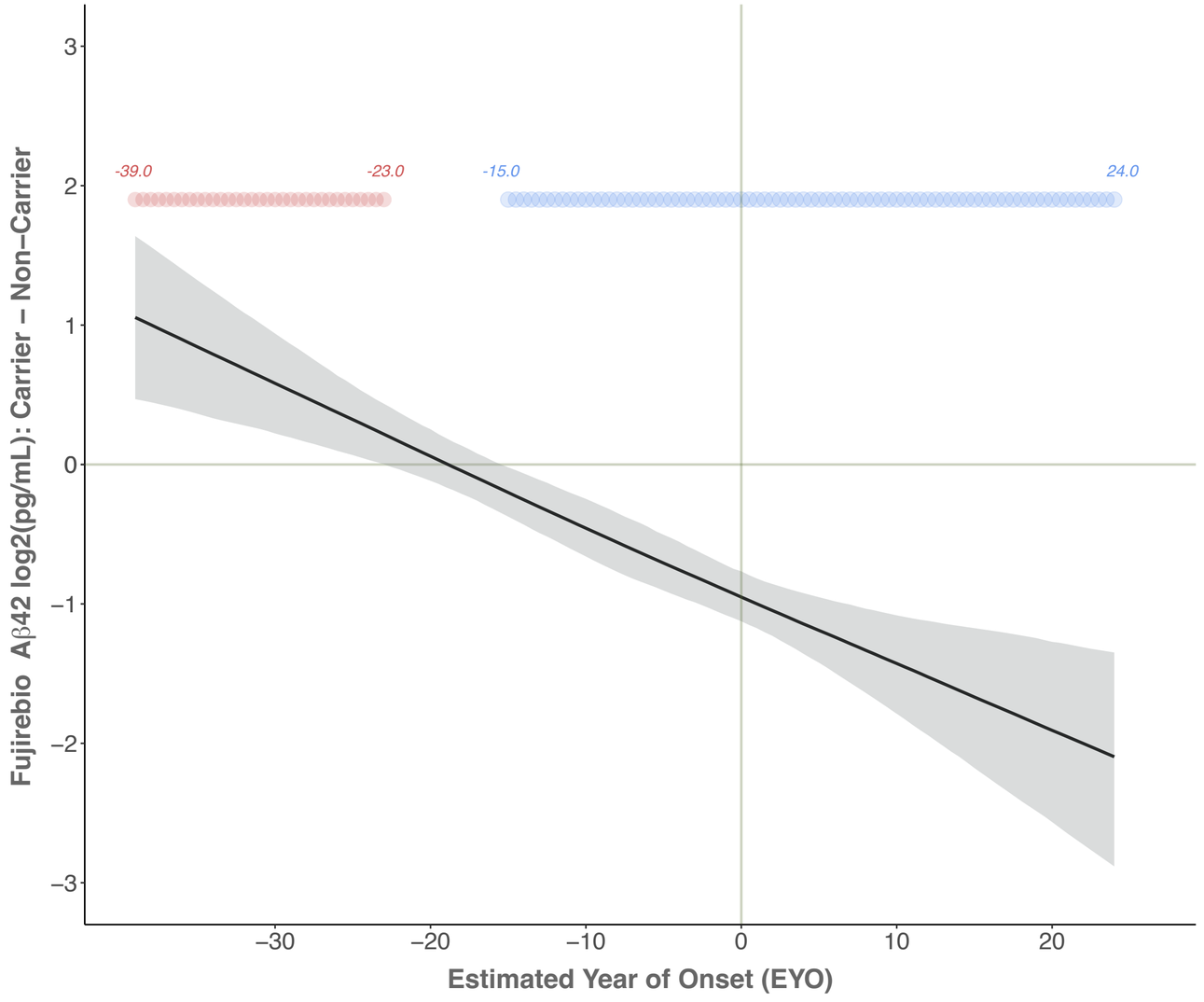
pTau181–Plasma level difference in mutation carriers and non–carriers with 99% confidence interval.



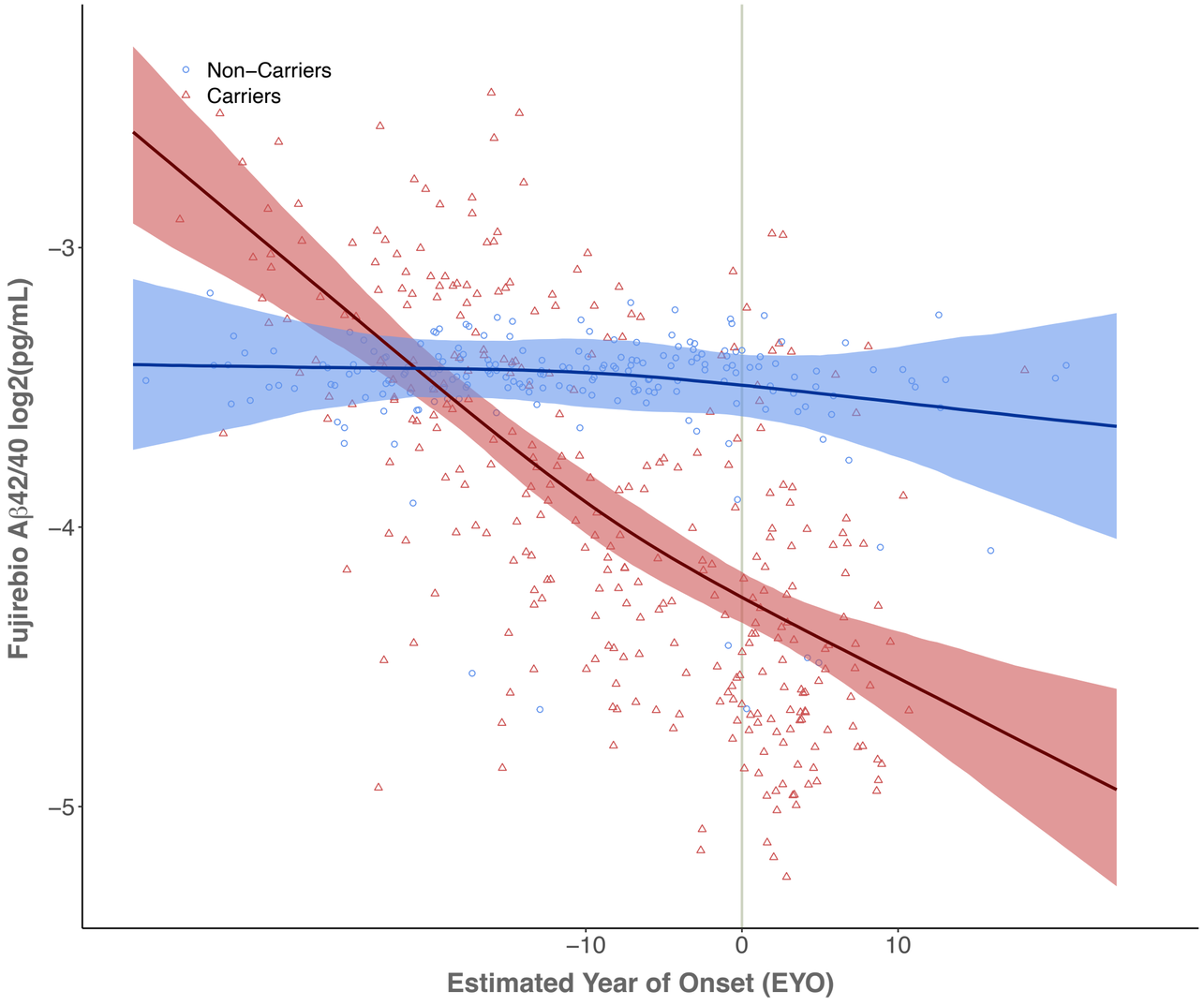
Fujirebio Aβ42 level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



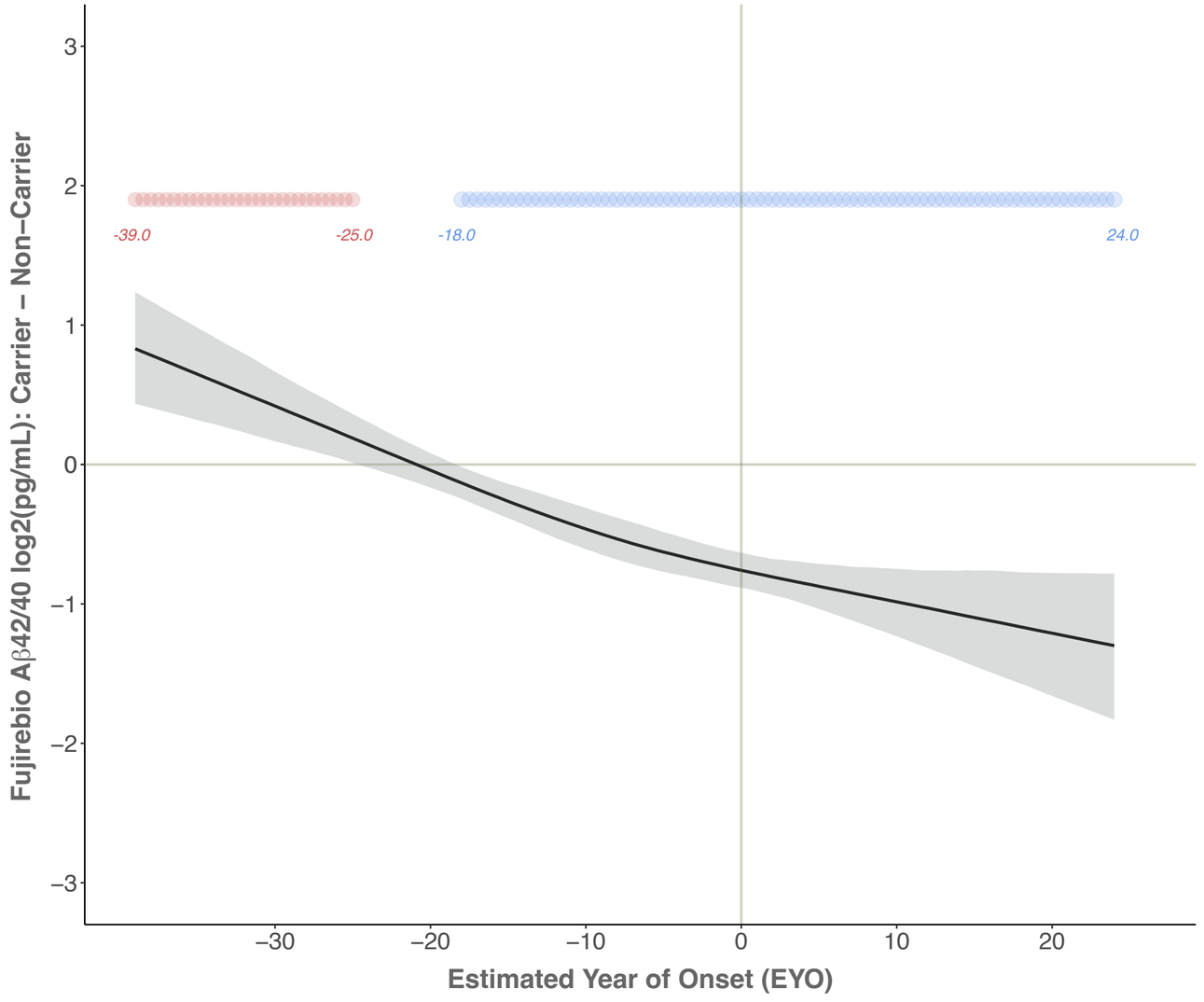
Fujirebio Aβ42 level difference in mutation carriers and non−carriers with 99% confidence interval.



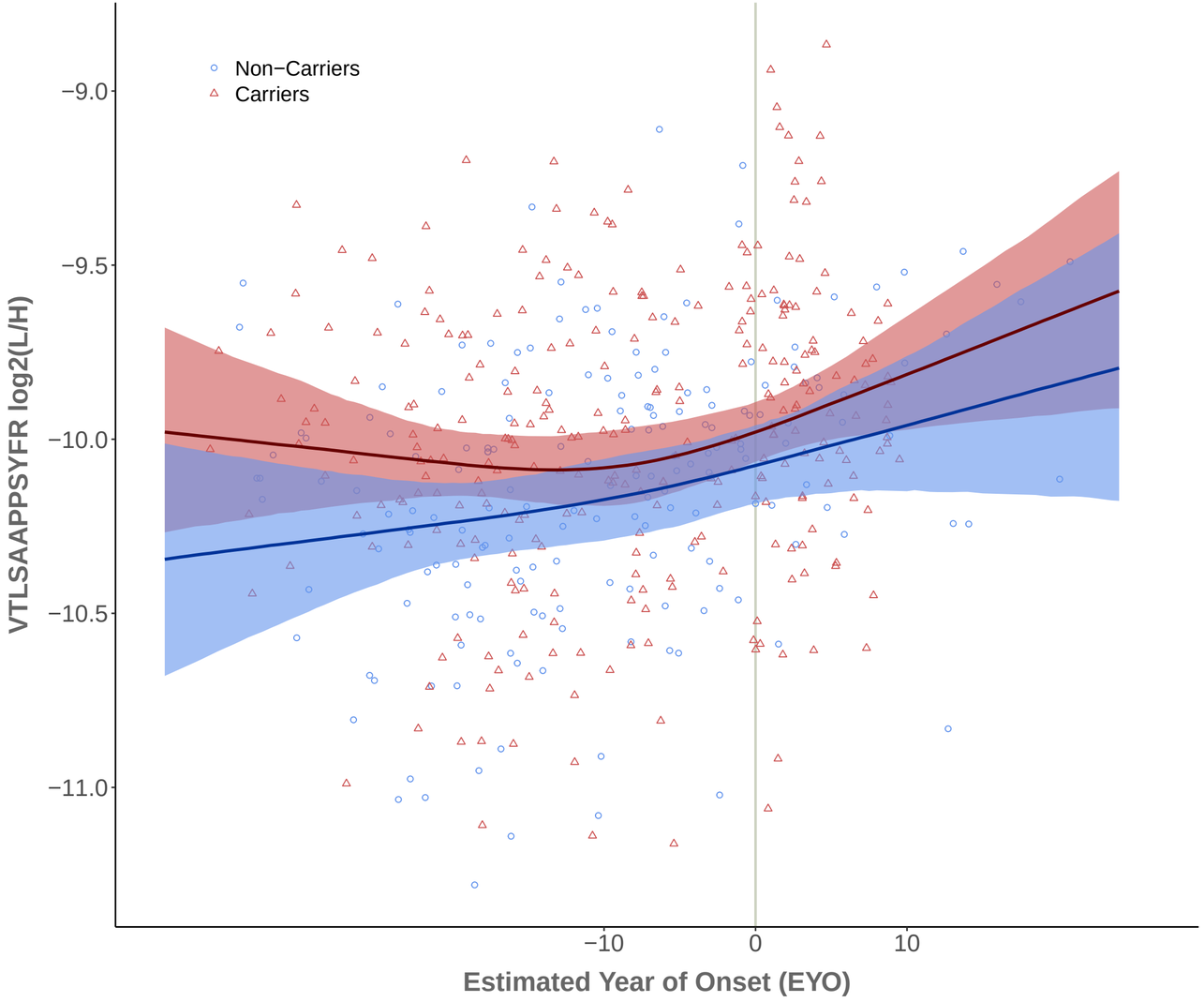
Fujirebio Aβ42/40 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



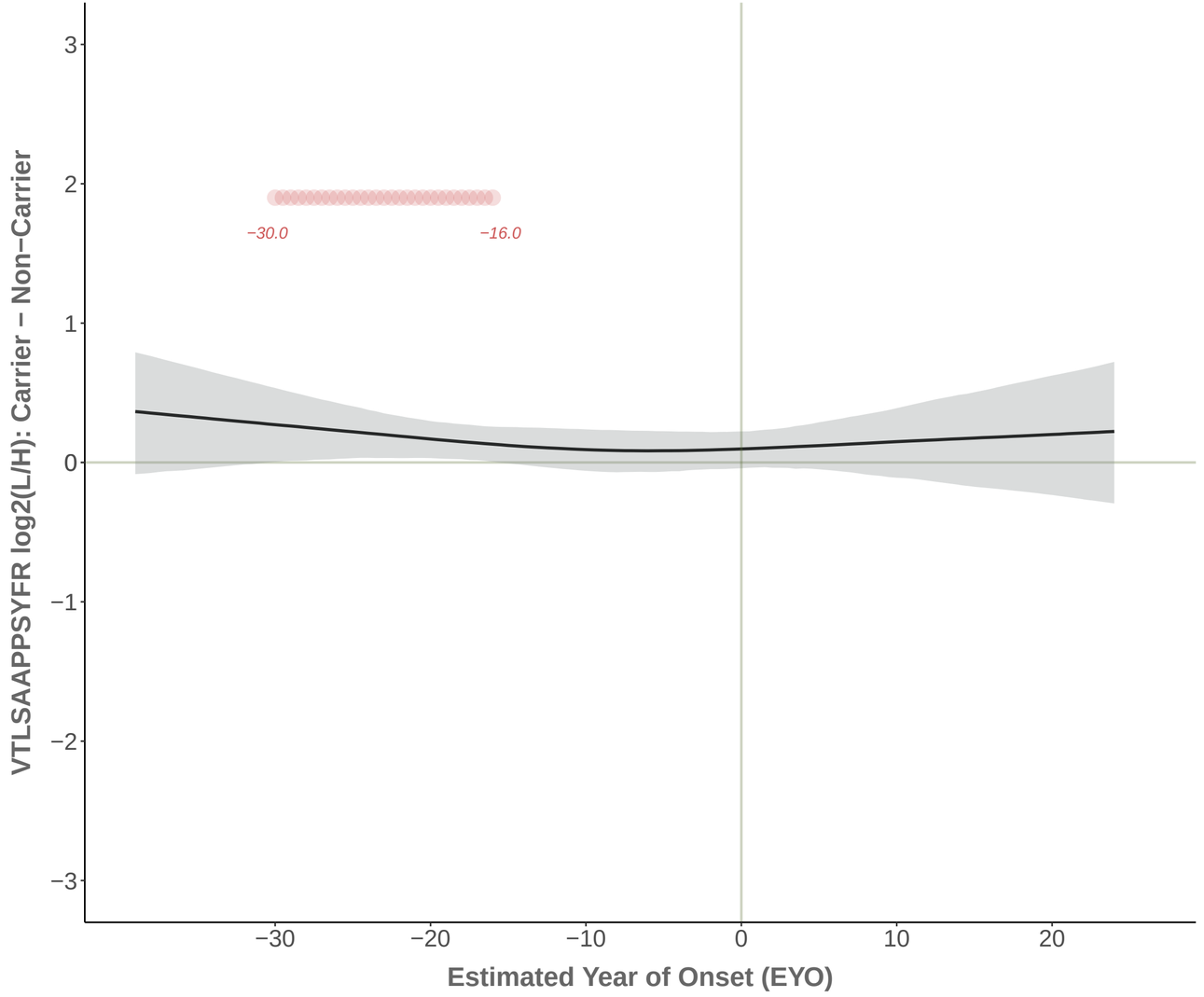
Fujirebio Aβ42/40 level difference in mutation carriers and non−carriers with 99% confidence interval.



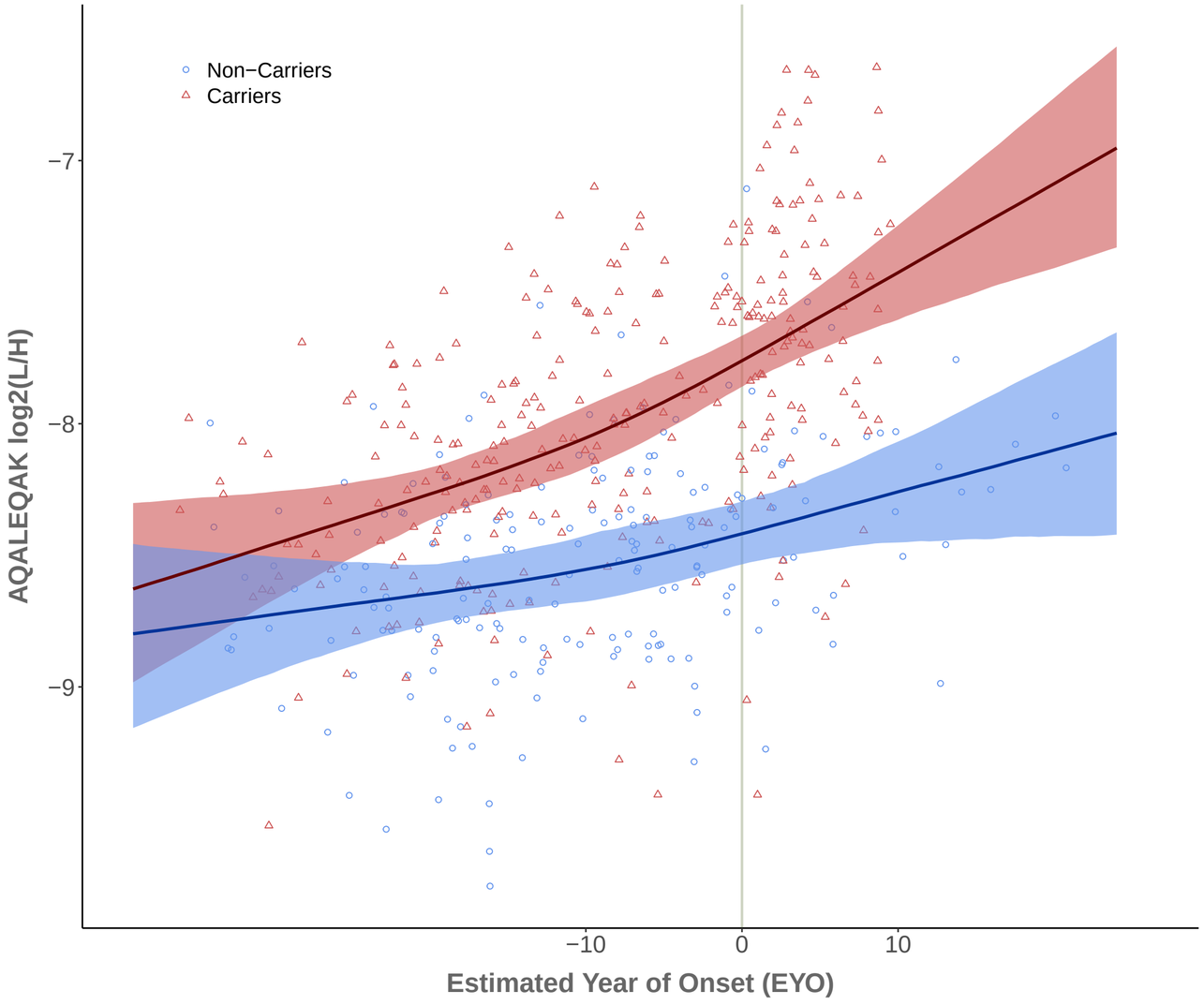
SPON1 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



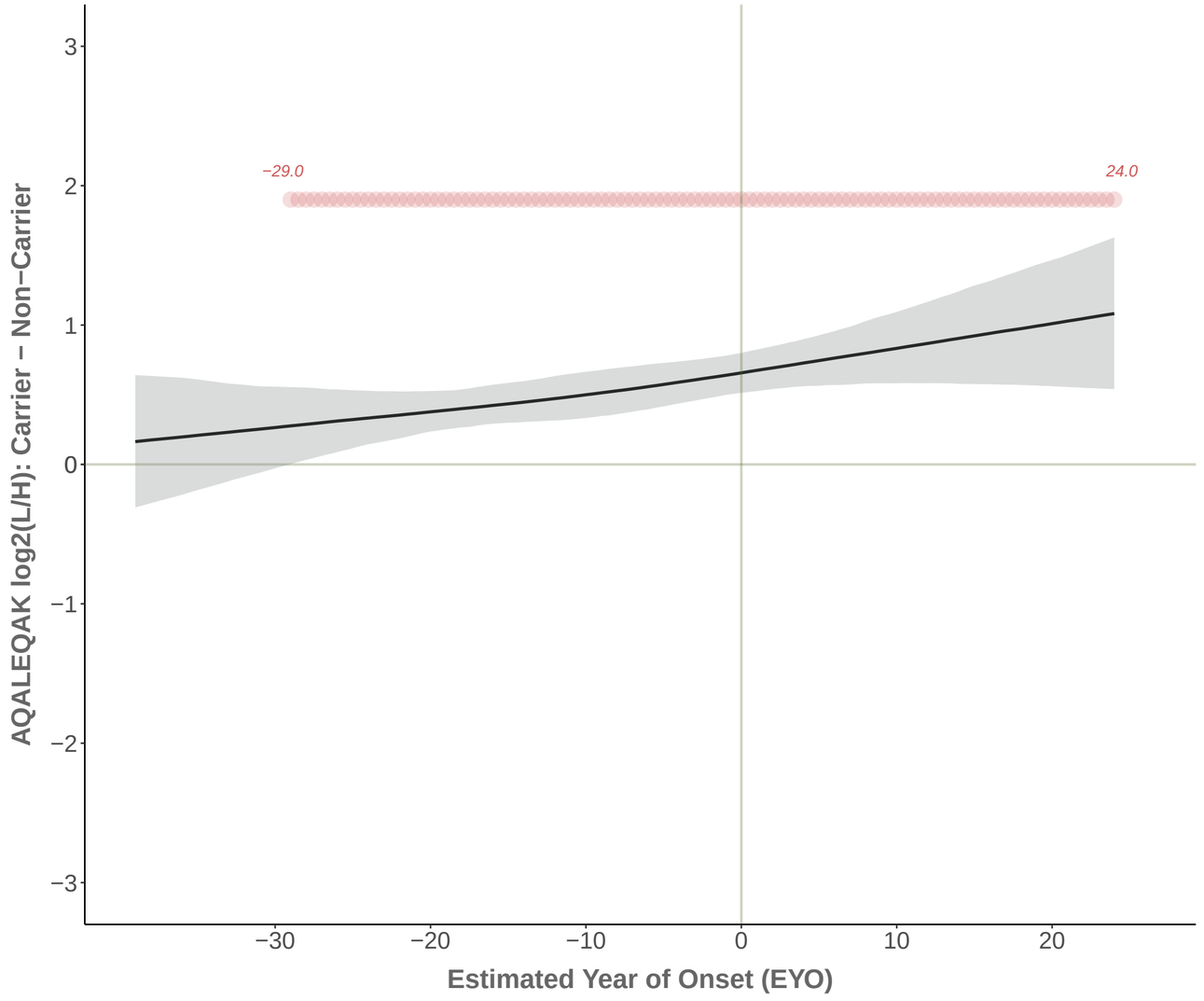
SPON1 level difference in mutation carriers and non−carriers with 99% confidence interval.



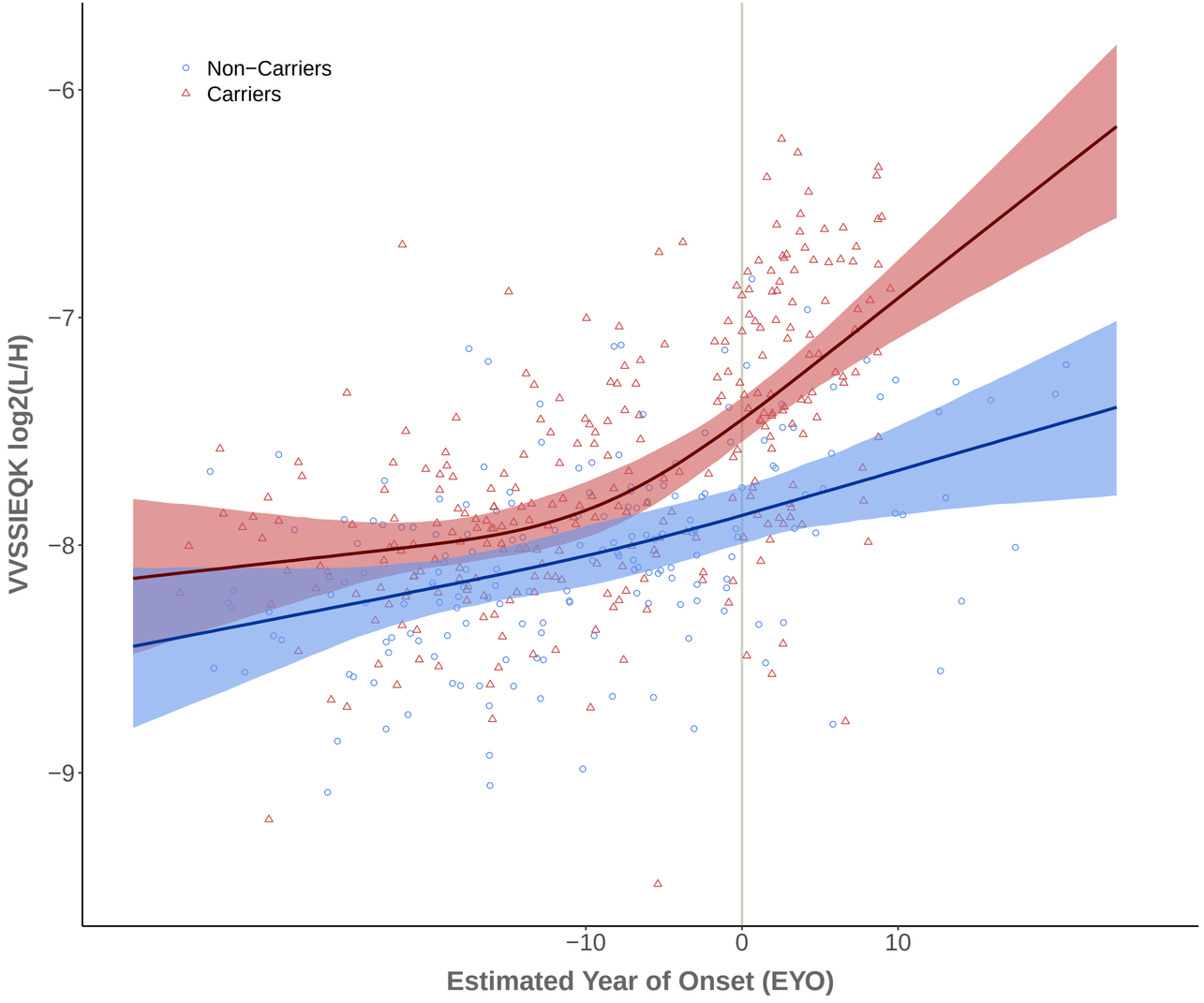
SMOC1 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



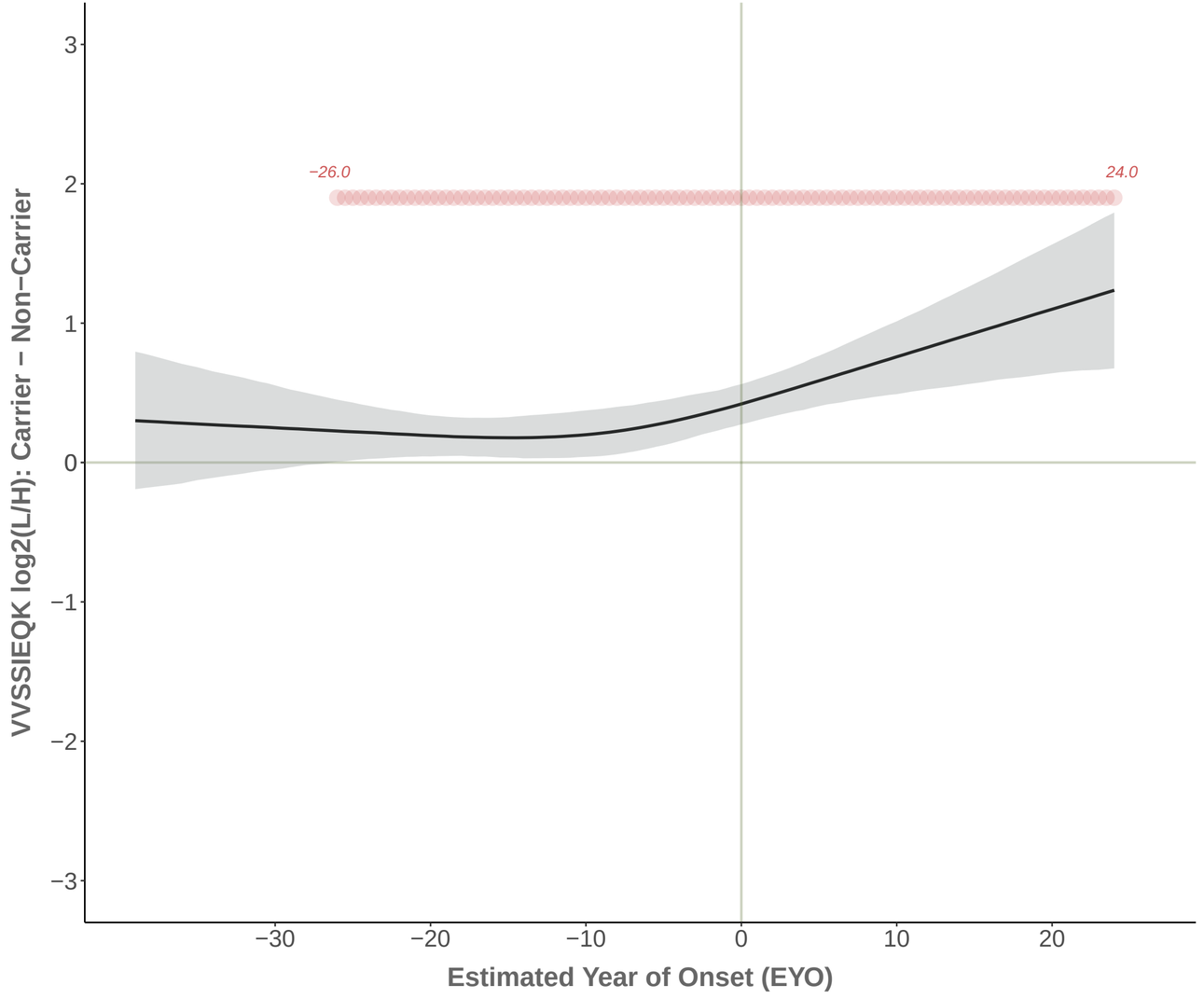
SMOC1 level difference in mutation carriers and non−carriers with 99% confidence interval.



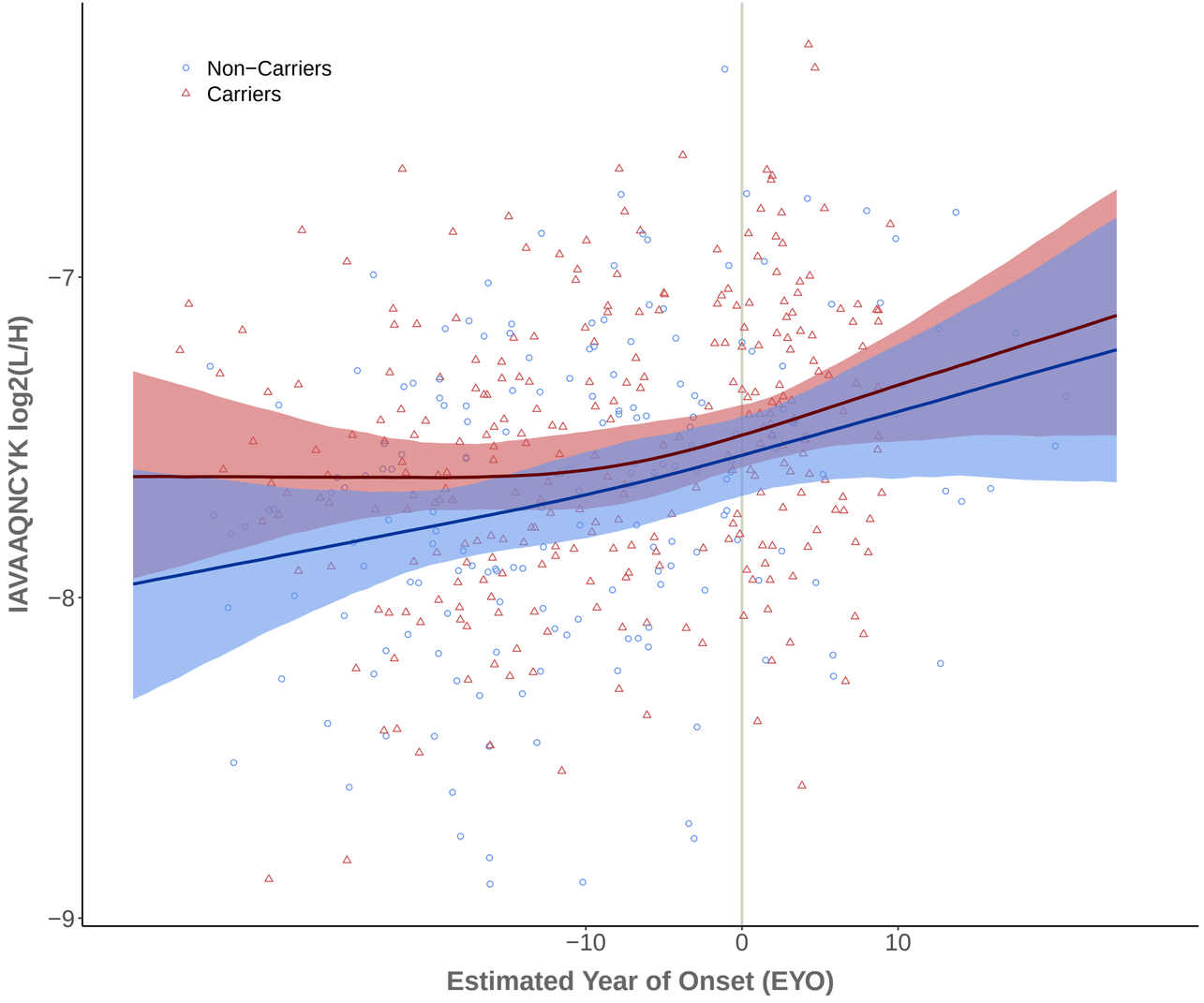
YWHAZ level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



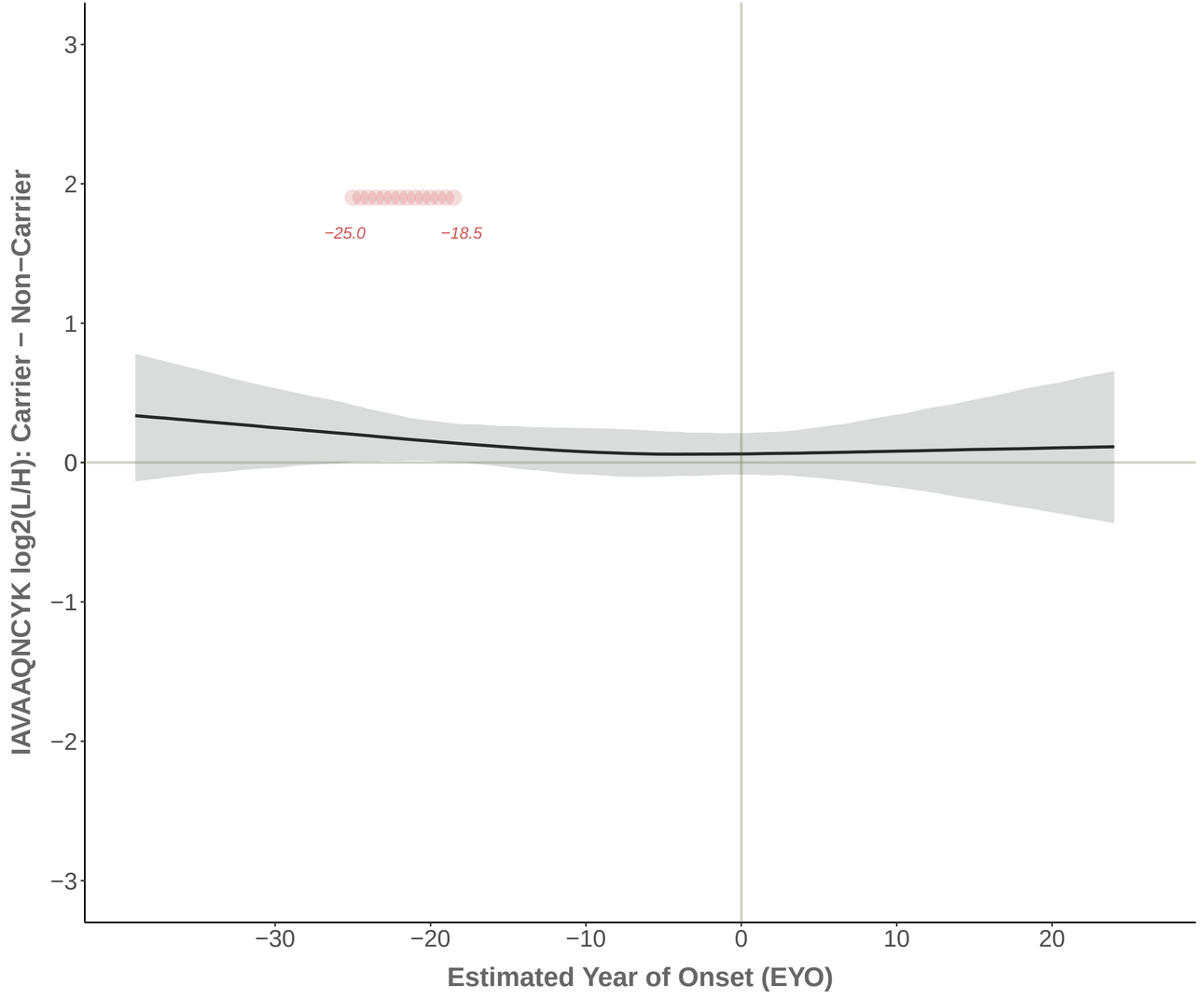
YWHAZ level difference in mutation carriers and non−carriers with 99% confidence interval.



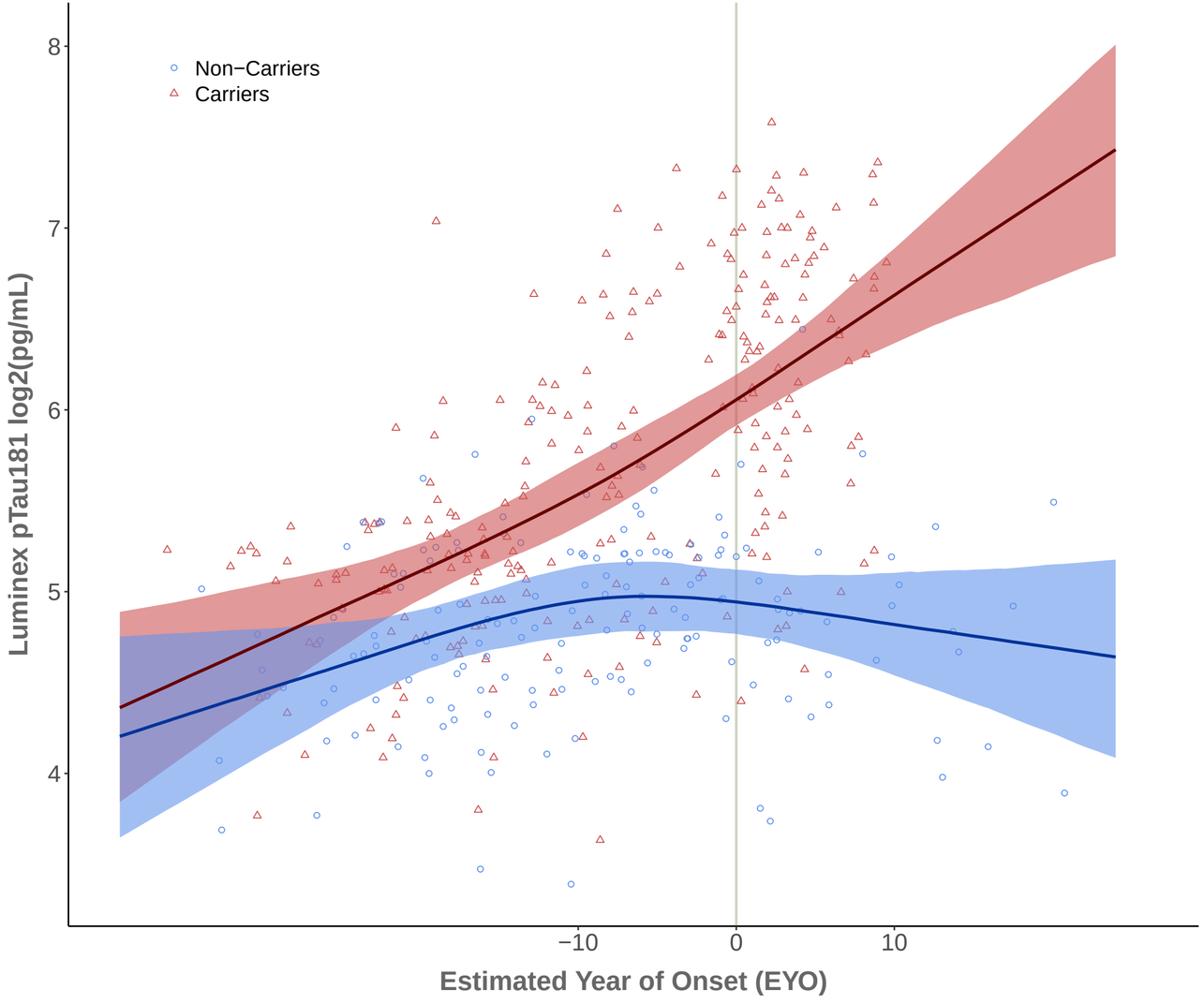
TPI1 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



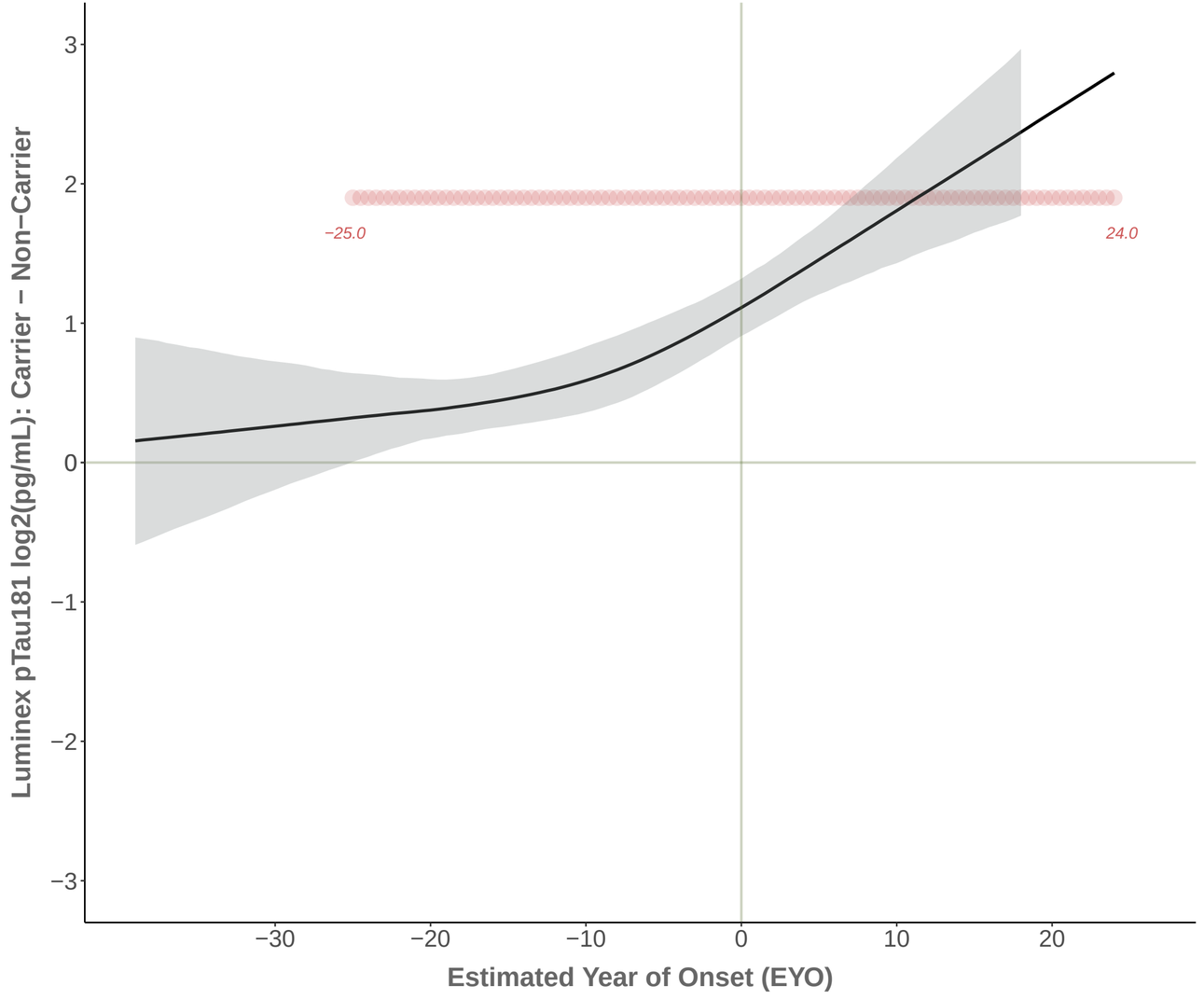
TPI1 level difference in mutation carriers and non−carriers with 99% confidence interval.



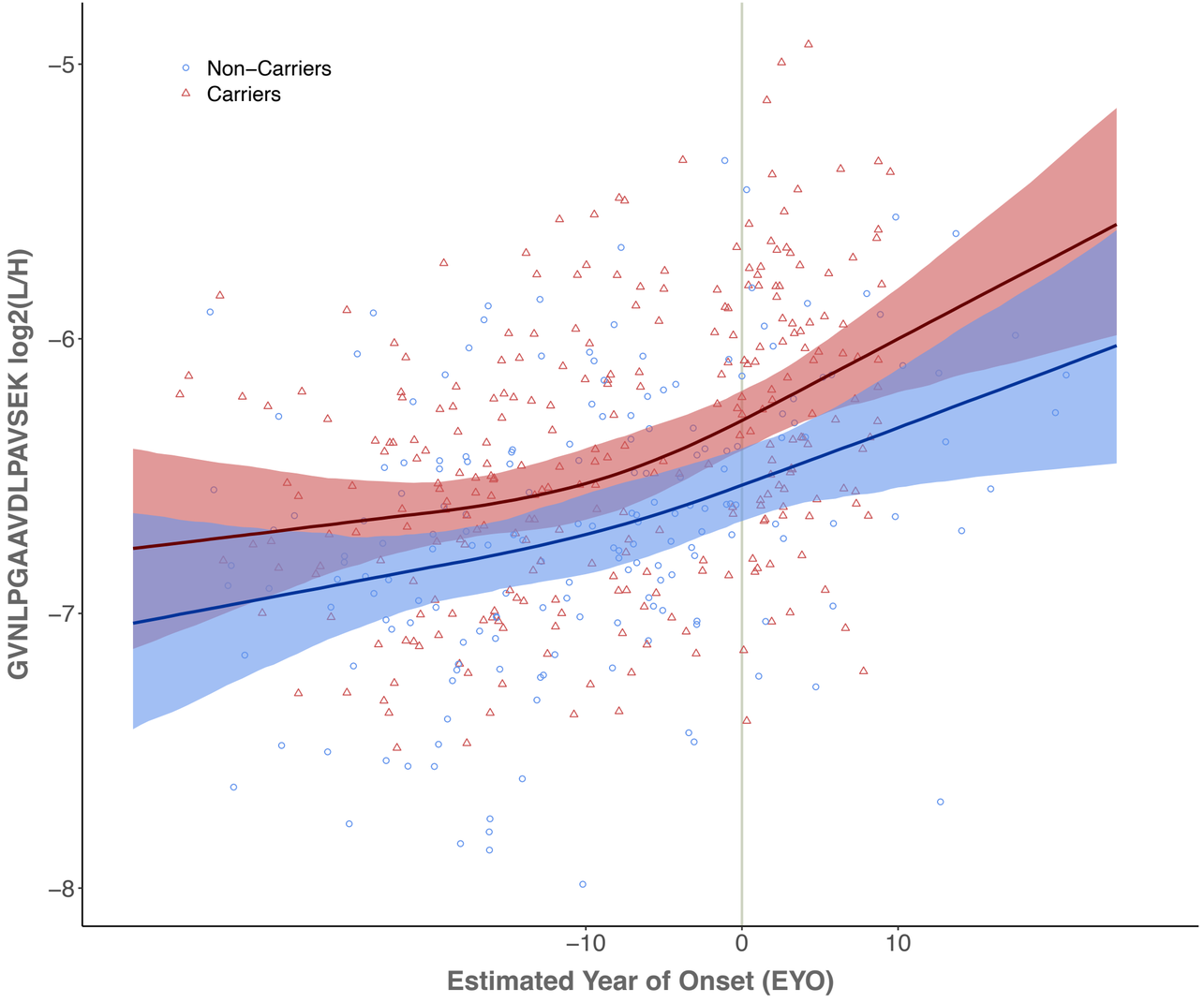
Luminex pTau181 level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



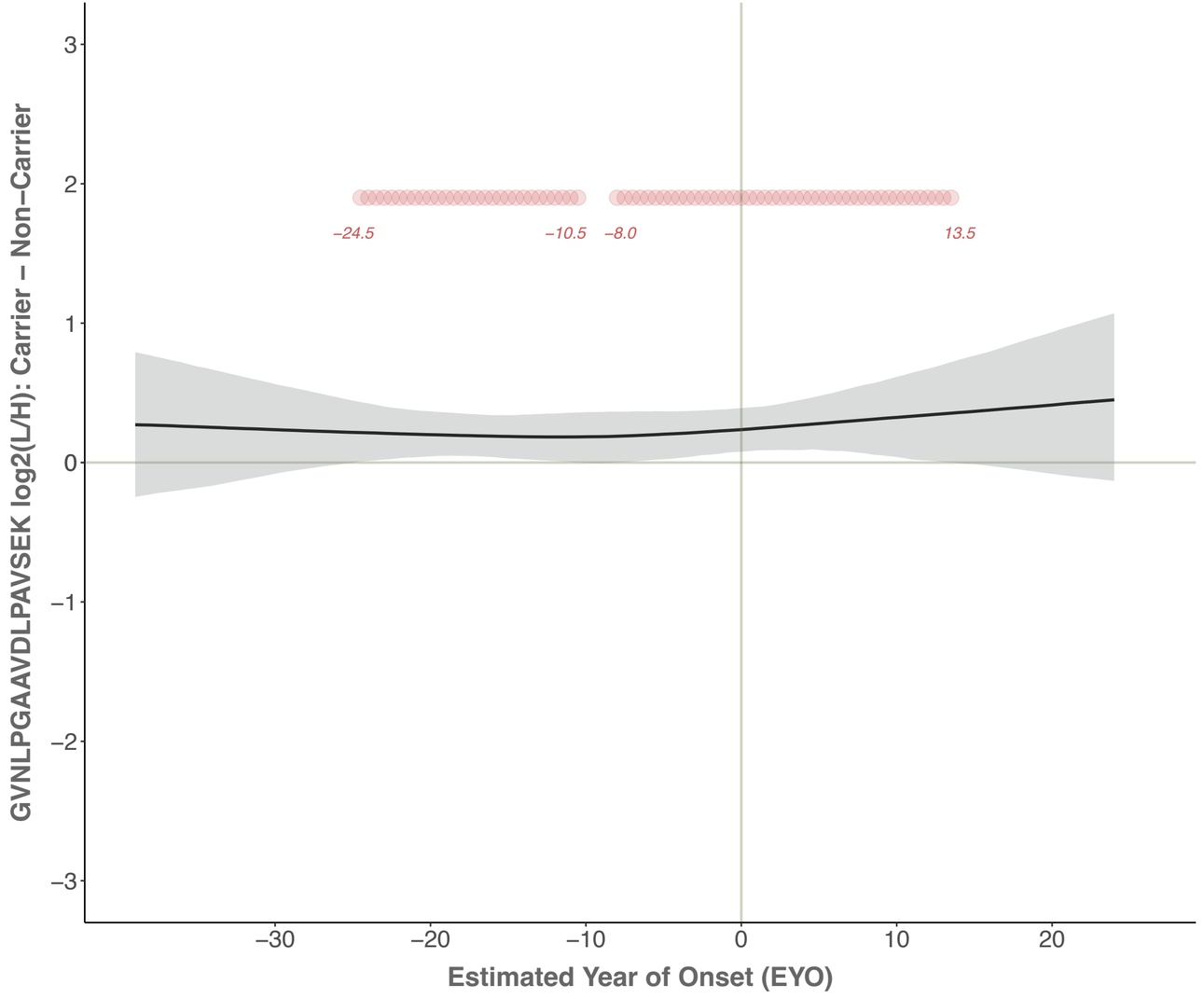
Luminex pTau181 level difference in mutation carriers and non−carriers with 99% confidence interval.



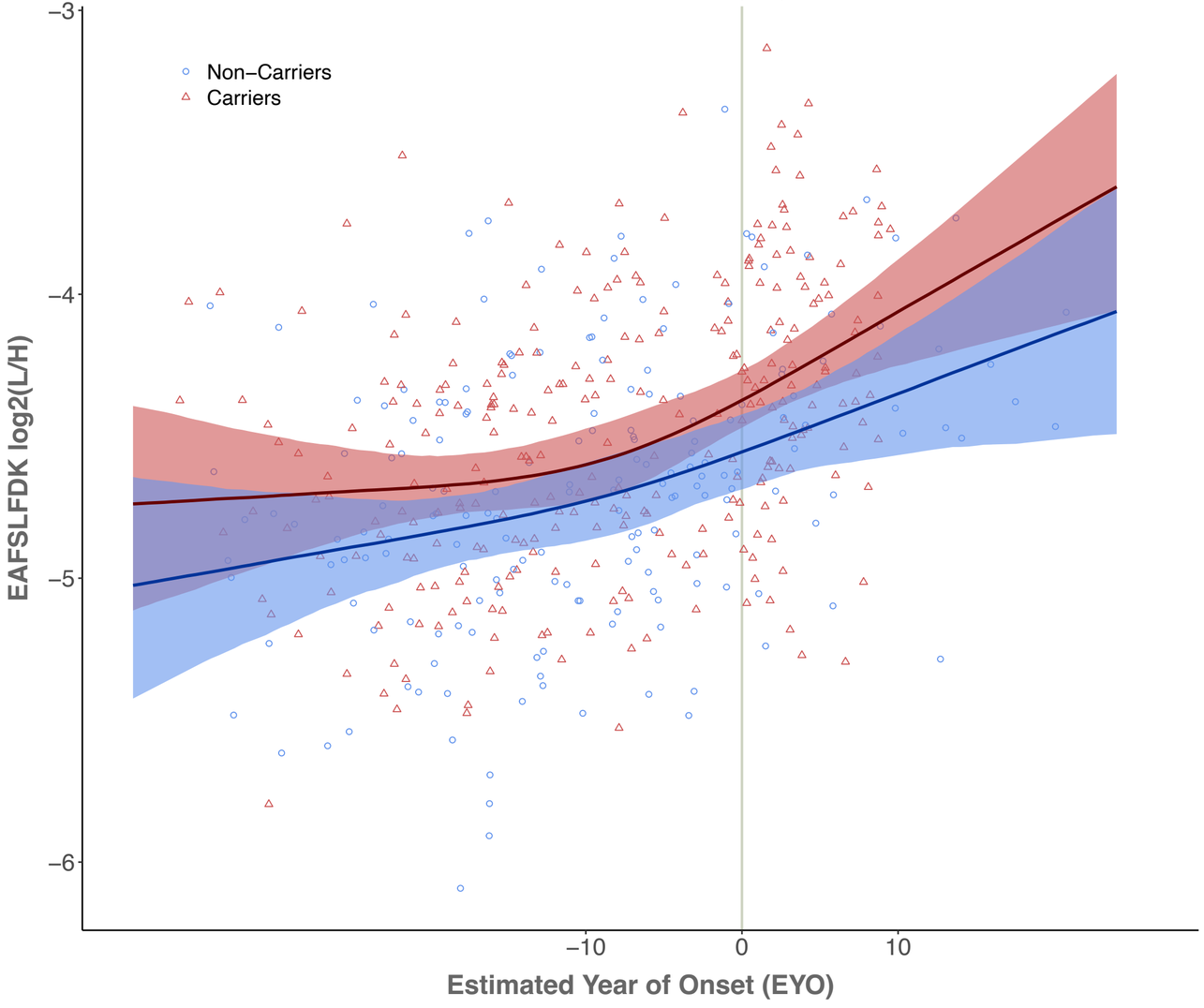
PKM level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



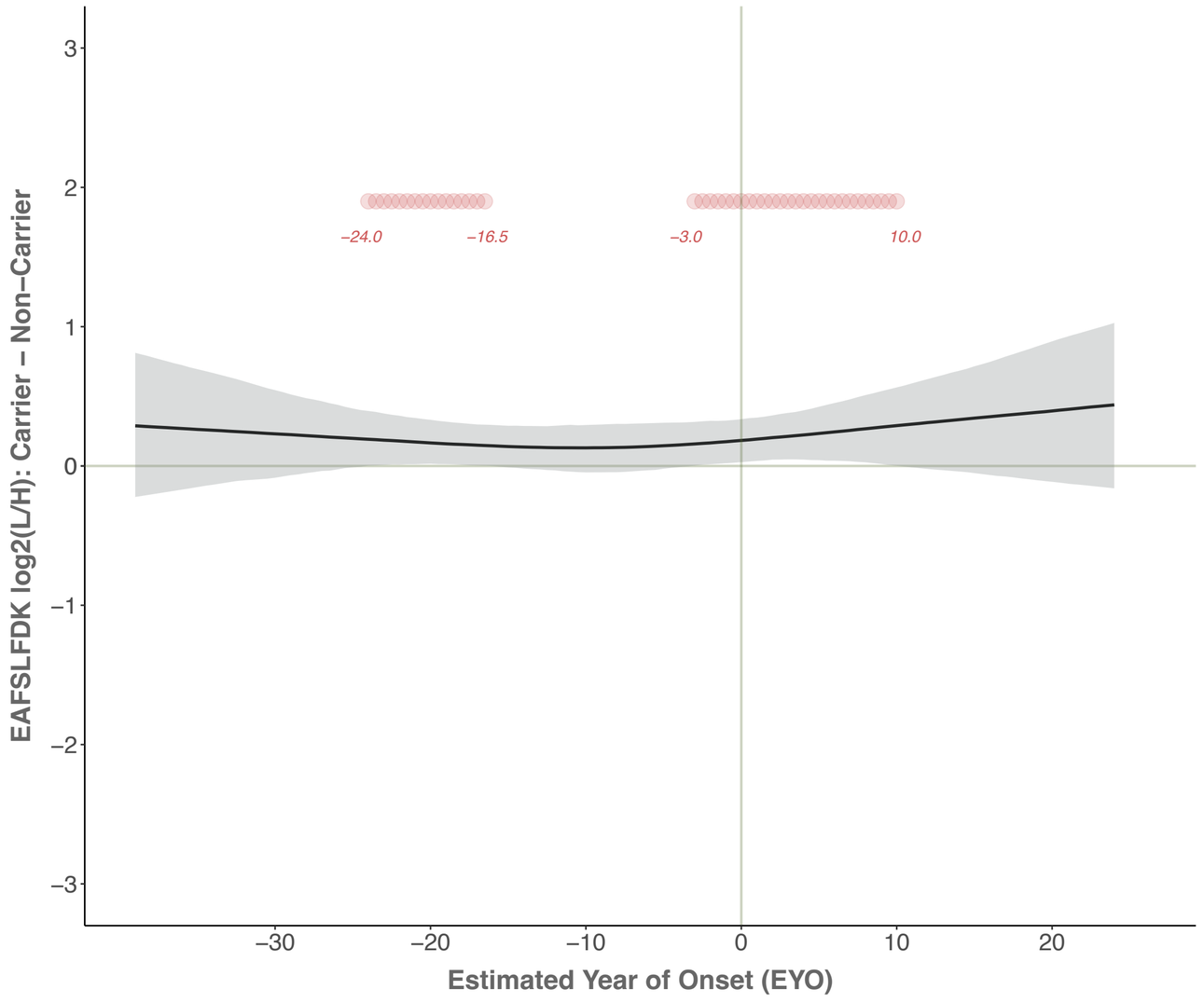
PKM level difference in mutation carriers and non−carriers with 99% confidence interval.

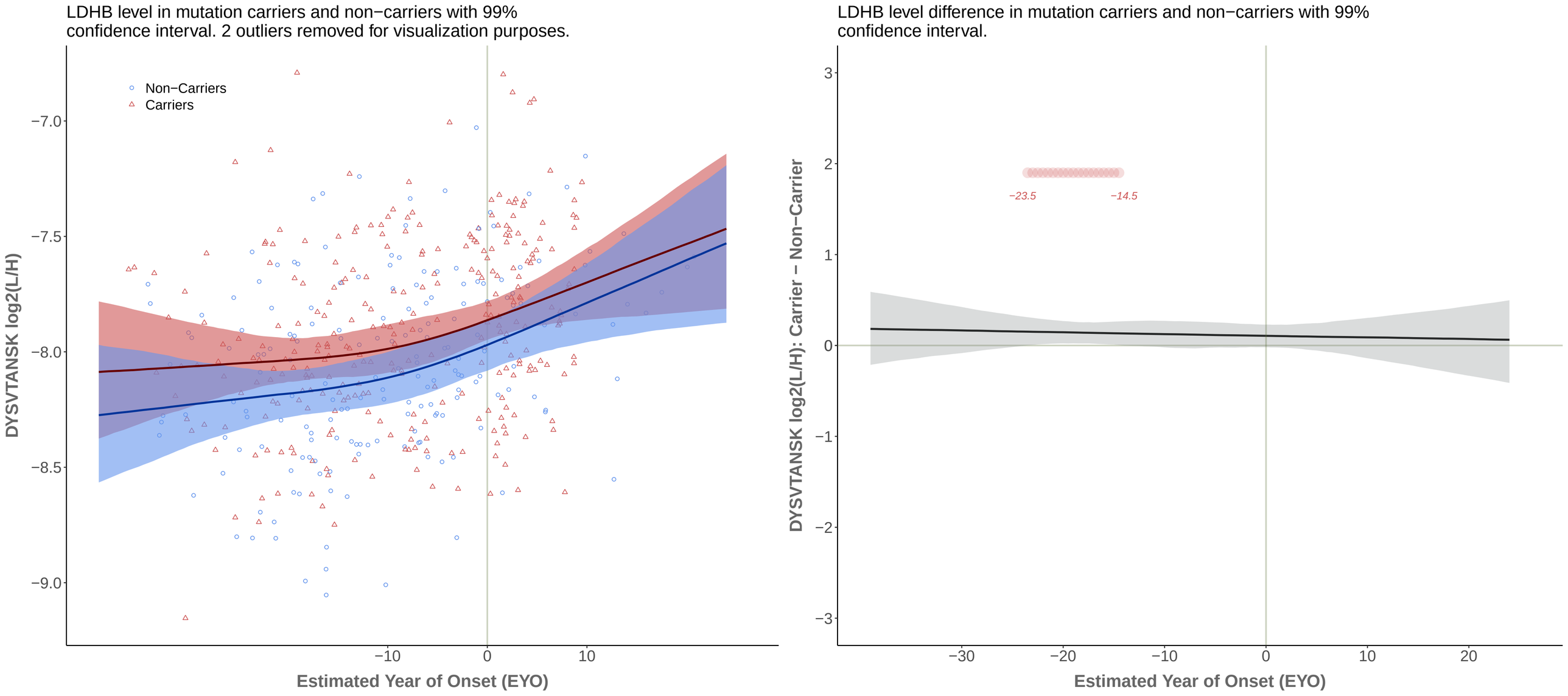


CALM2 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.

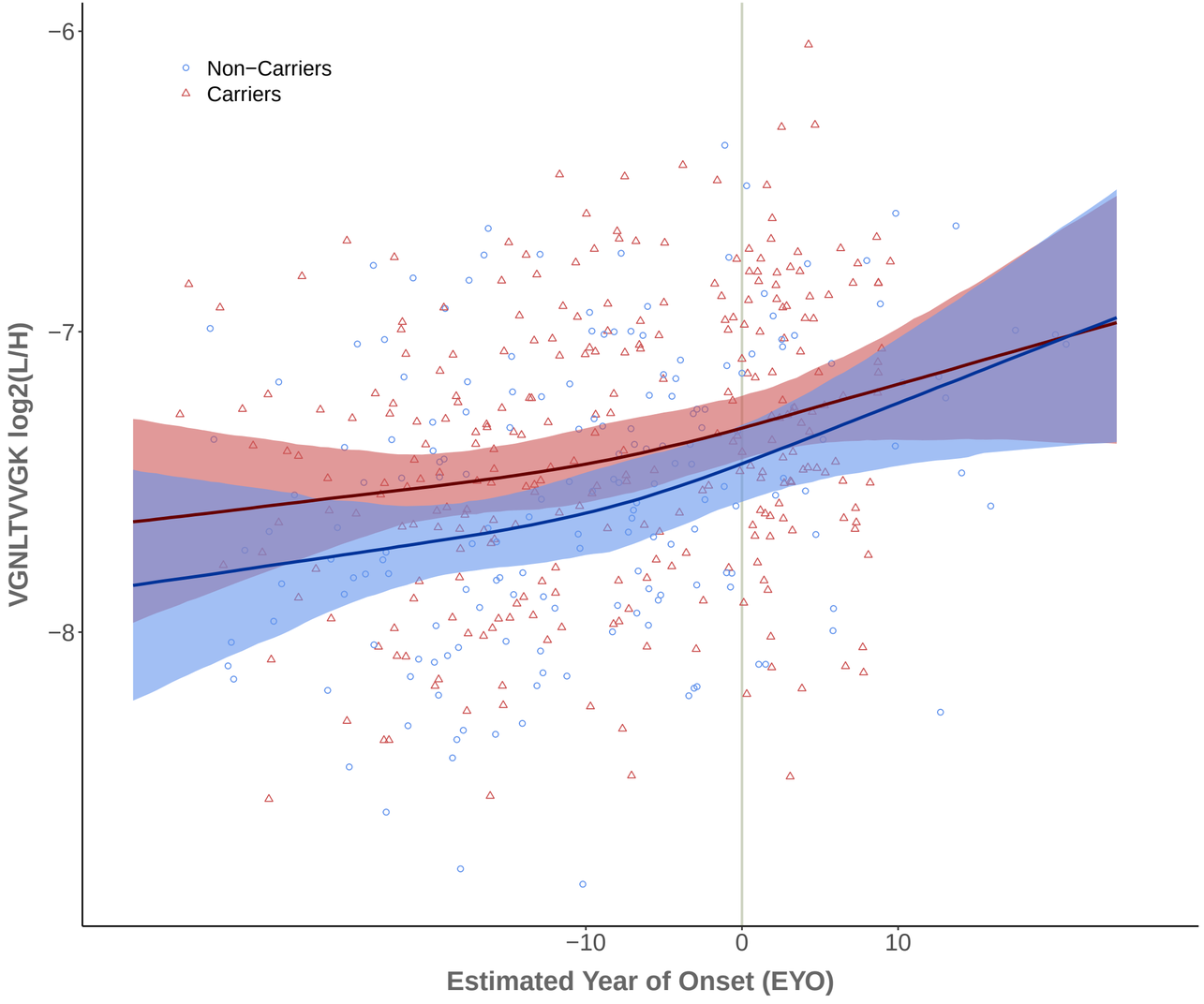


CALM2 level difference in mutation carriers and non−carriers with 99% confidence interval.

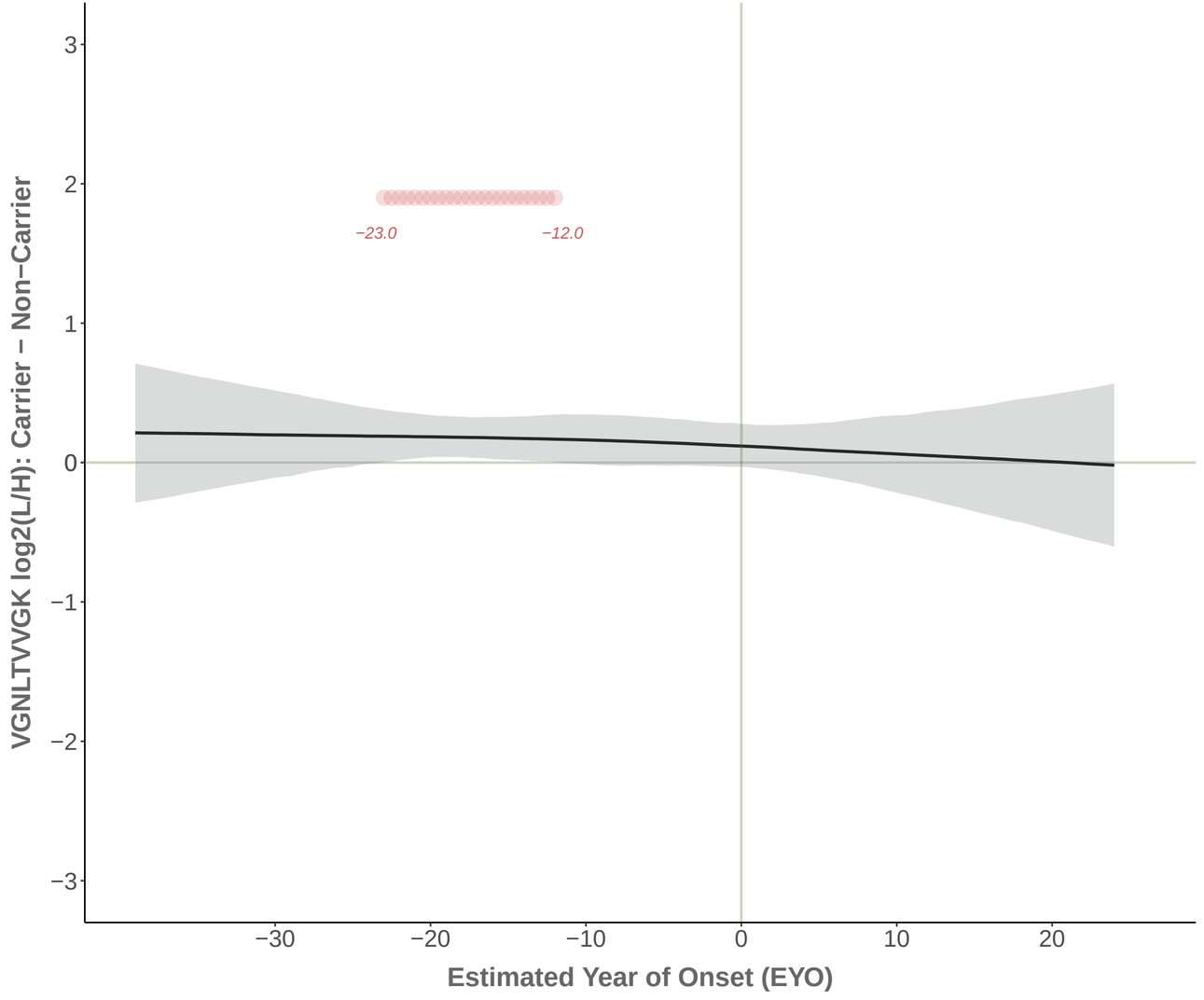



LDHB level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.
Non−Carriers
Carriers
DYSVTANSK log2(L/H)
−7.0
−7.5
−8.0
−8.5
−9.0
−10
0
10
Estimated Year of Onset (EYO)
LDHB level difference in mutation carriers and non−carriers with 99% confidence interval.
DYSVTANSK log2(L/H): Carrier − Non−Carrier
3
2
1
0
−1
−2
−3
−23.5
−14.5
−30
−20
−10
0
10
20
Estimated Year of Onset (EYO)

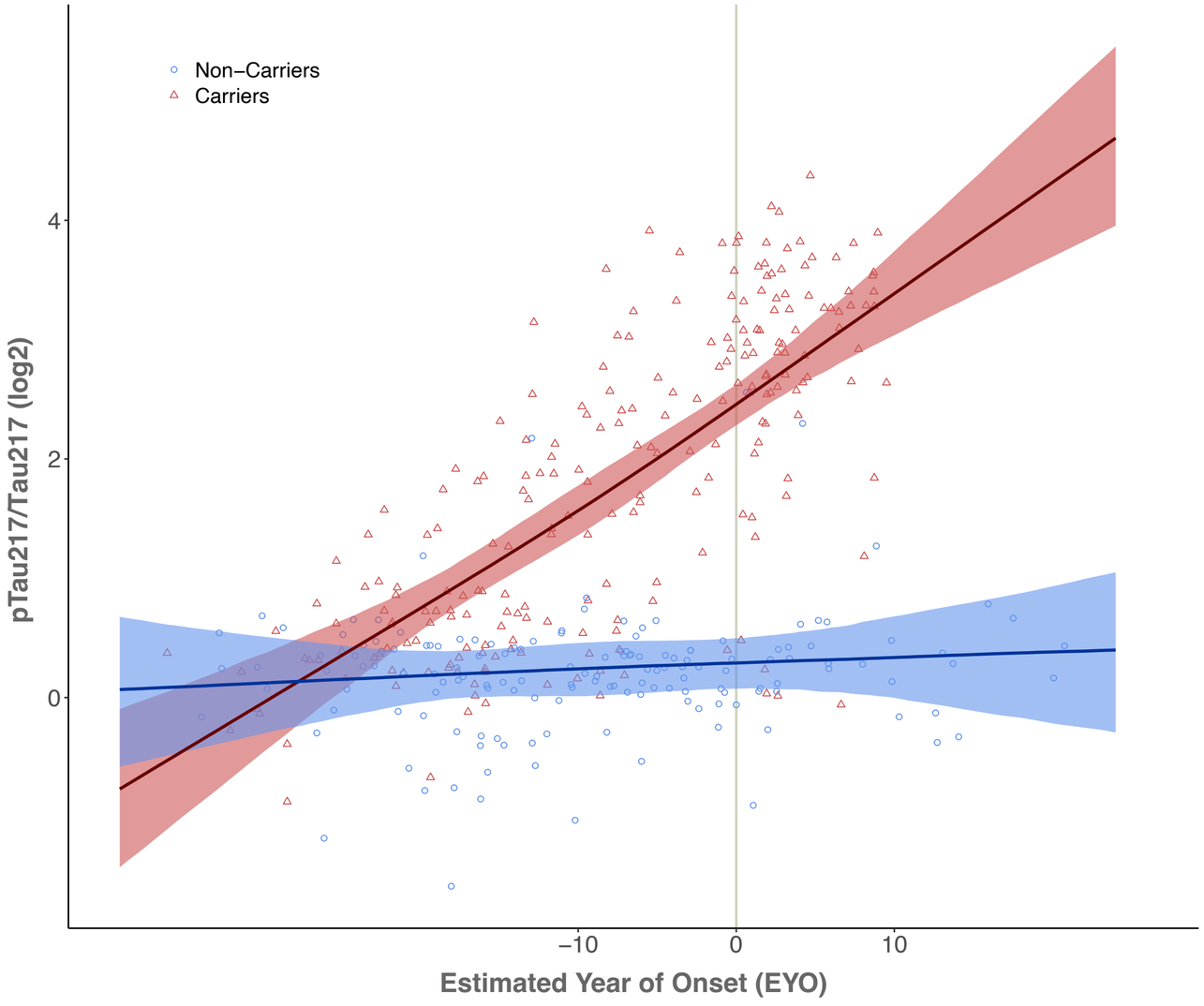
GOT1 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



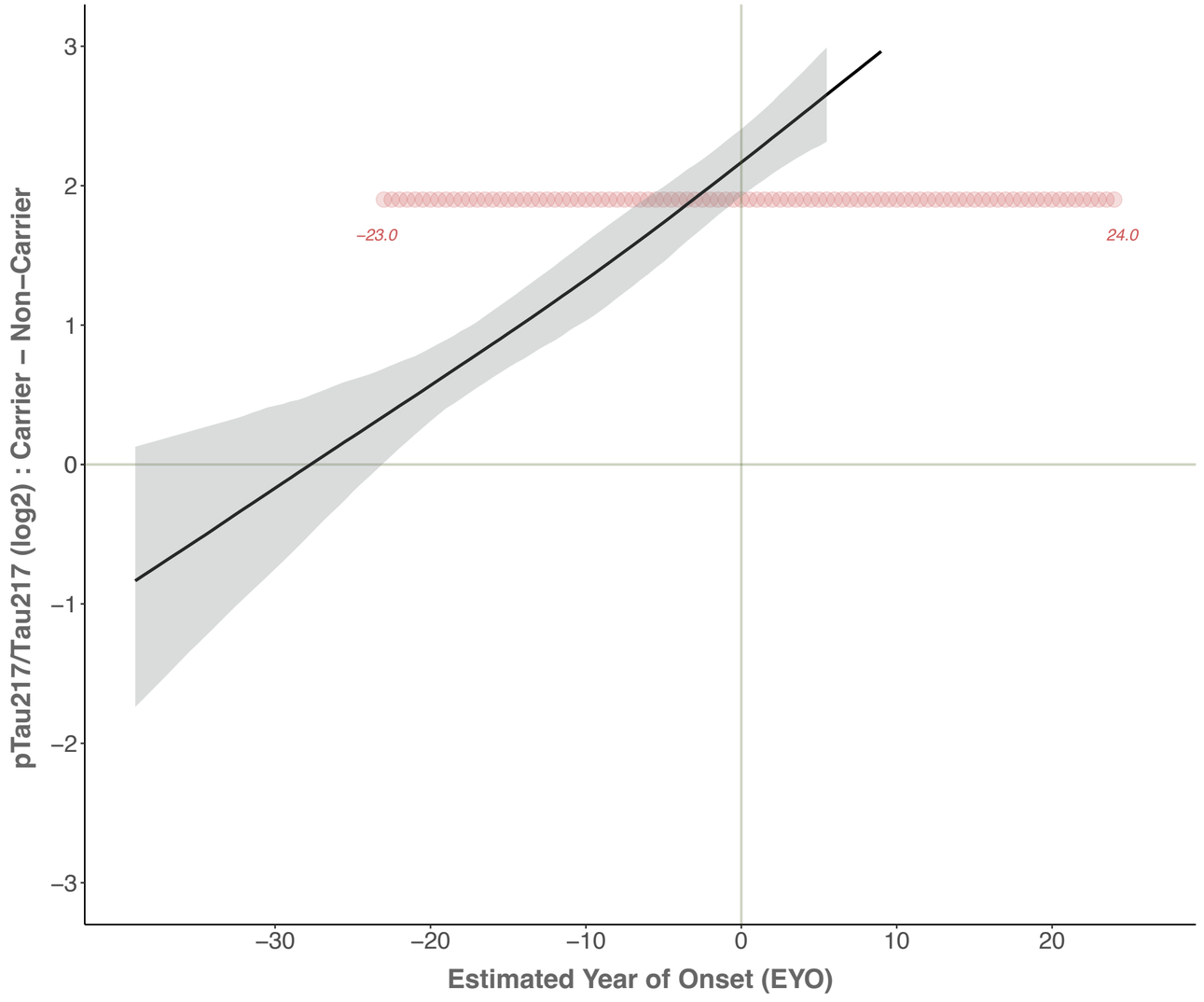
GOT1 level difference in mutation carriers and non−carriers with 99% confidence interval.



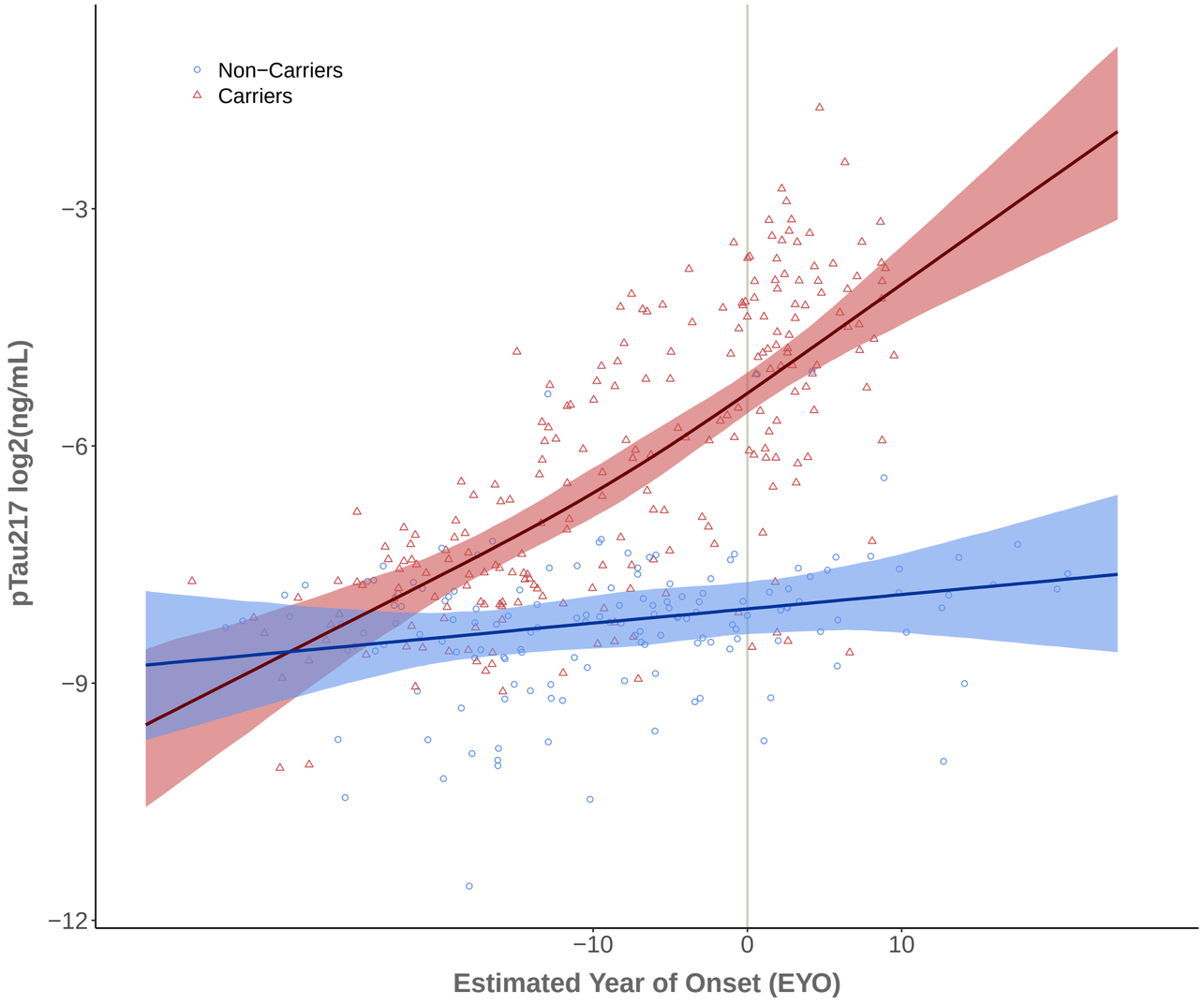
pTau217/Tau217 ratio in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



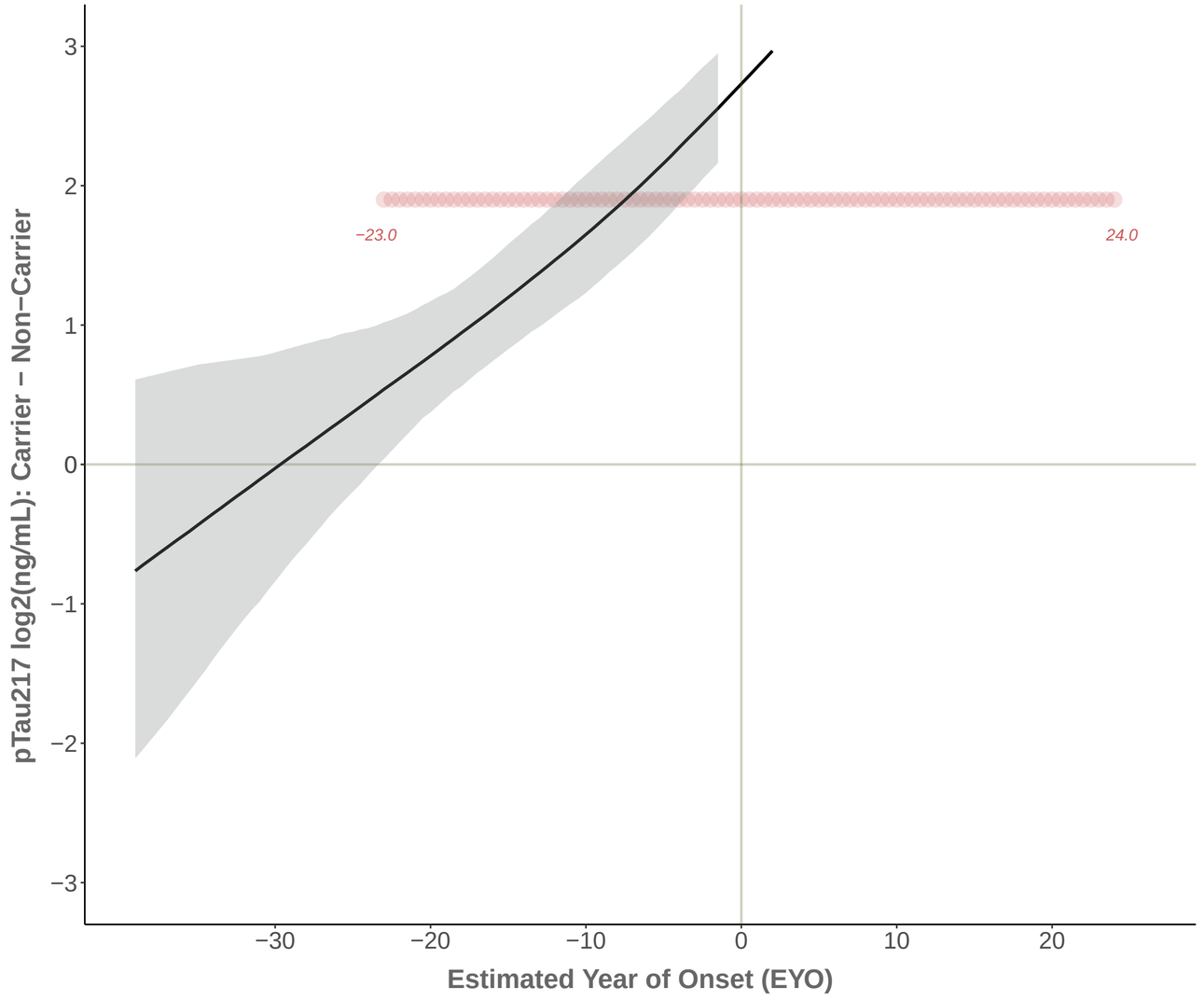
pTau217/Tau217 ratio difference in mutation carriers and non−carriers with 99% confidence interval.



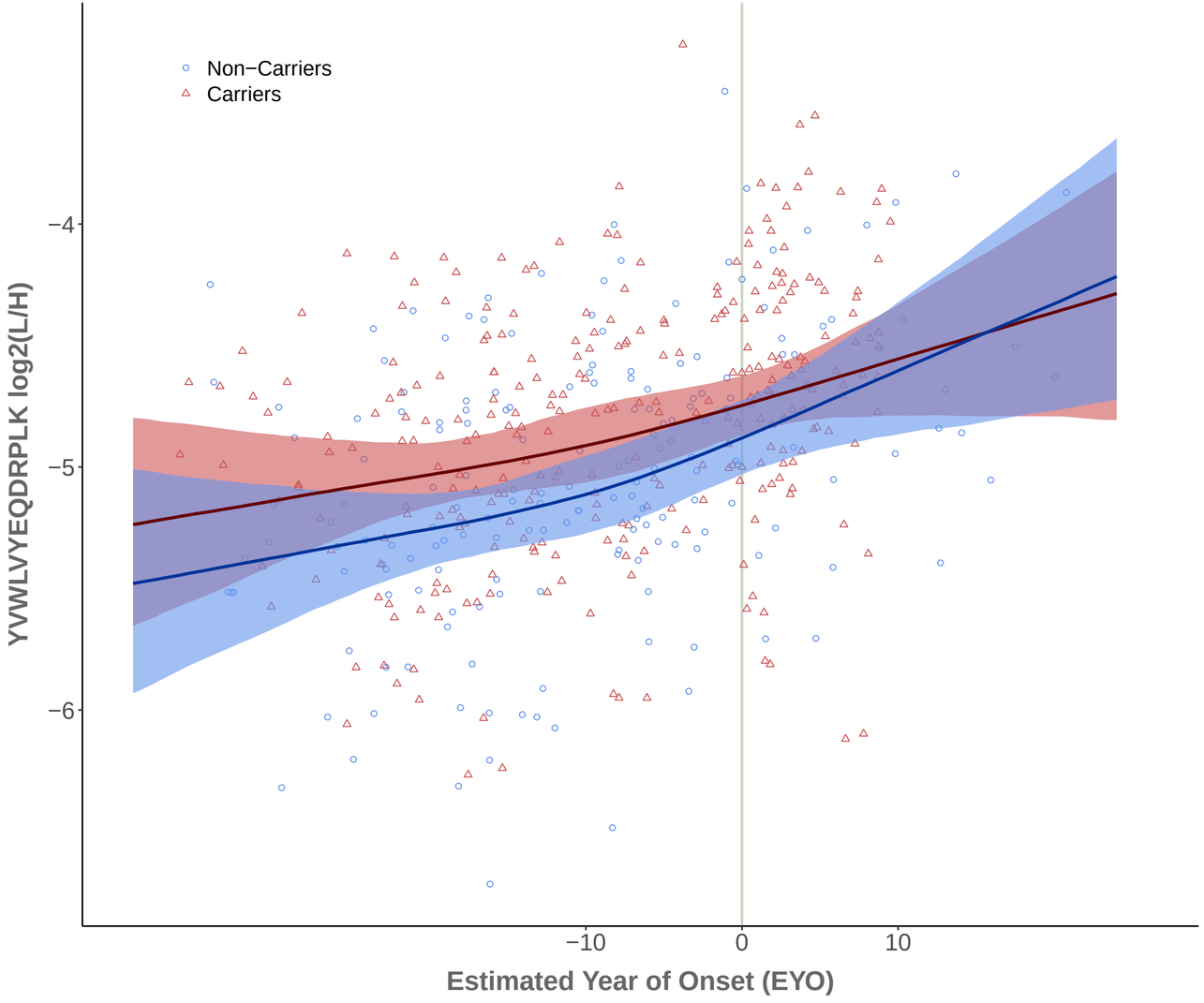
pTau217 level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



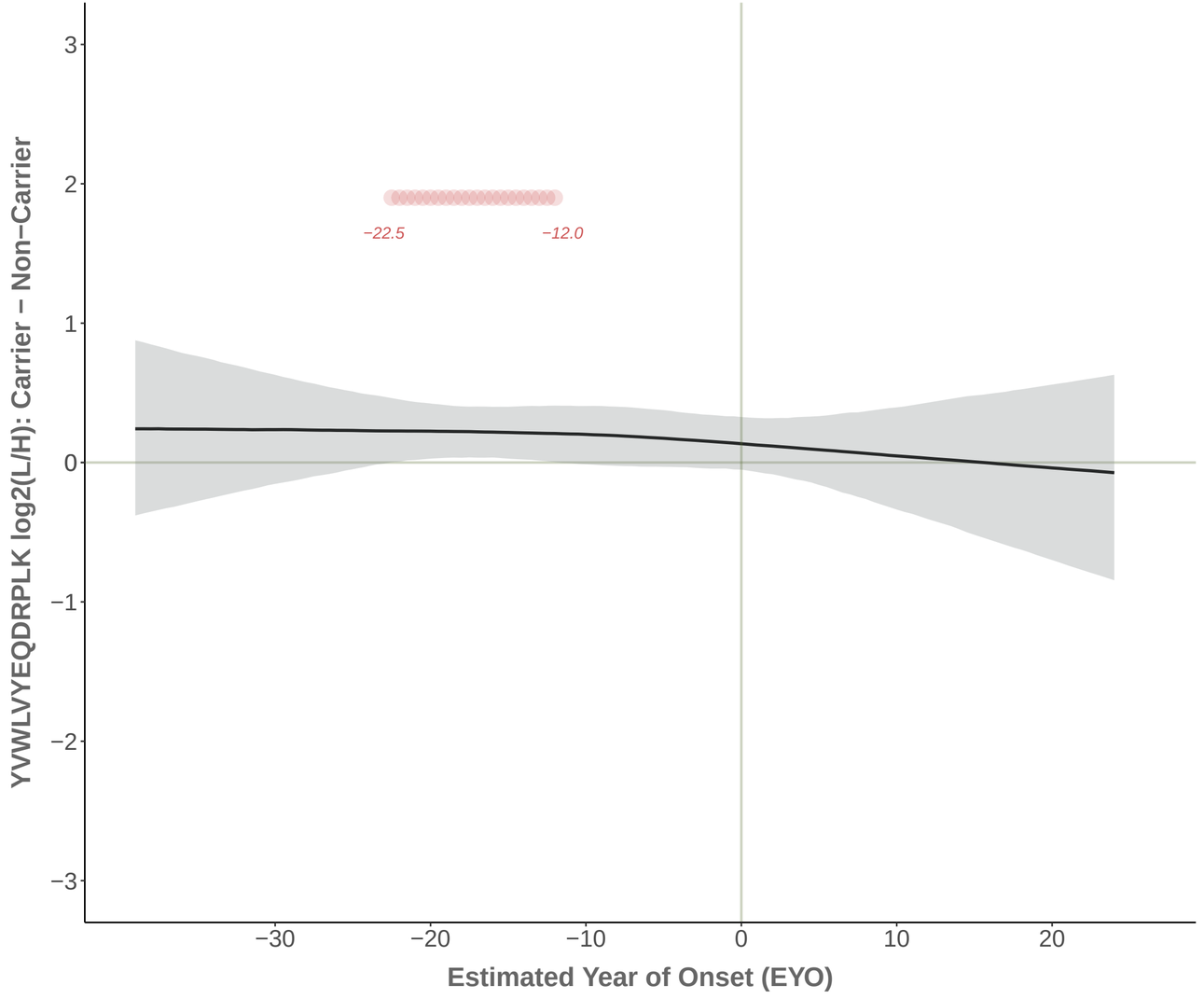
pTau217 level difference in mutation carriers and non−carriers with 99% confidence interval.



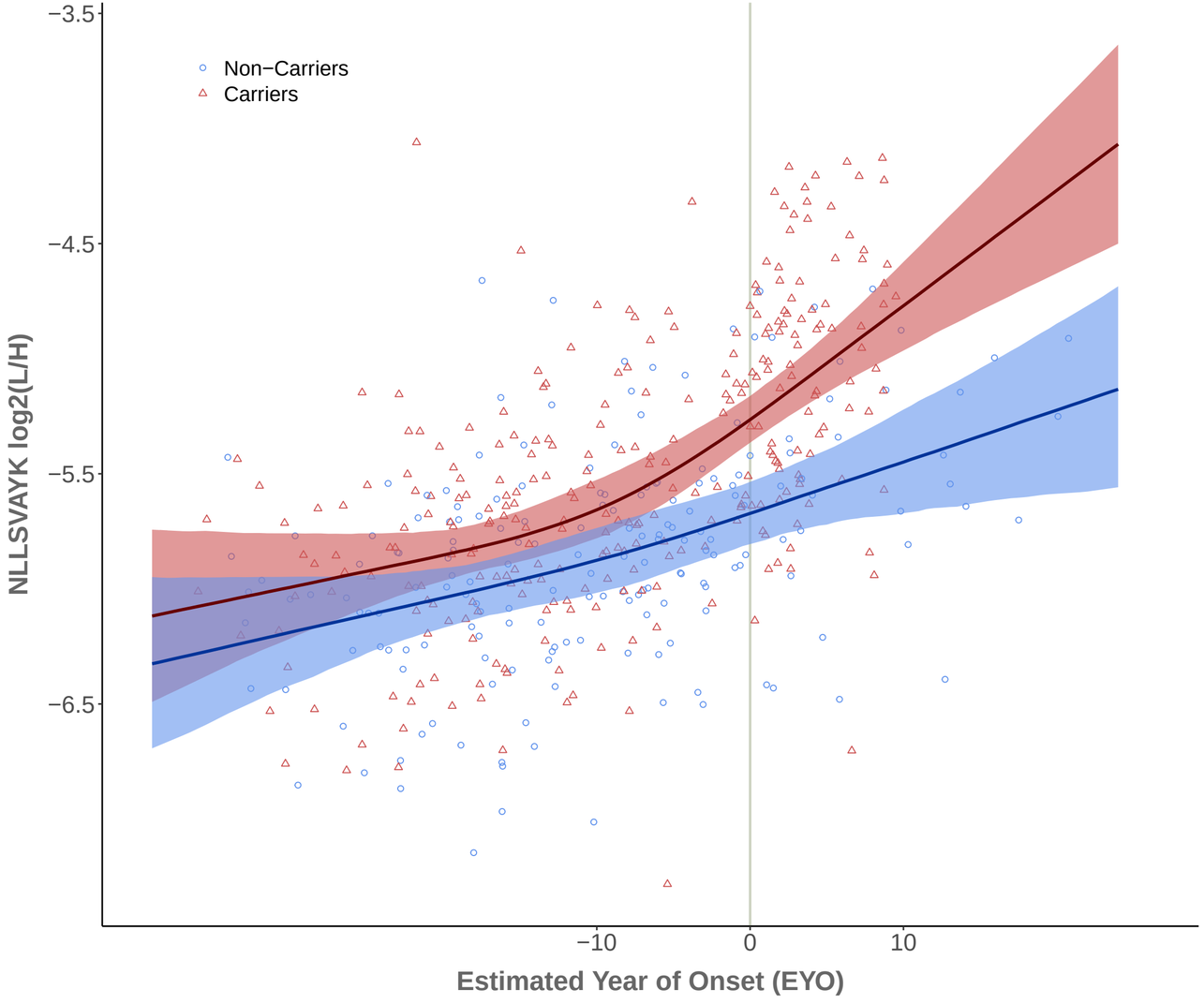
PEBP1 level in mutation carriers and non−carriers with 99% confidence interval. 6 outliers removed for visualization purposes.



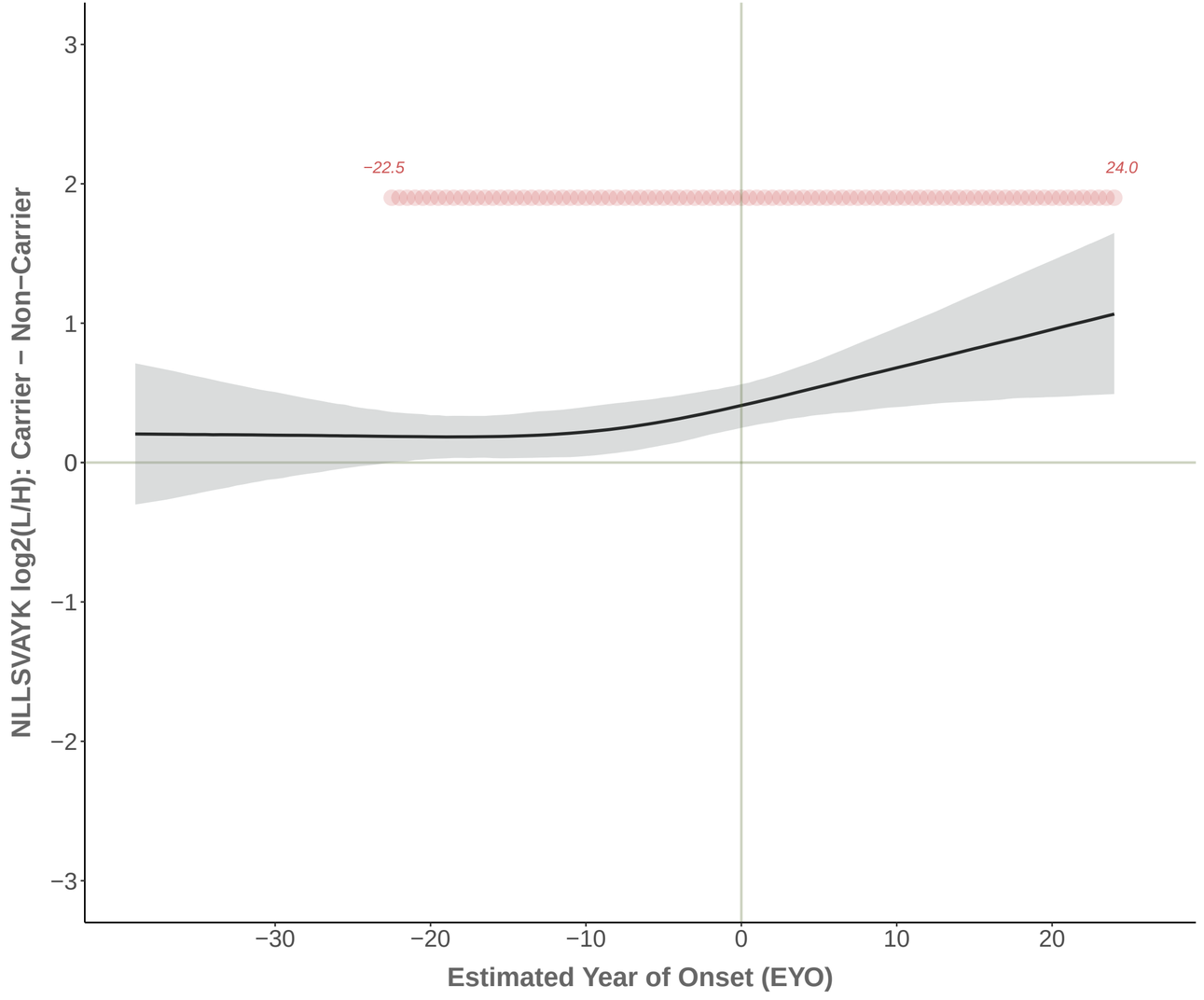
PEBP1 level difference in mutation carriers and non−carriers with 99% confidence interval.



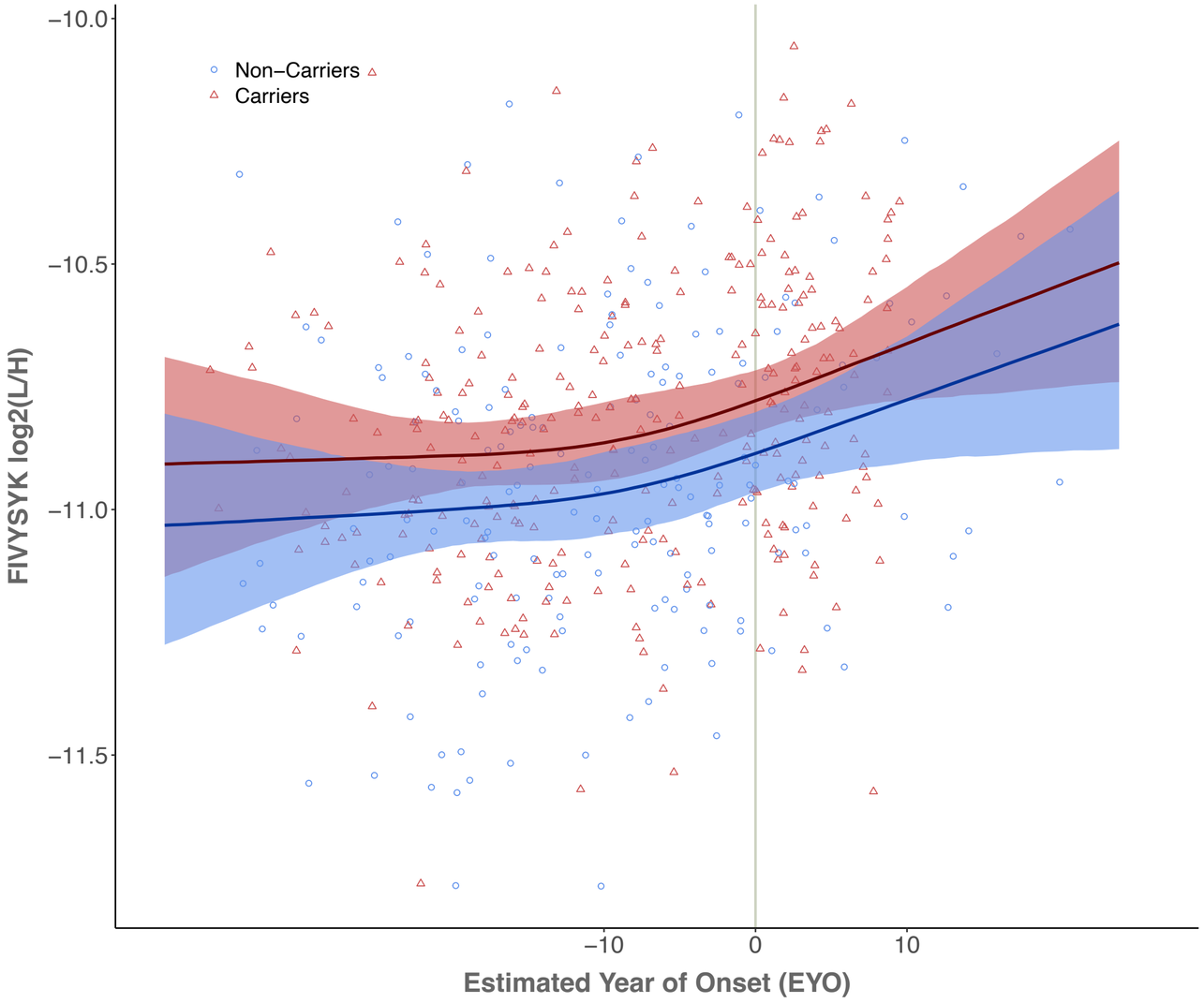
YWHAB level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



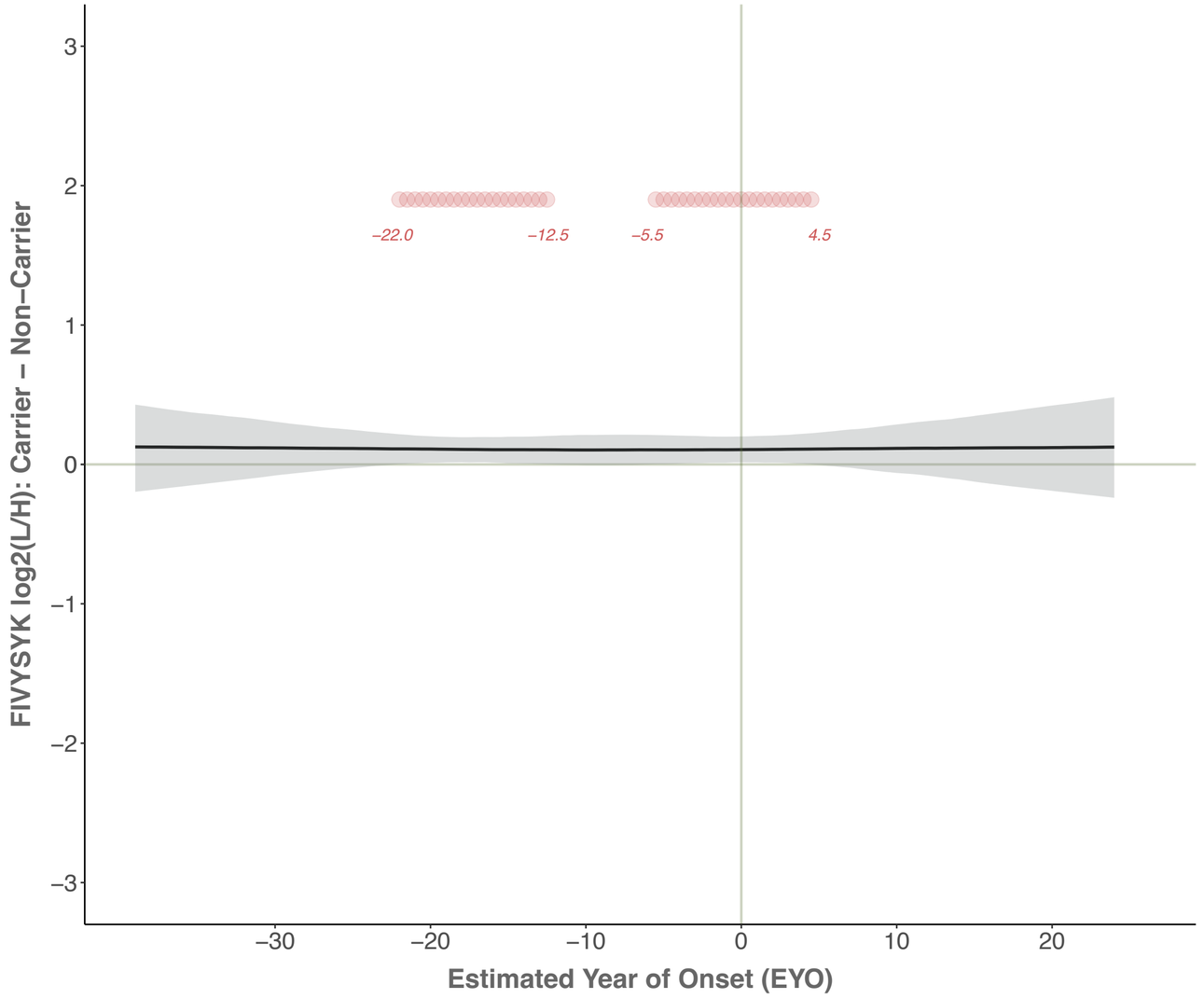
YWHAB level difference in mutation carriers and non−carriers with 99% confidence interval.



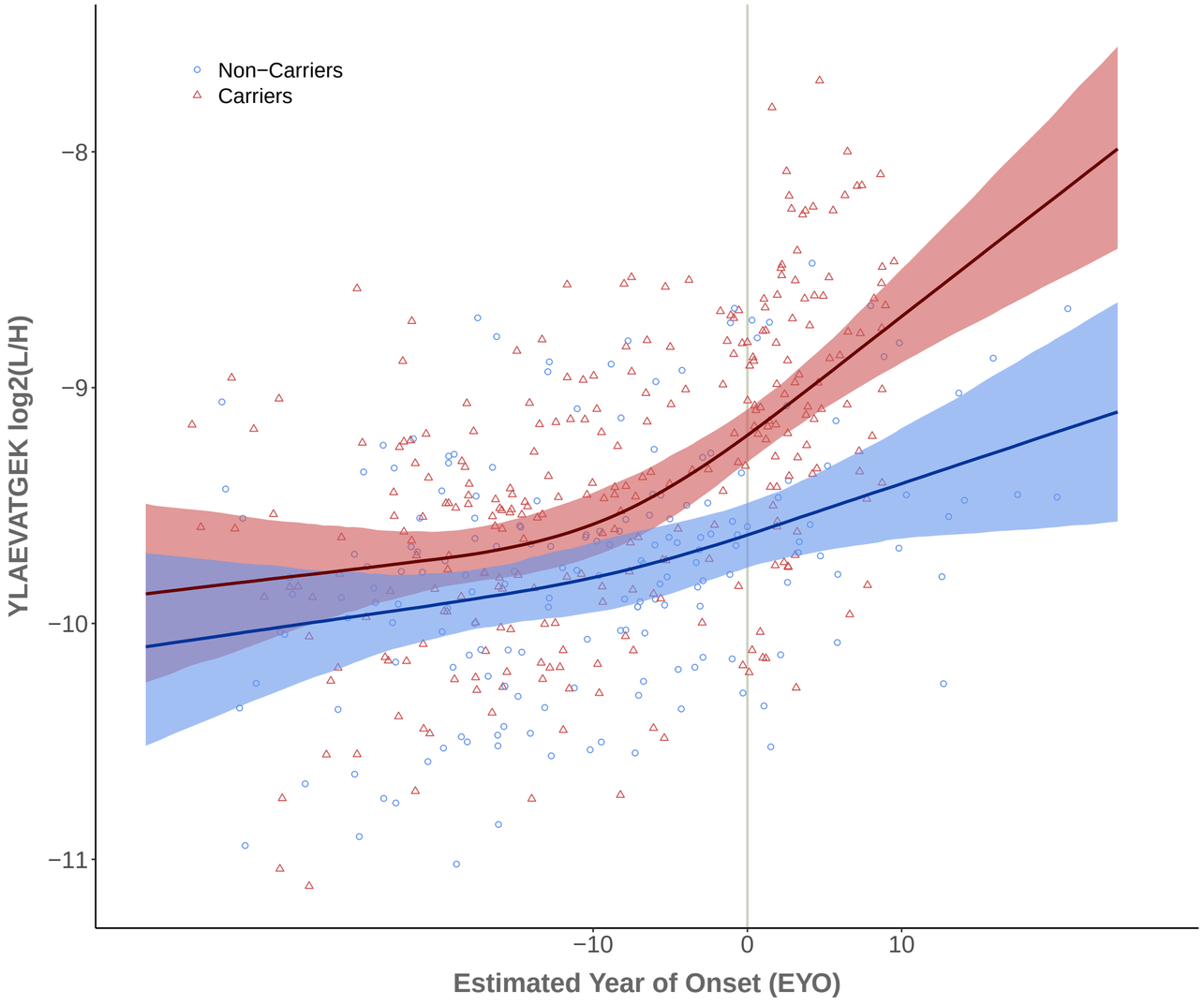
GMFB level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



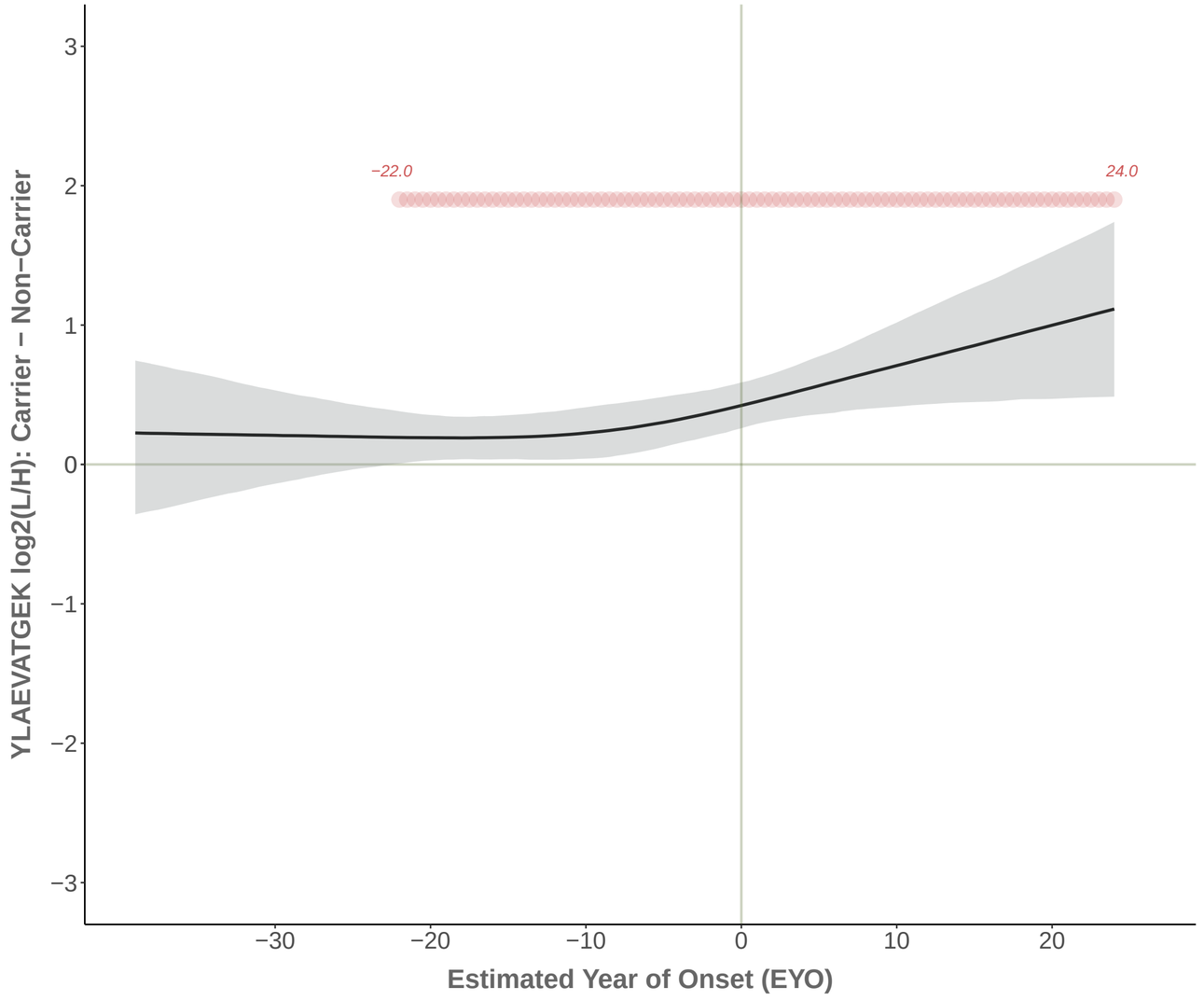
GMFB level difference in mutation carriers and non−carriers with 99% confidence interval.



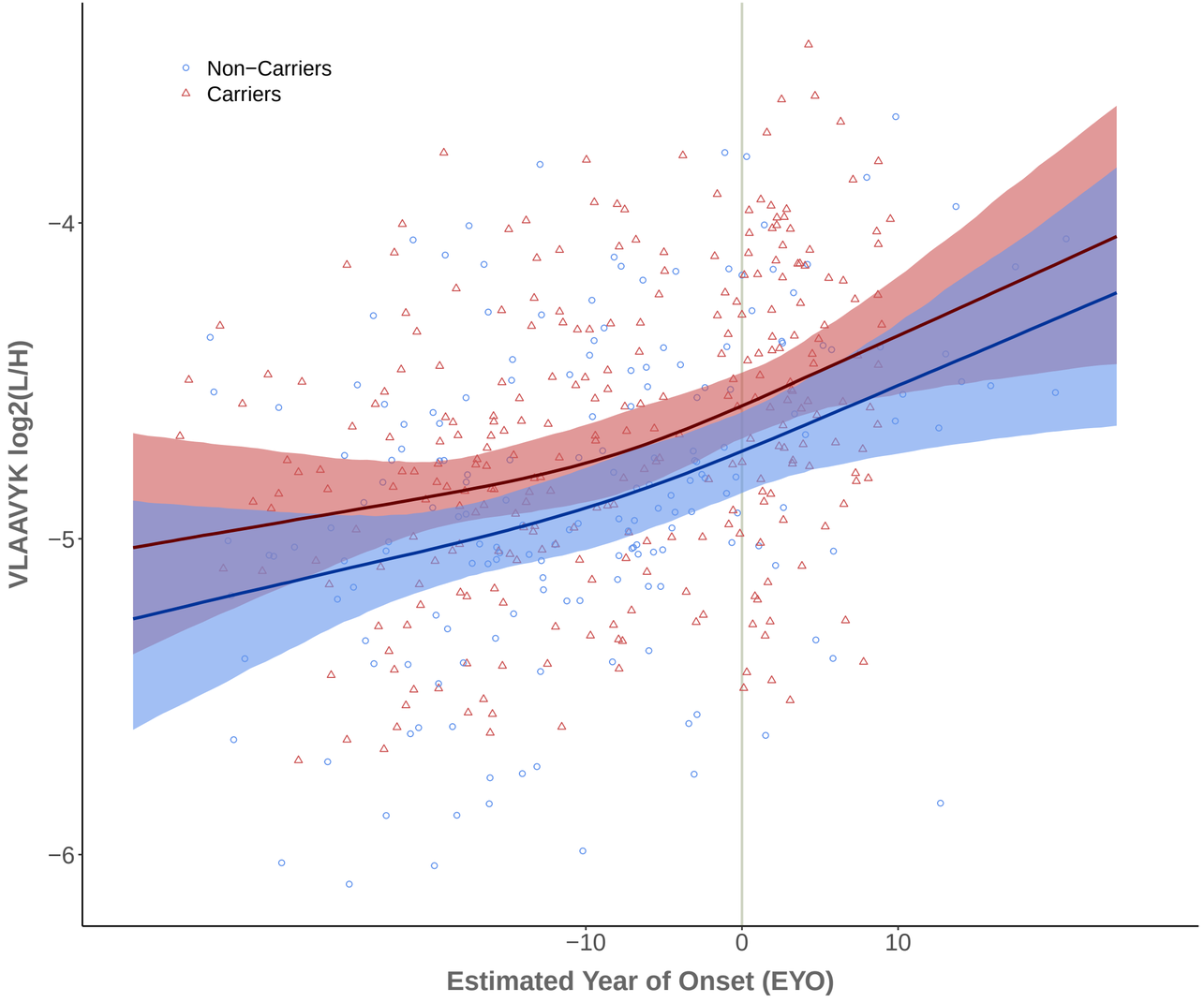
YWHAG level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



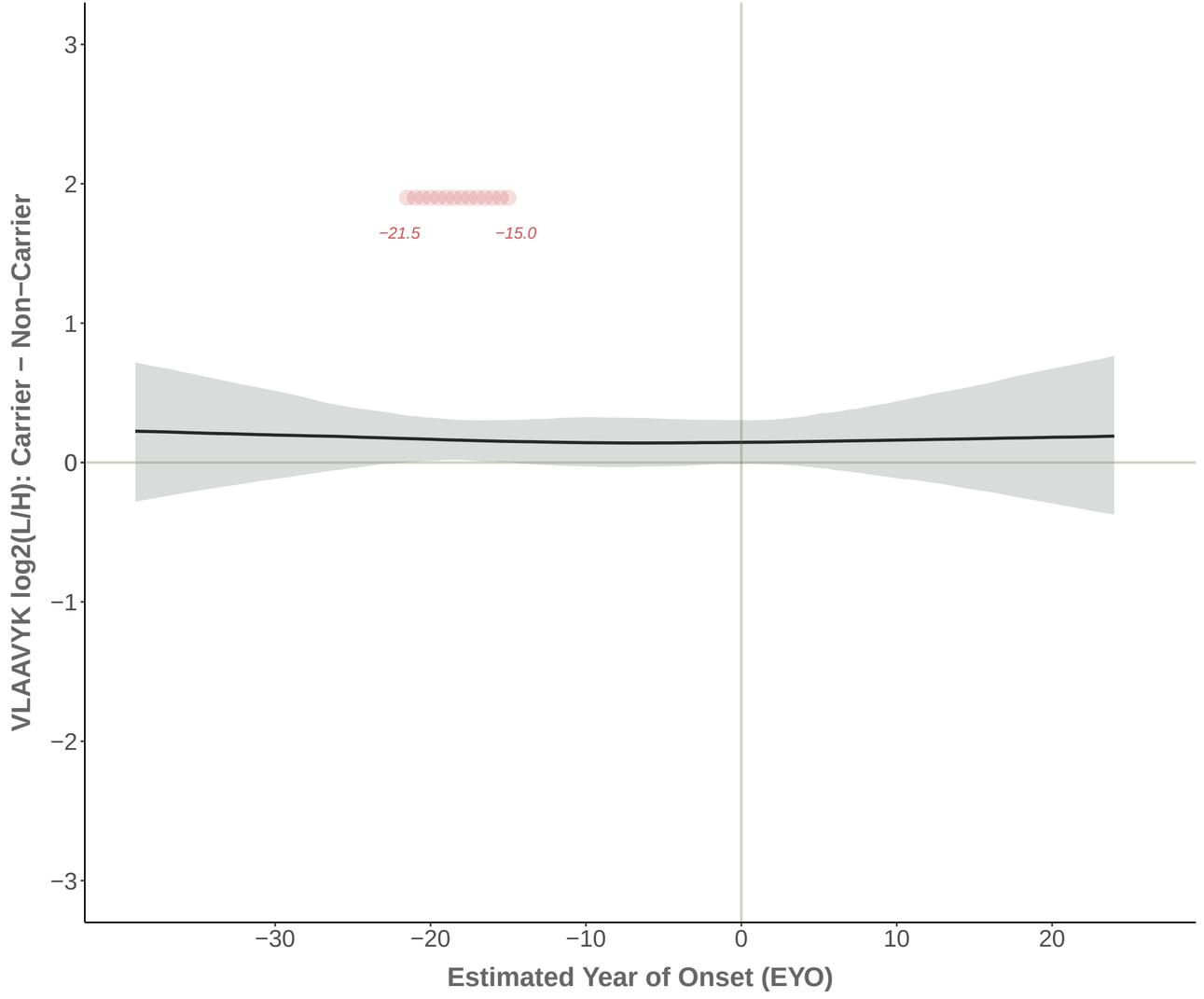
YWHAG level difference in mutation carriers and non−carriers with 99% confidence interval.



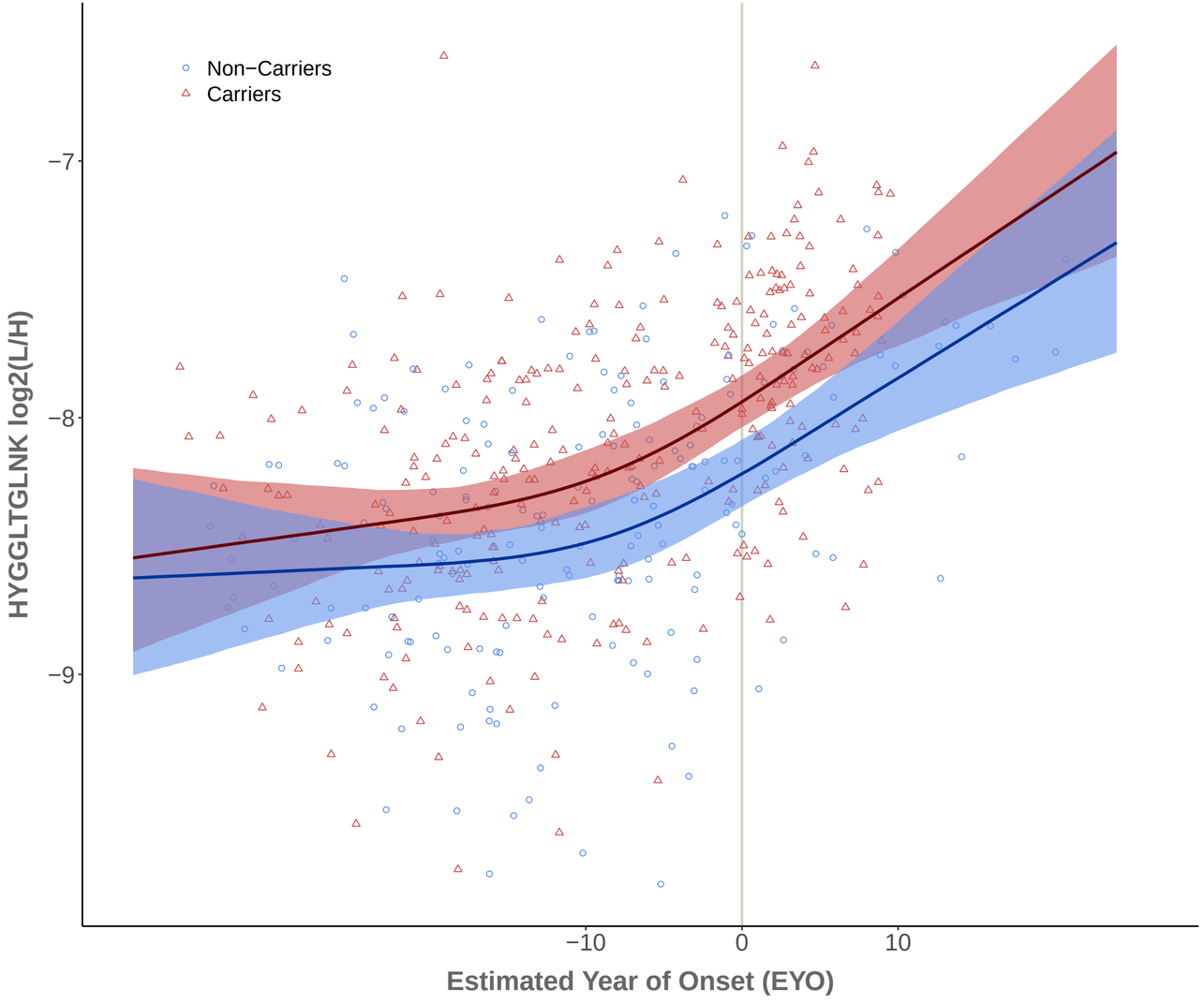
ALDOA level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



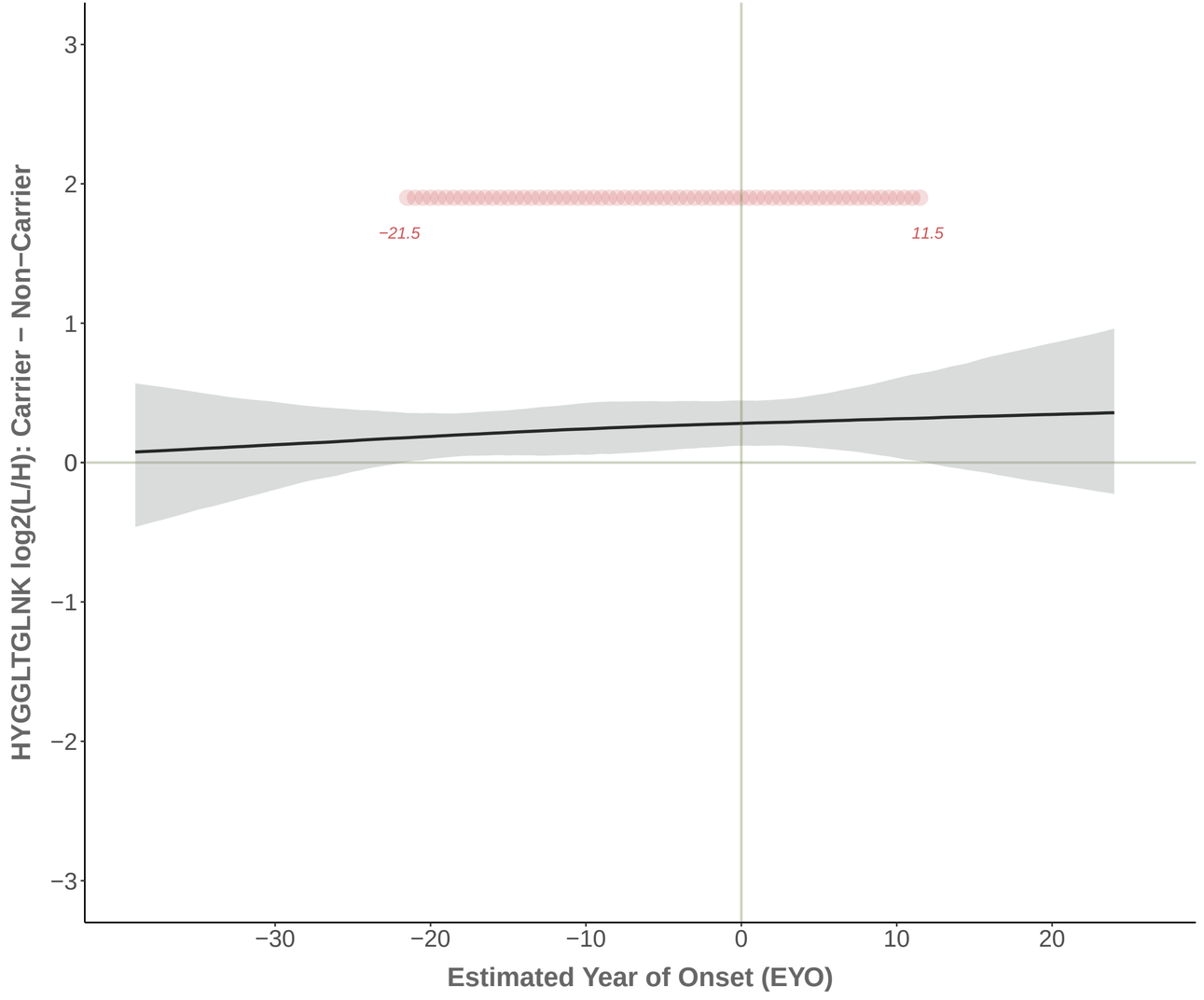
ALDOA level difference in mutation carriers and non−carriers with 99% confidence interval.



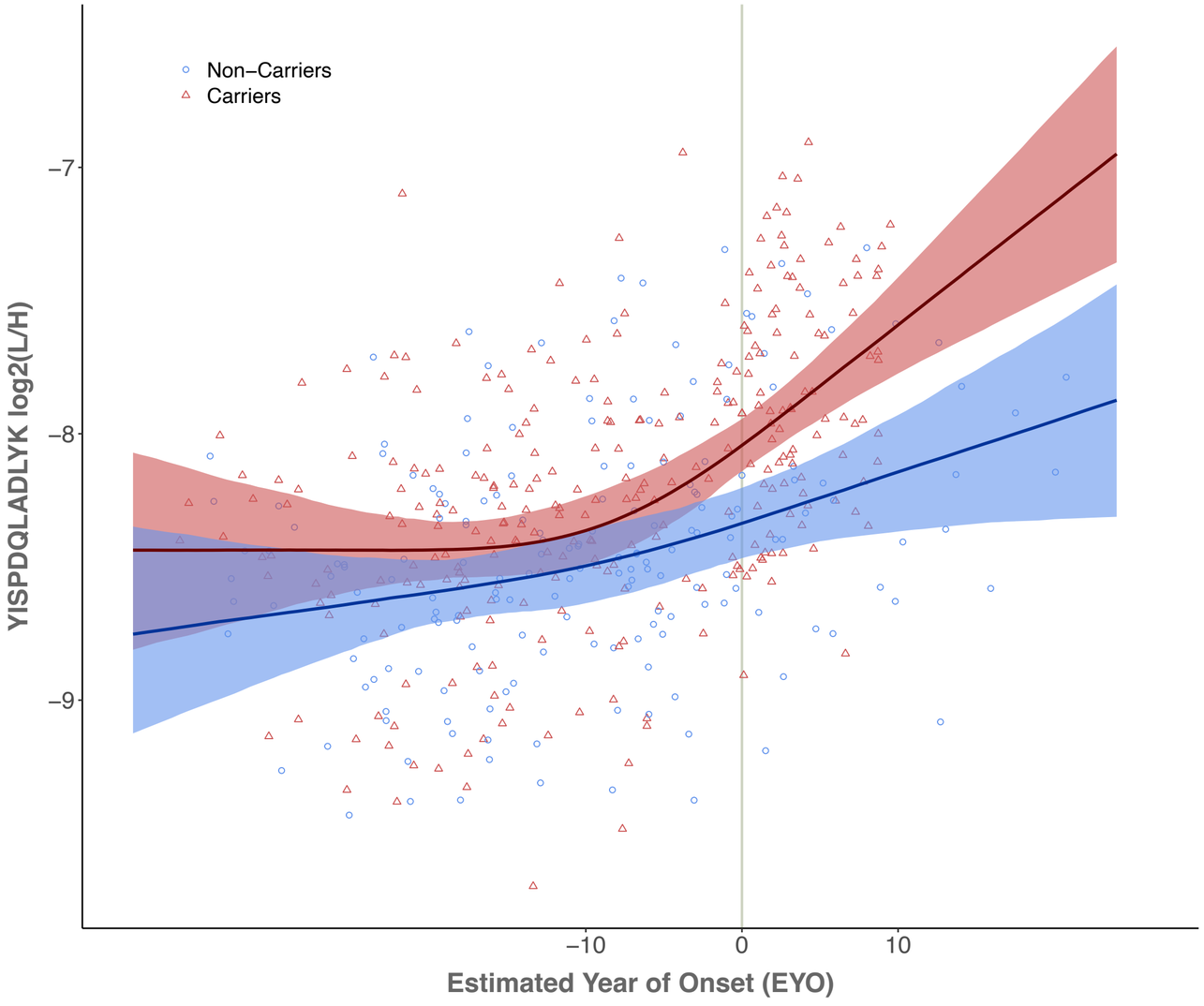
PGAM1 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



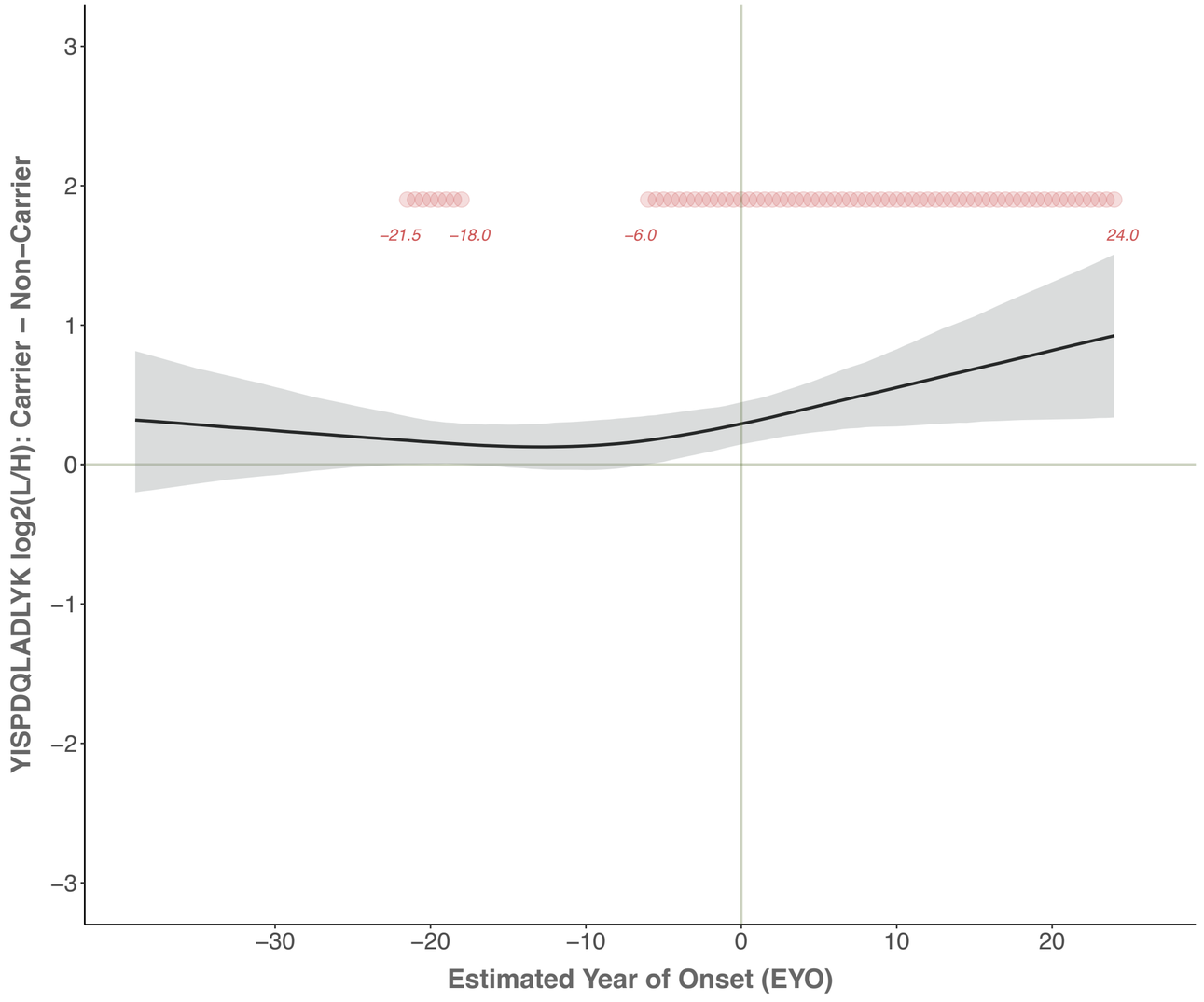
PGAM1 level difference in mutation carriers and non−carriers with 99% confidence interval.



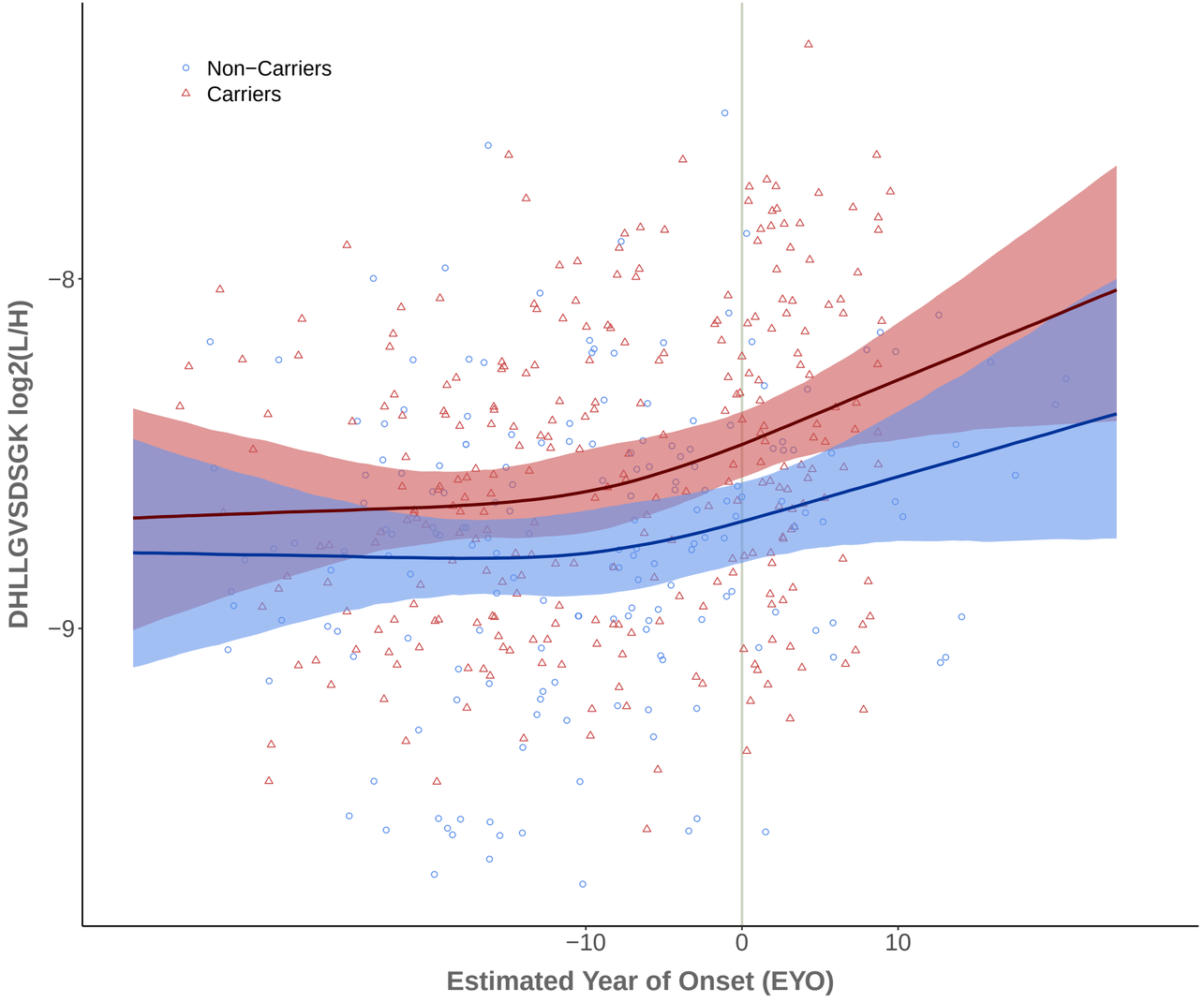
ENO1 level in mutation carriers and non−carriers with 99% confidence interval. 6 outliers removed for visualization purposes.



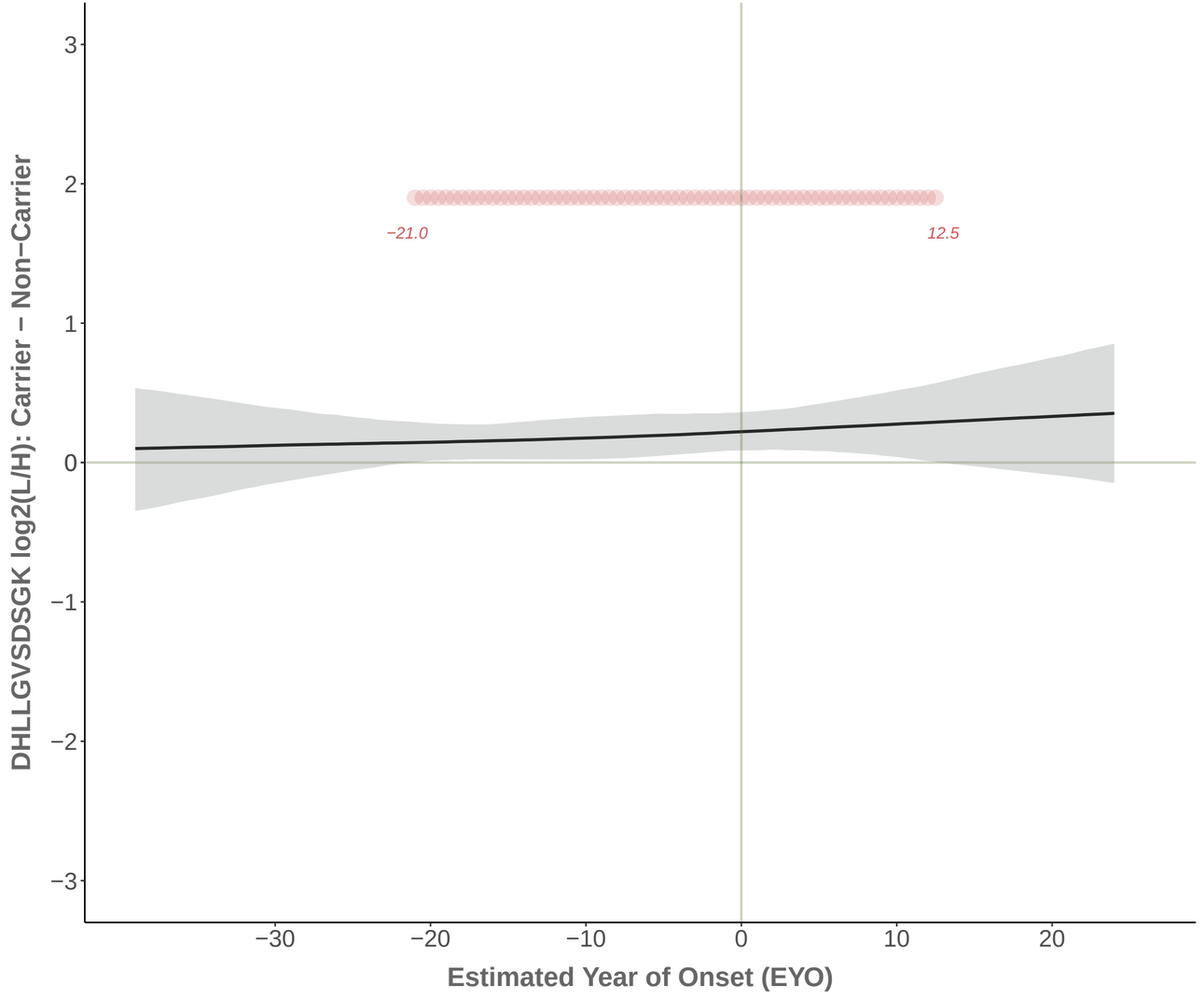
ENO1 level difference in mutation carriers and non−carriers with 99% confidence interval.



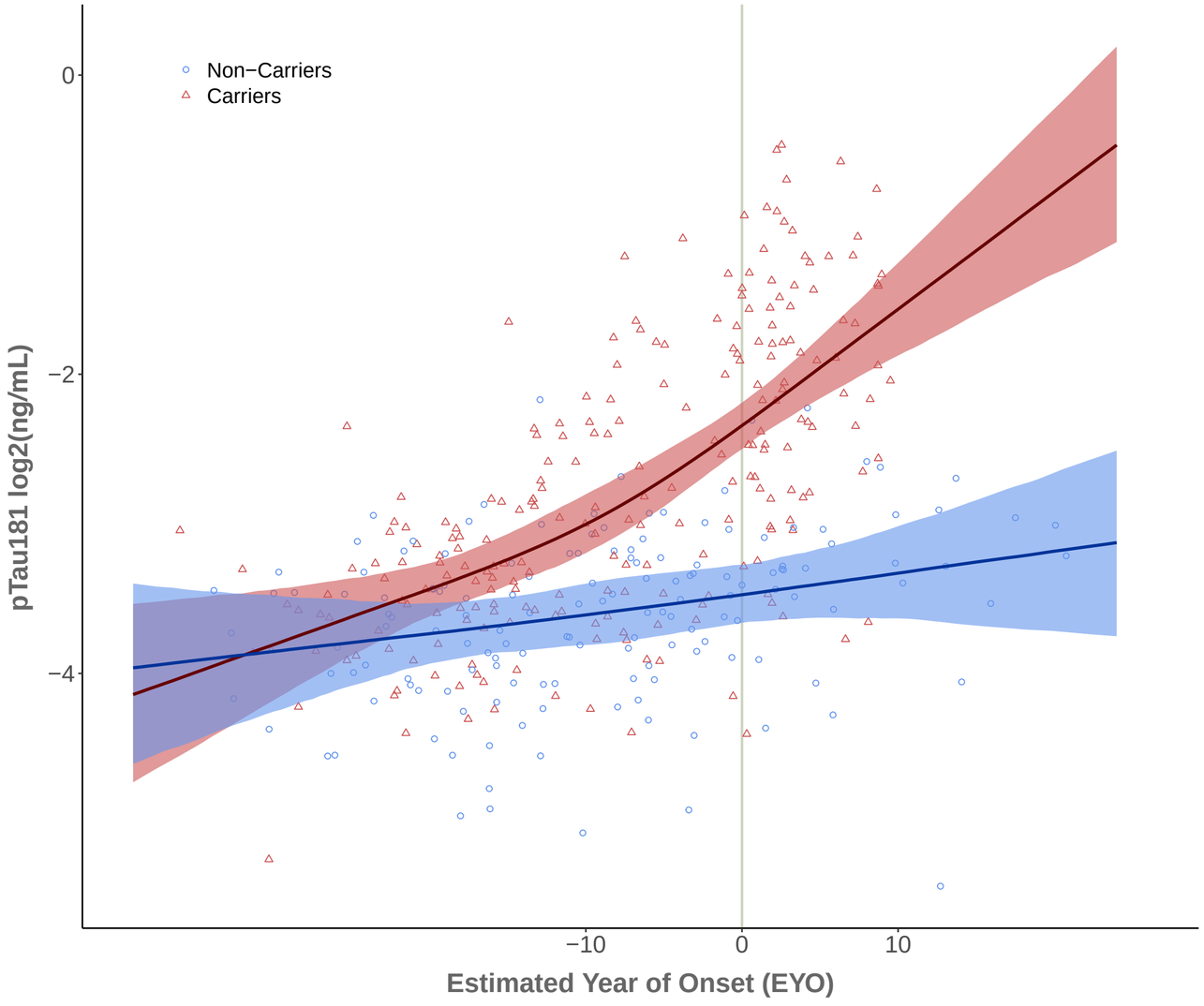
GDA level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



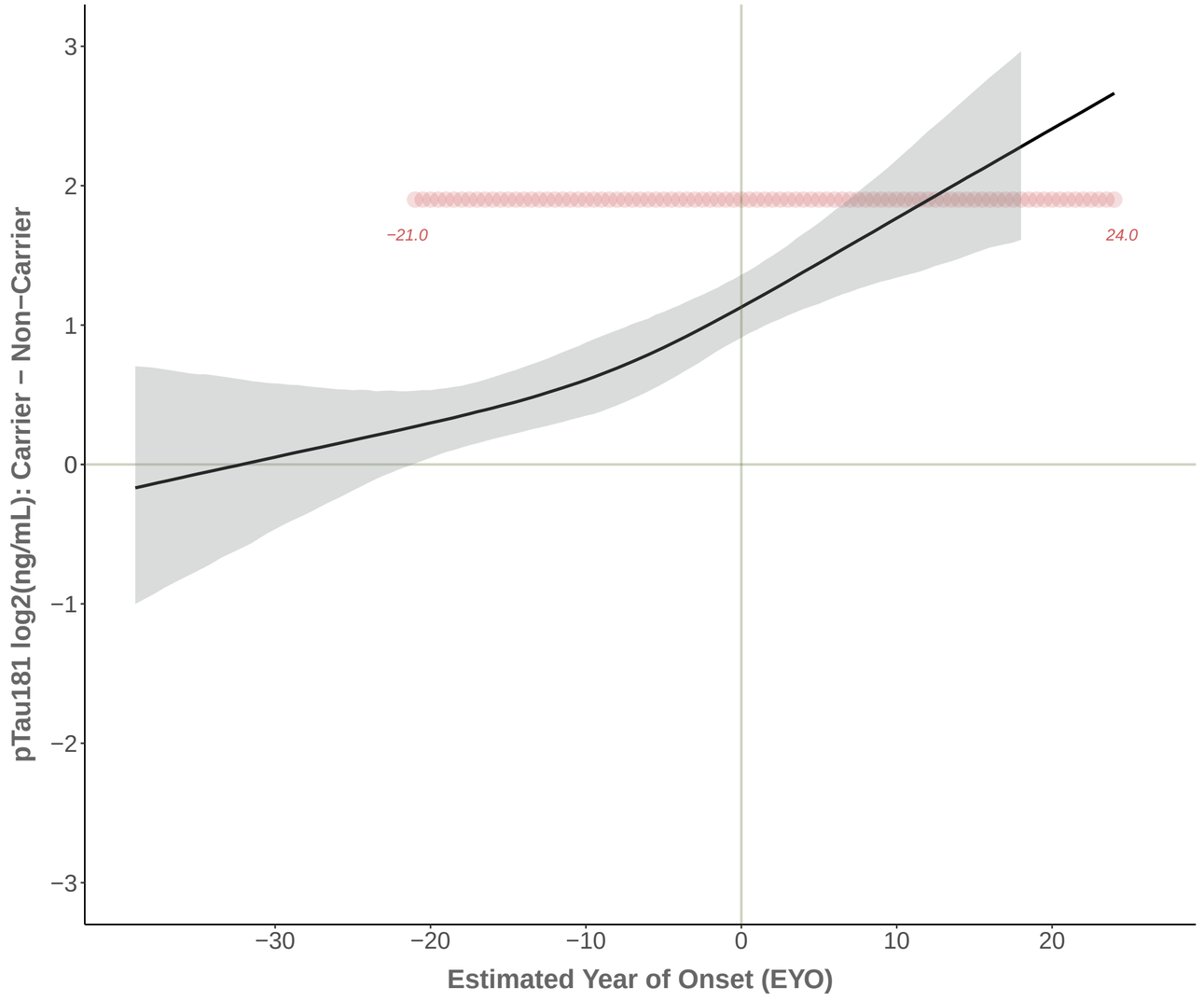
GDA level difference in mutation carriers and non−carriers with 99% confidence interval.



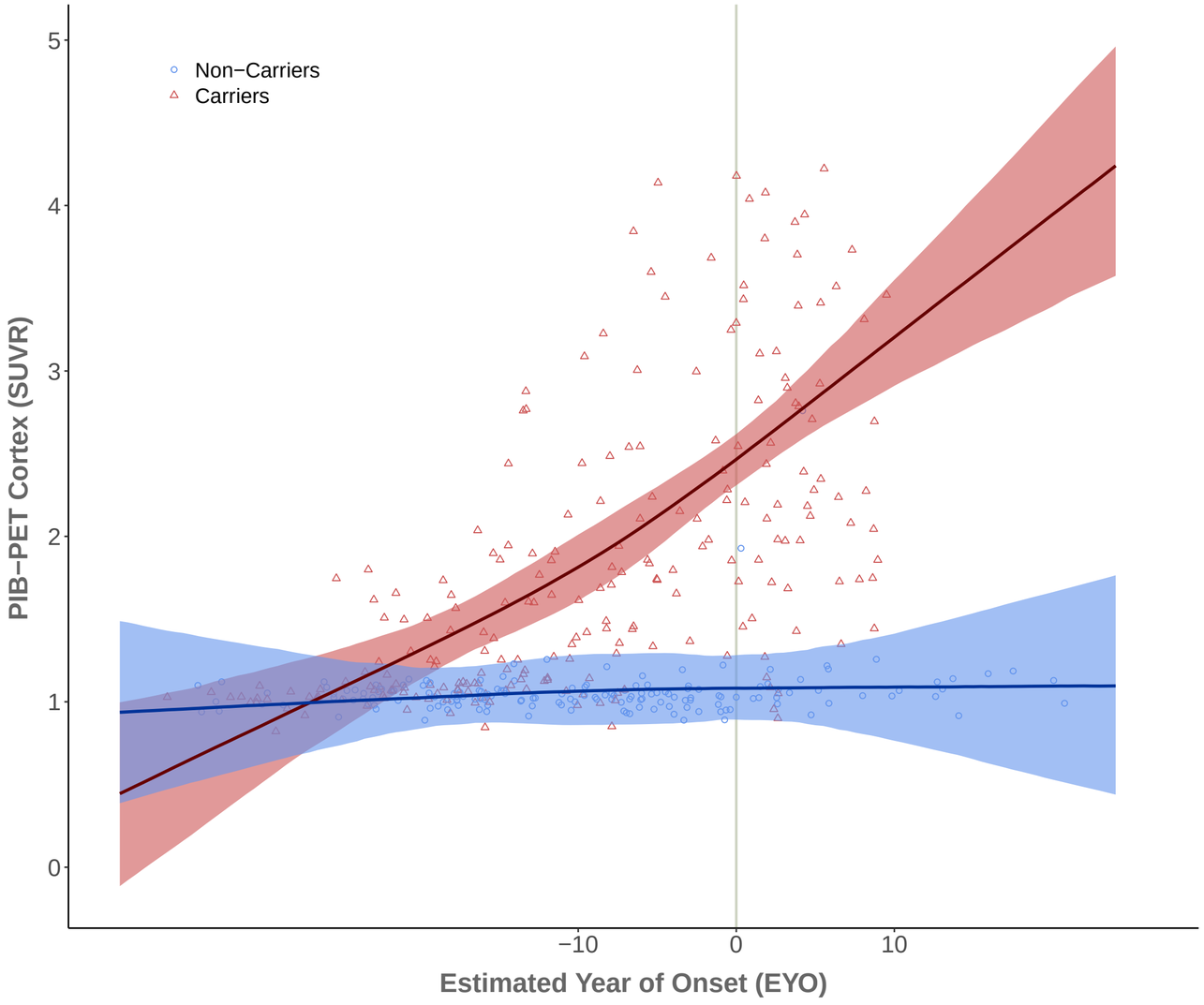
pTau181 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



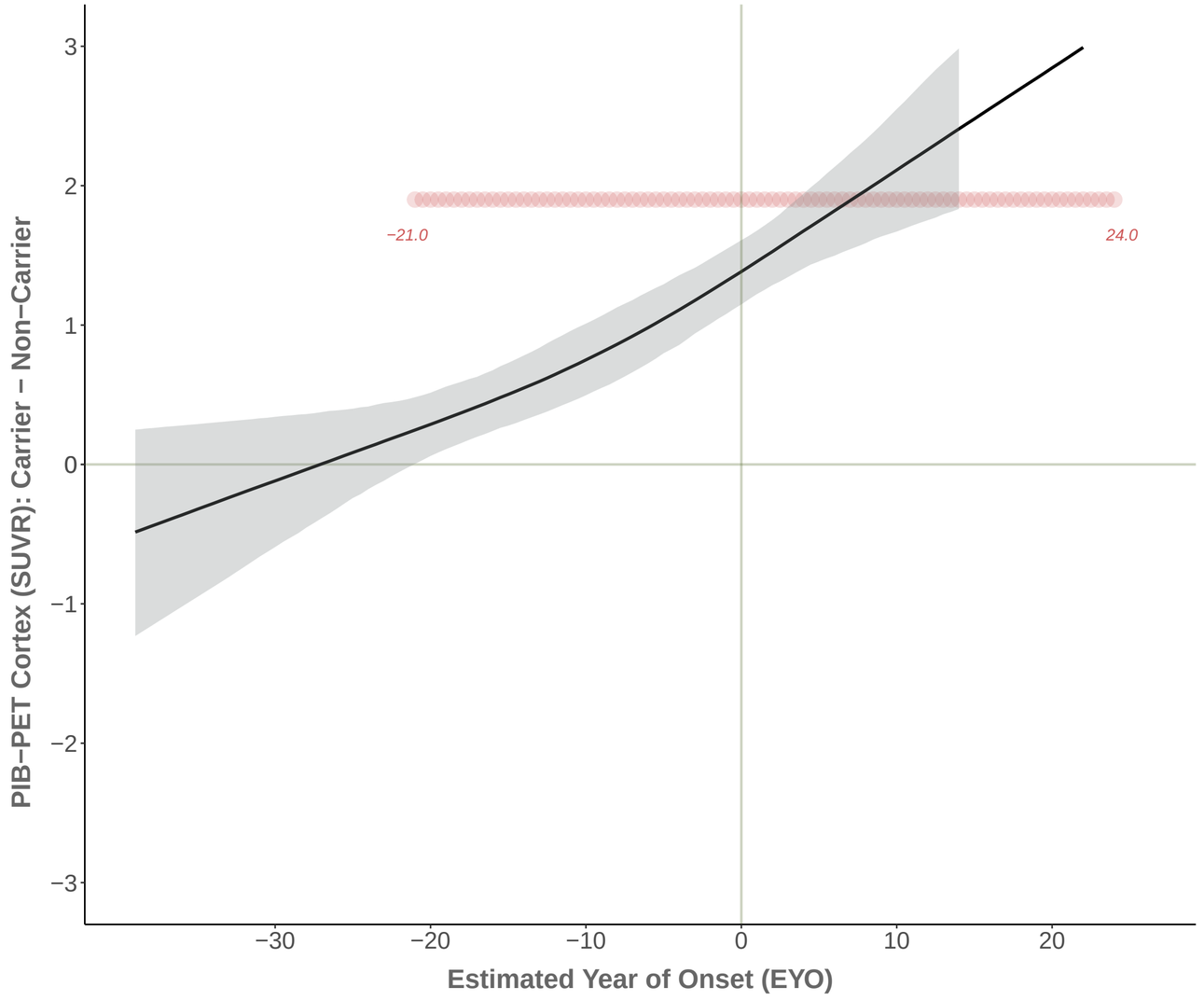
pTau181 level difference in mutation carriers and non−carriers with 99% confidence interval.



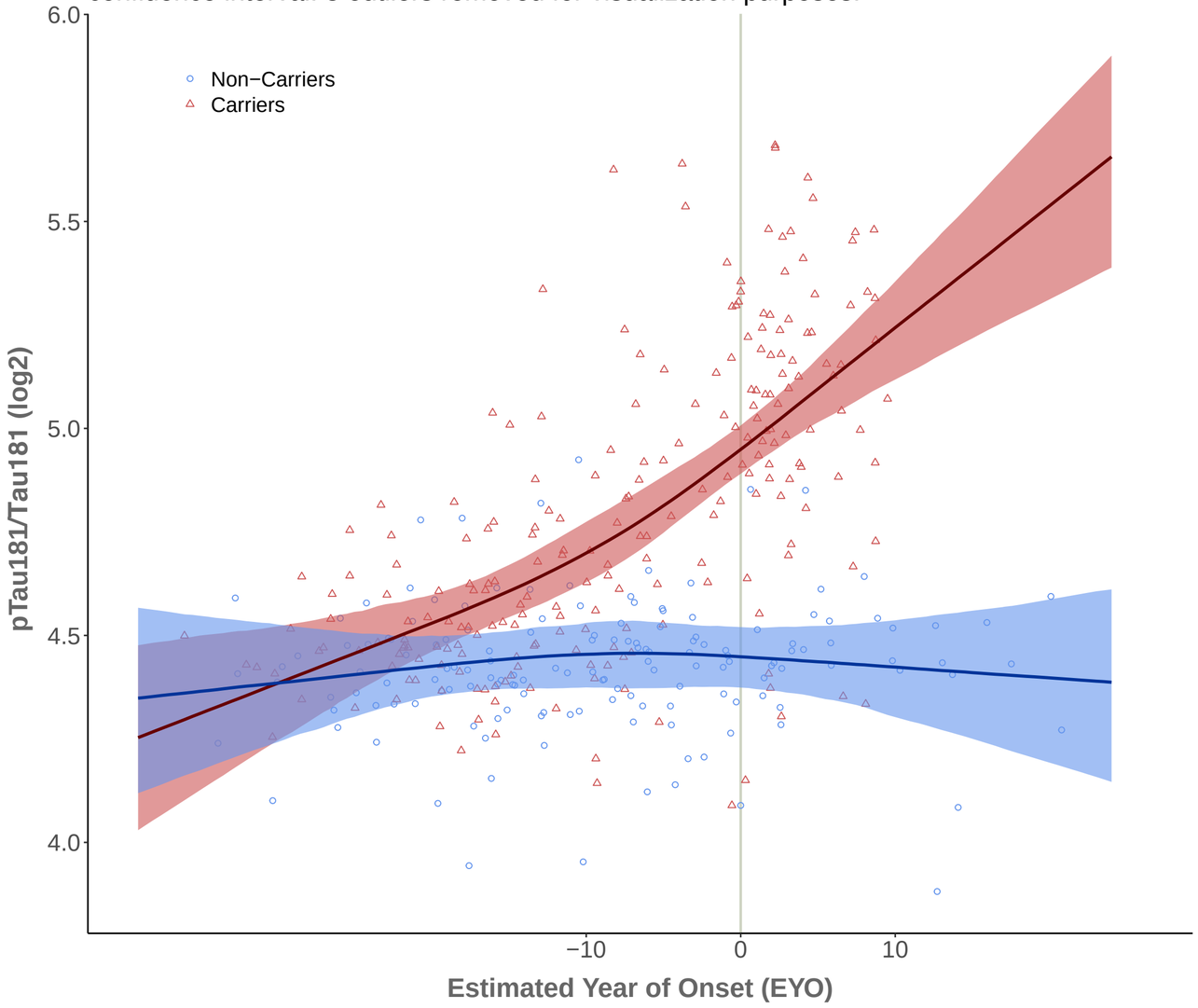
PIB−PET Cortex SUVR in mutation carriers and non−carriers with 99% confidence interval. 10 outliers removed for visualization purposes.



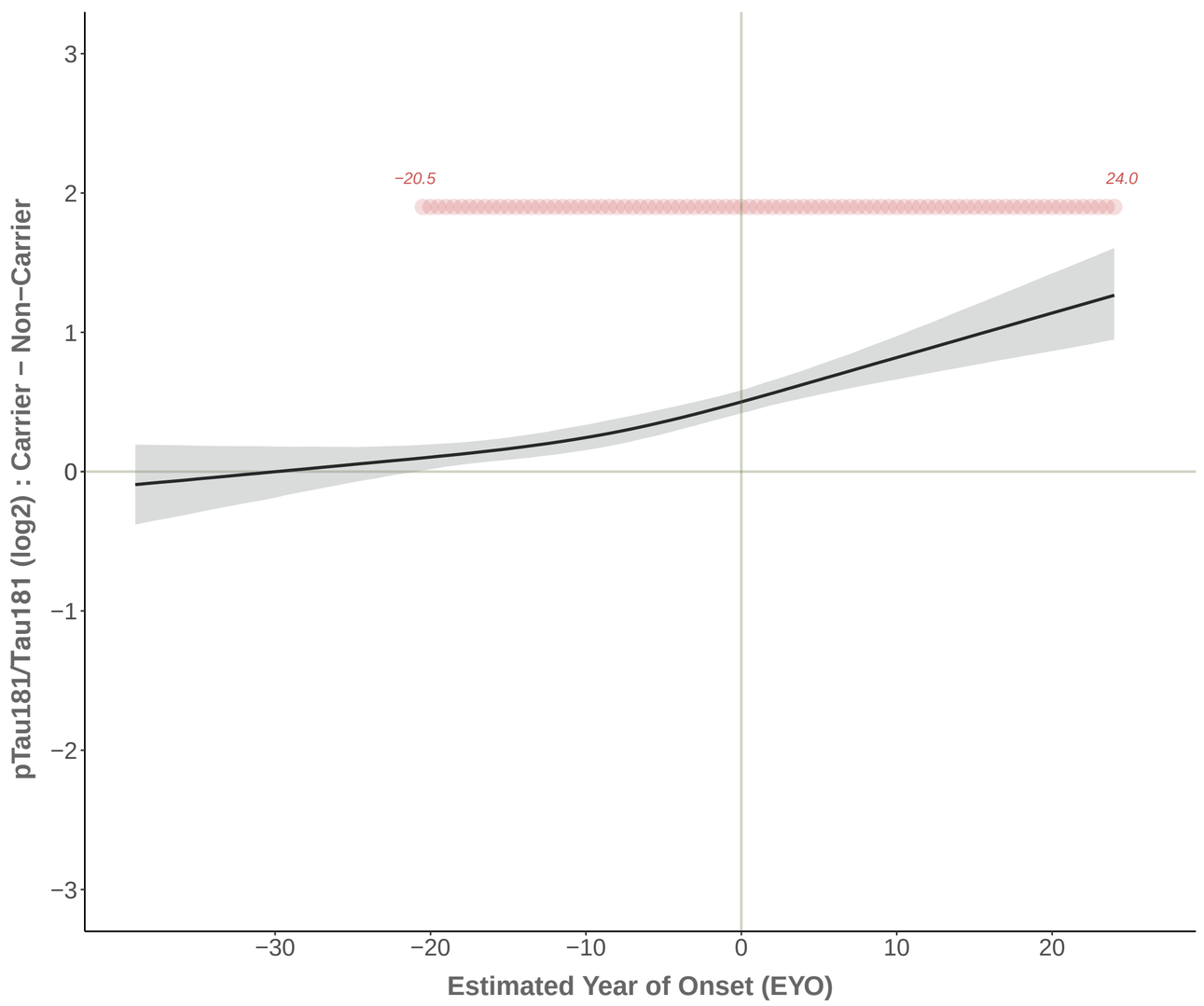
PIB−PET Cortex SUVR difference in mutation carriers and non−carriers with 99% confidence interval.



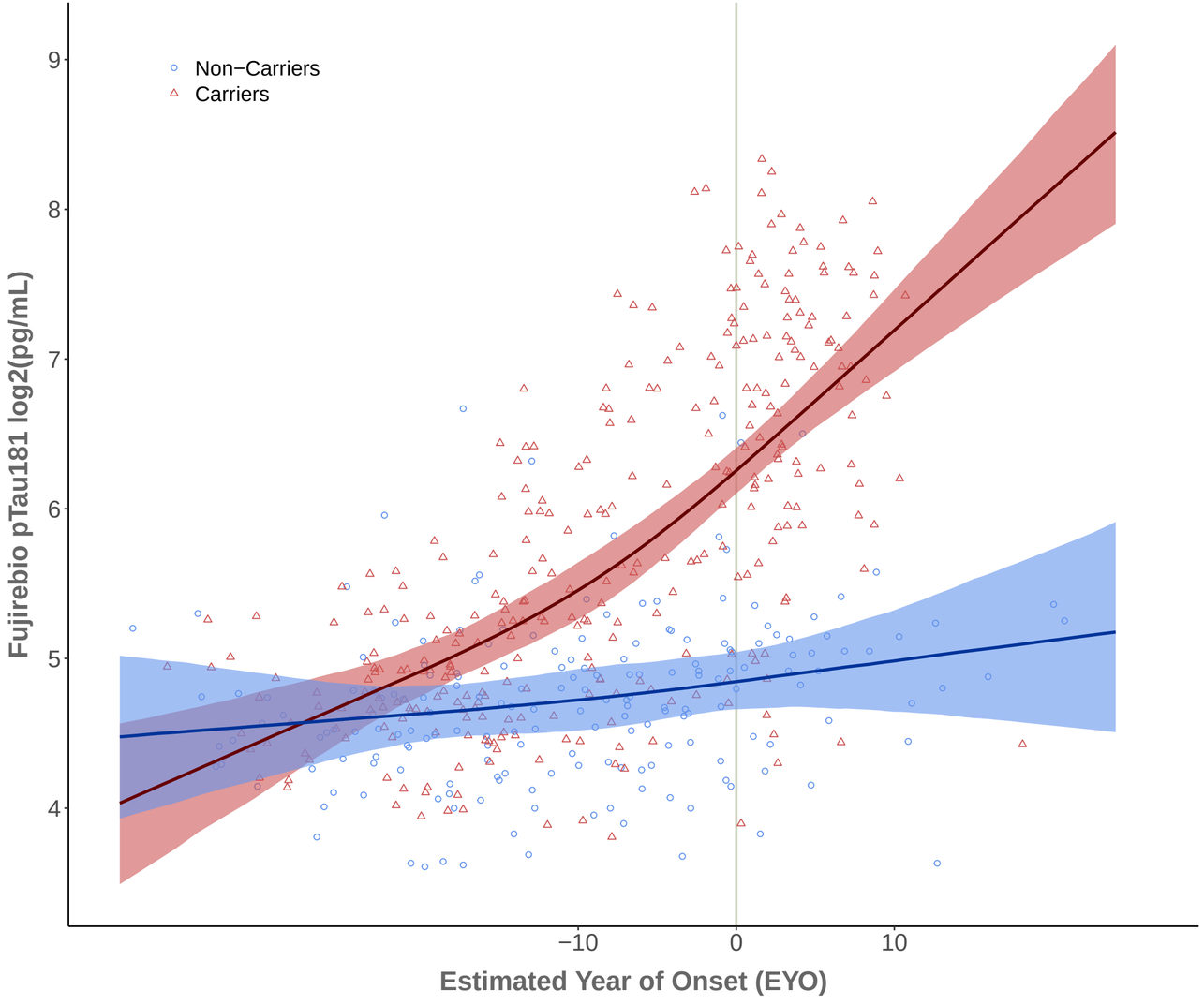
pTau181/Tau181 ratio in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



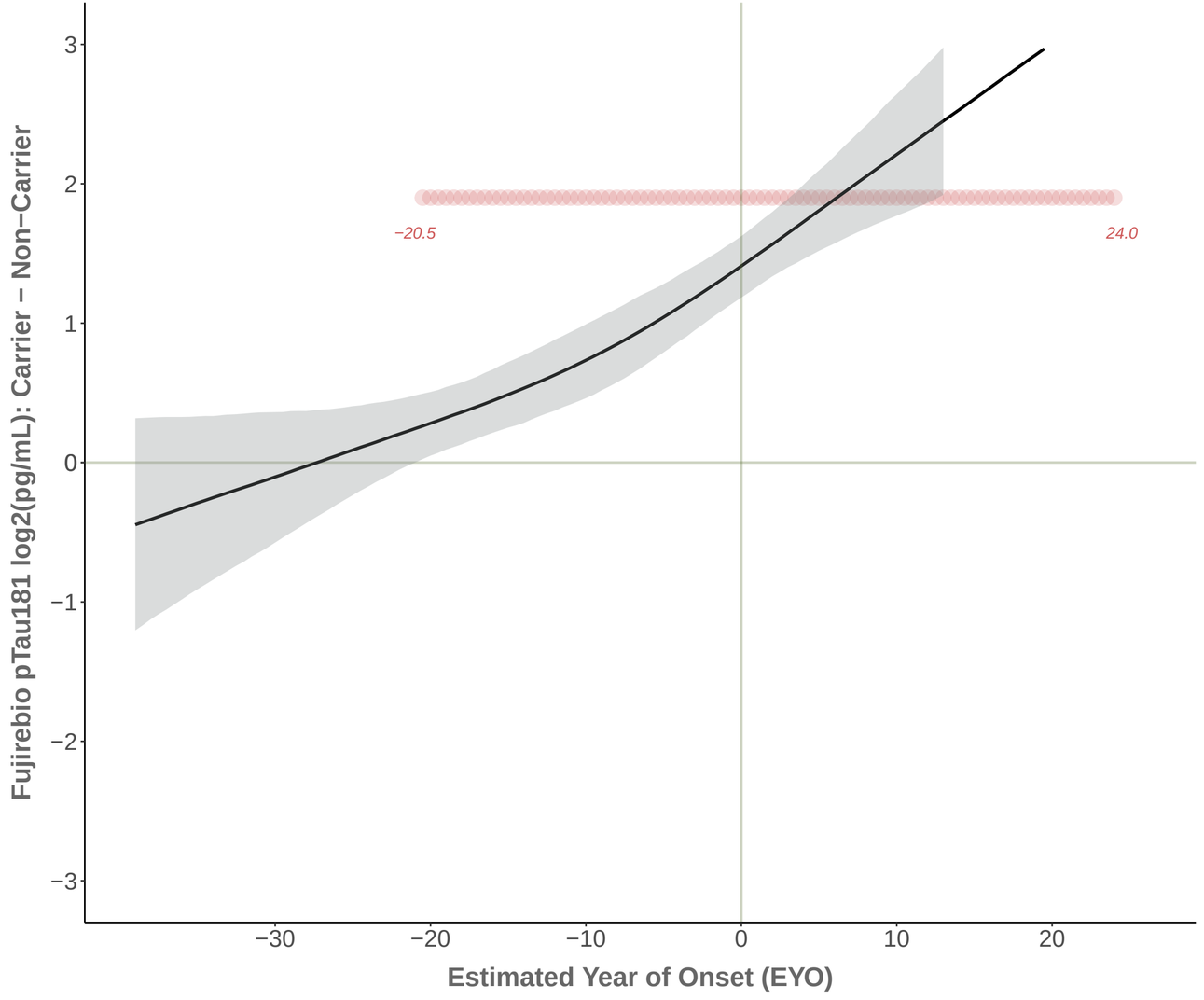
pTau181/Tau181 ratio difference in mutation carriers and non−carriers with 99% confidence interval.



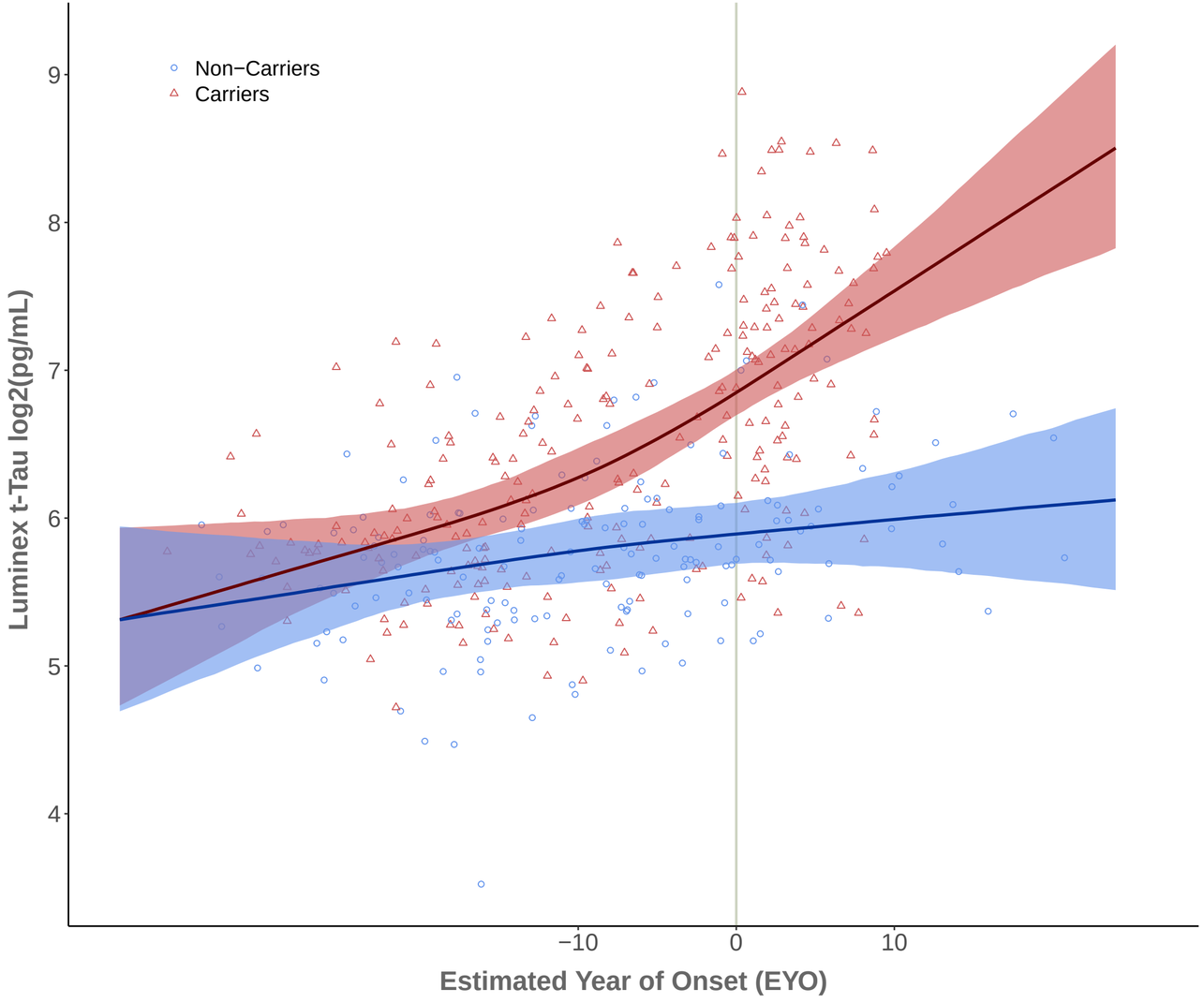
Fujirebio pTau181 level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



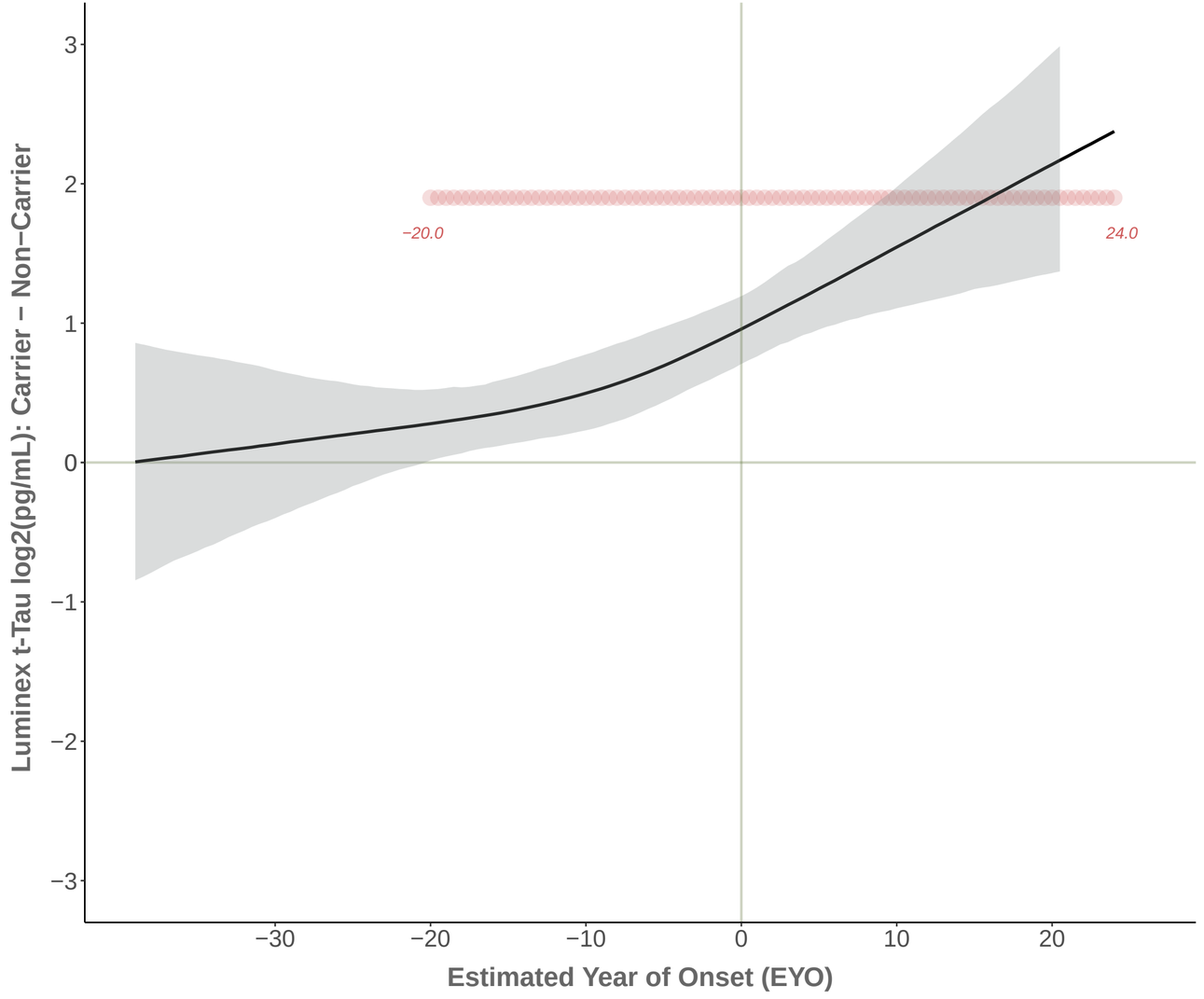
Fujirebio pTau181 level difference in mutation carriers and non−carriers with 99% confidence interval.



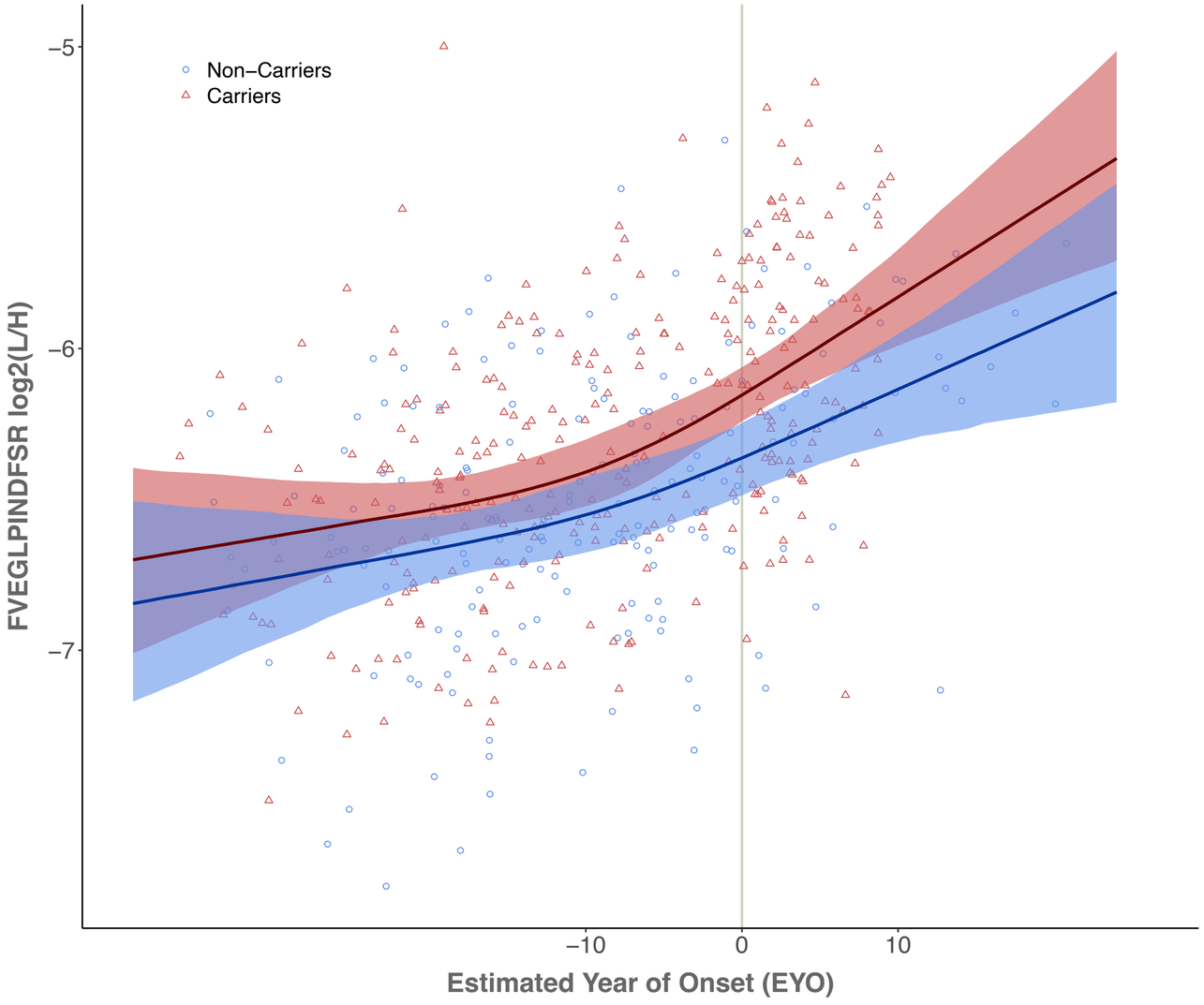
Luminex t-Tau level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



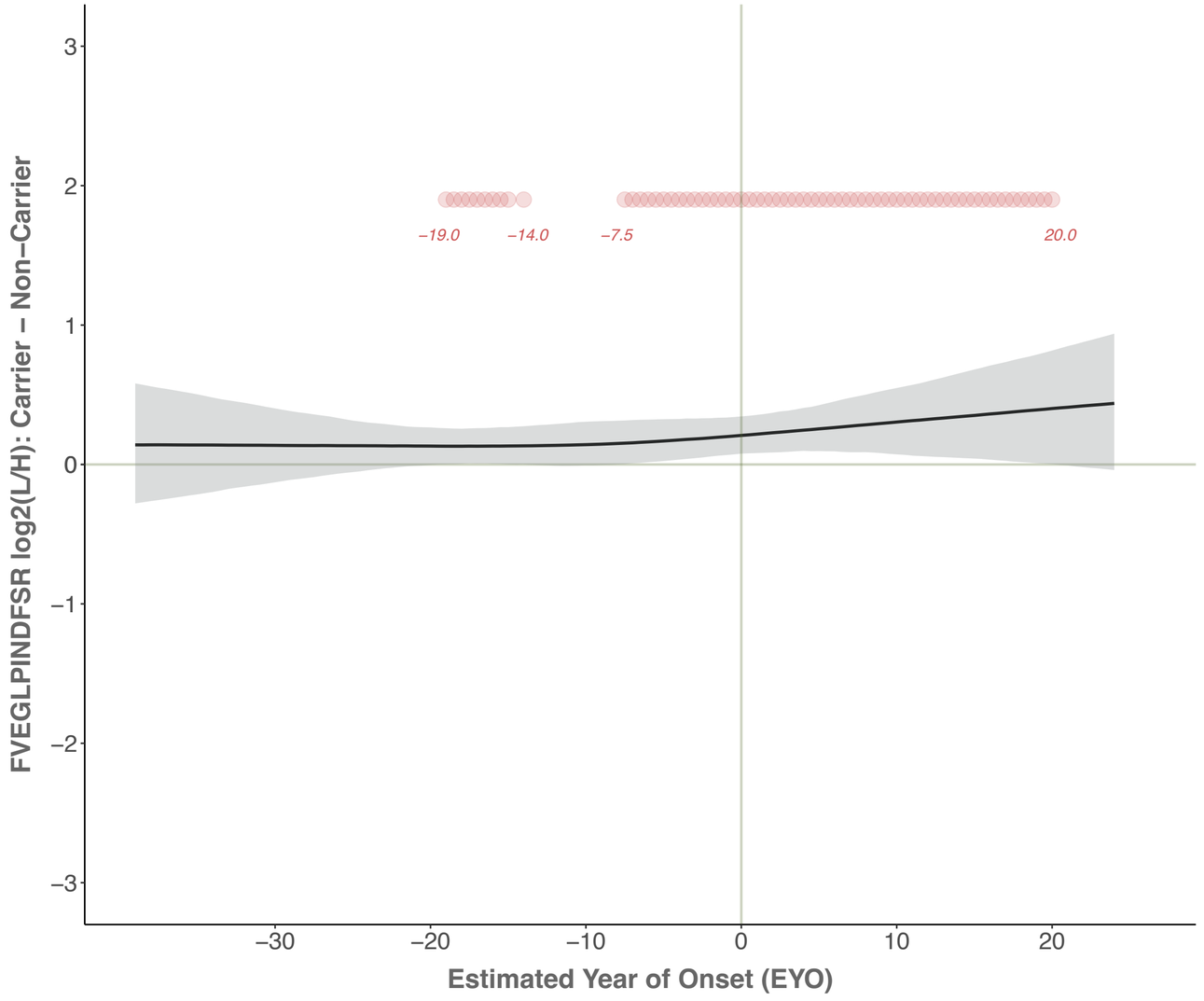
Luminex t-Tau level difference in mutation carriers and non−carriers with 99% confidence interval.



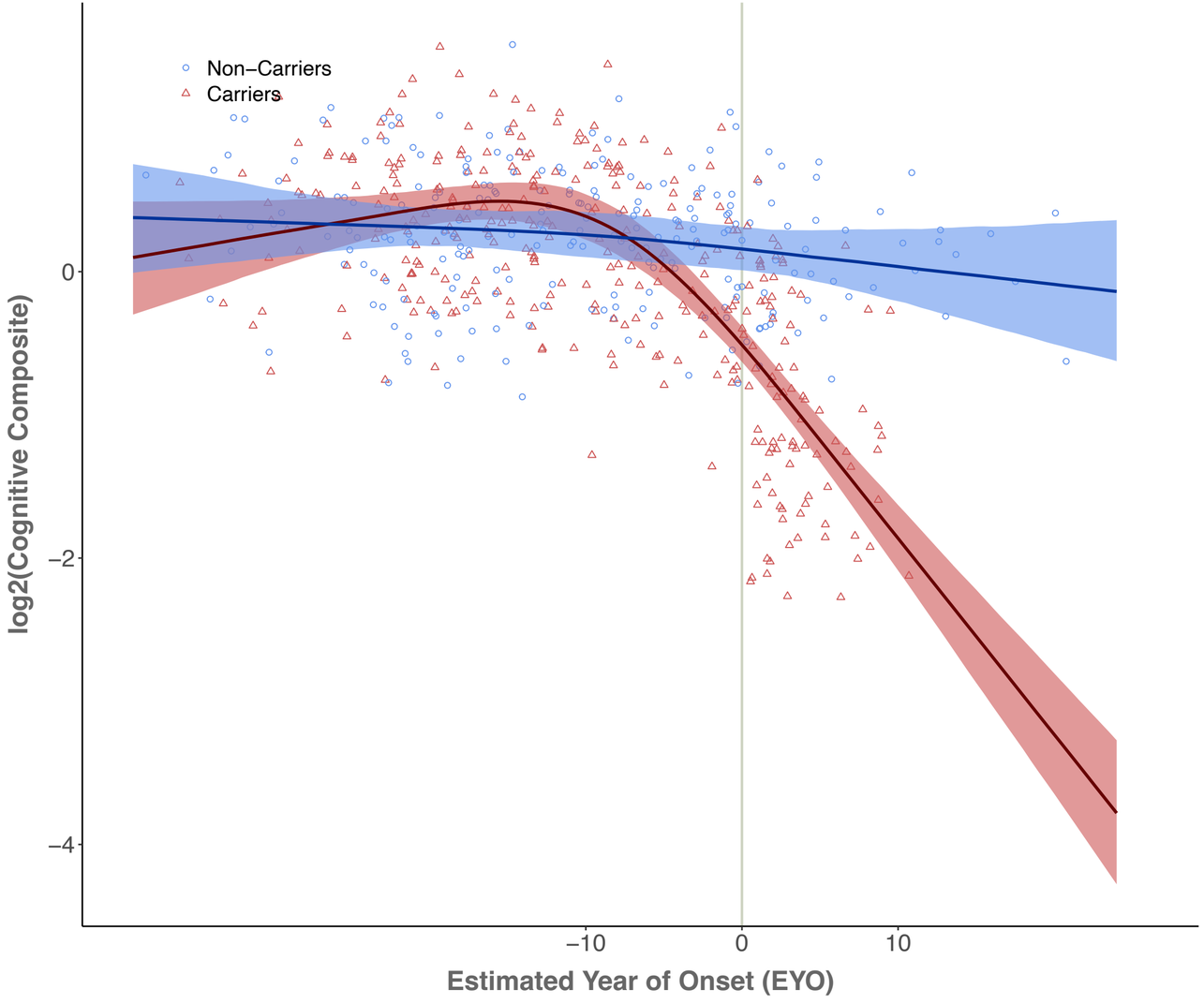
MDH1 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



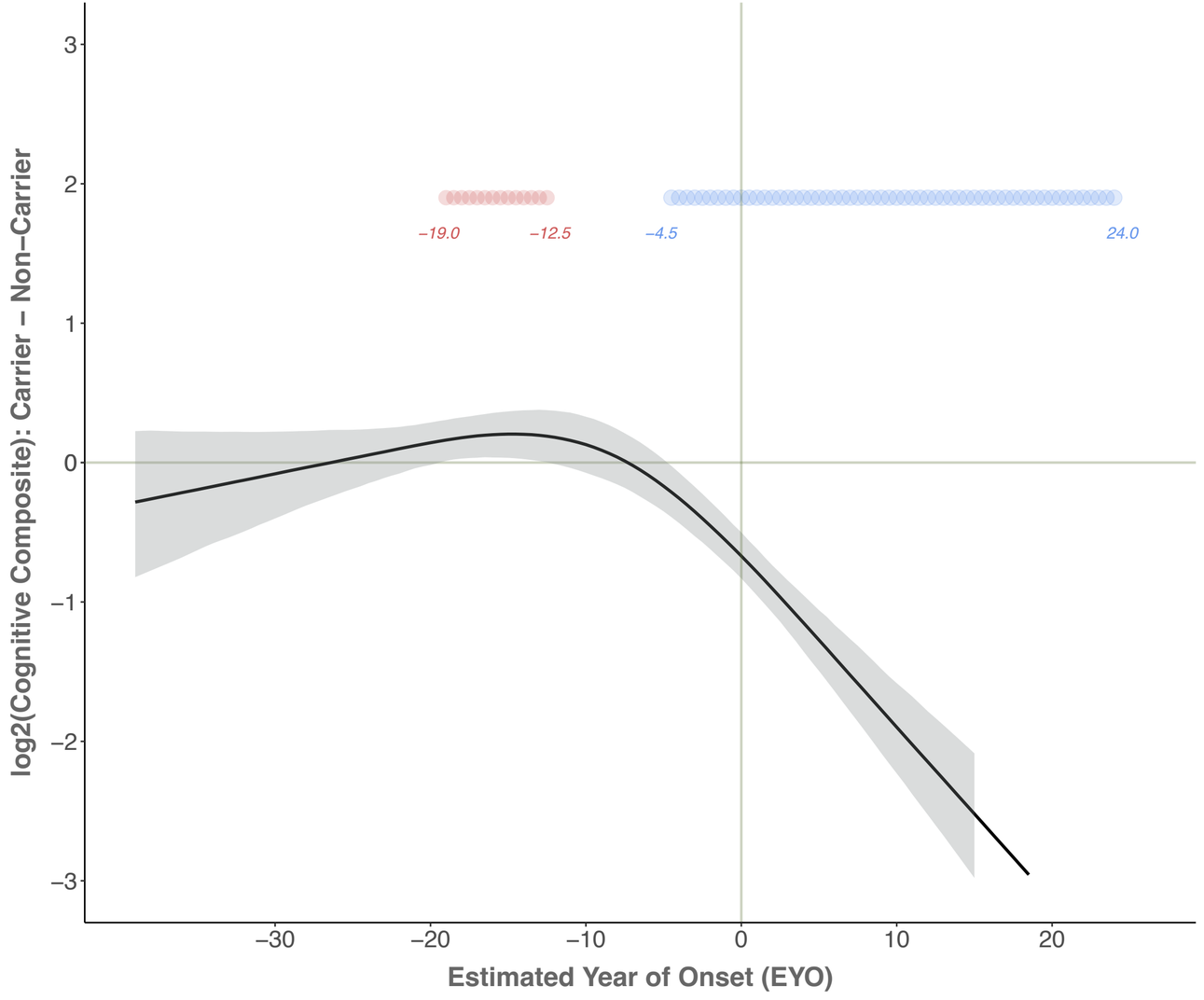
MDH1 level difference in mutation carriers and non−carriers with 99% confidence interval.



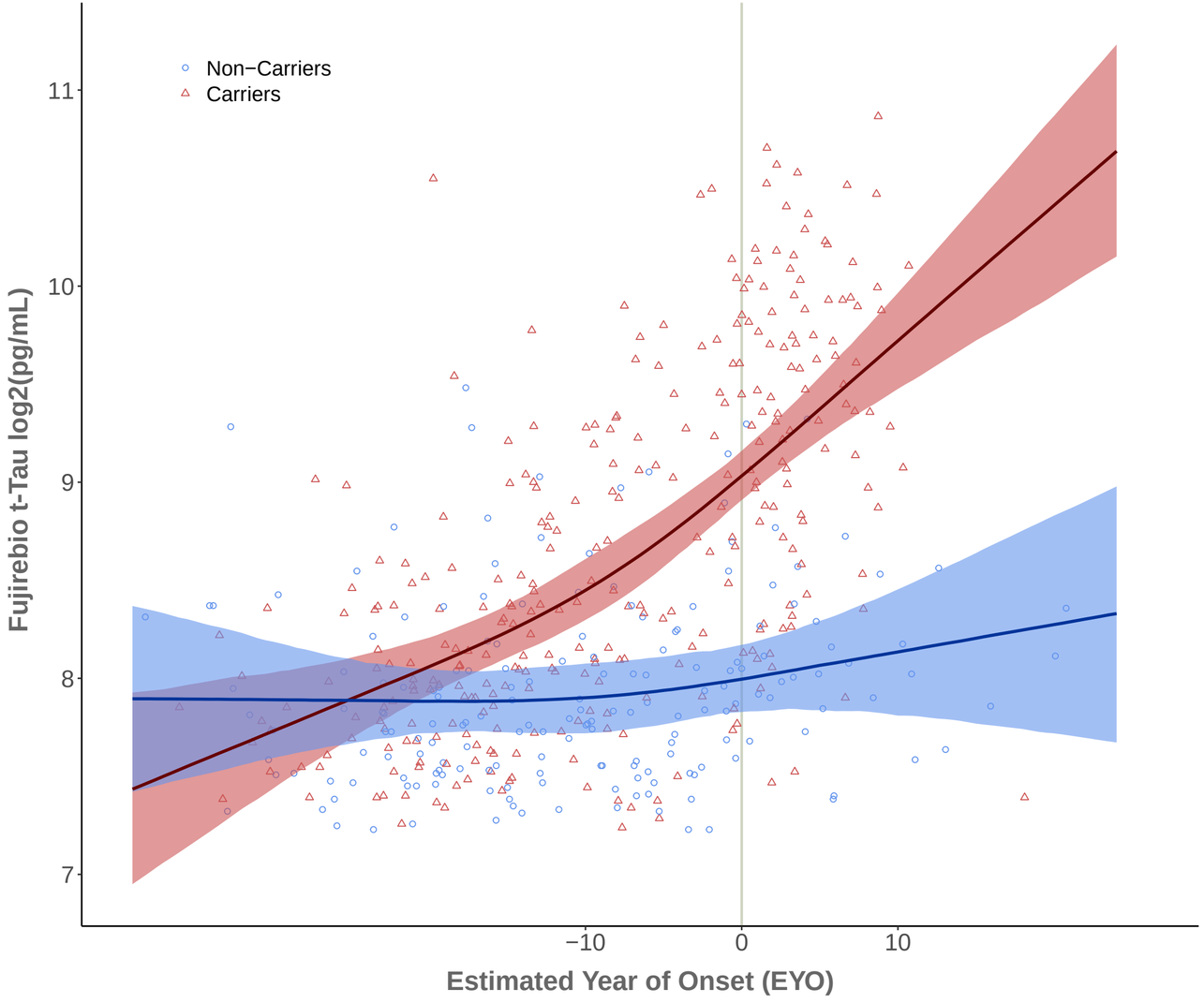
Cognitive Composite level in mutation carriers and non−carriers with 99% confidence interval. 11 outliers removed for visualization purposes.



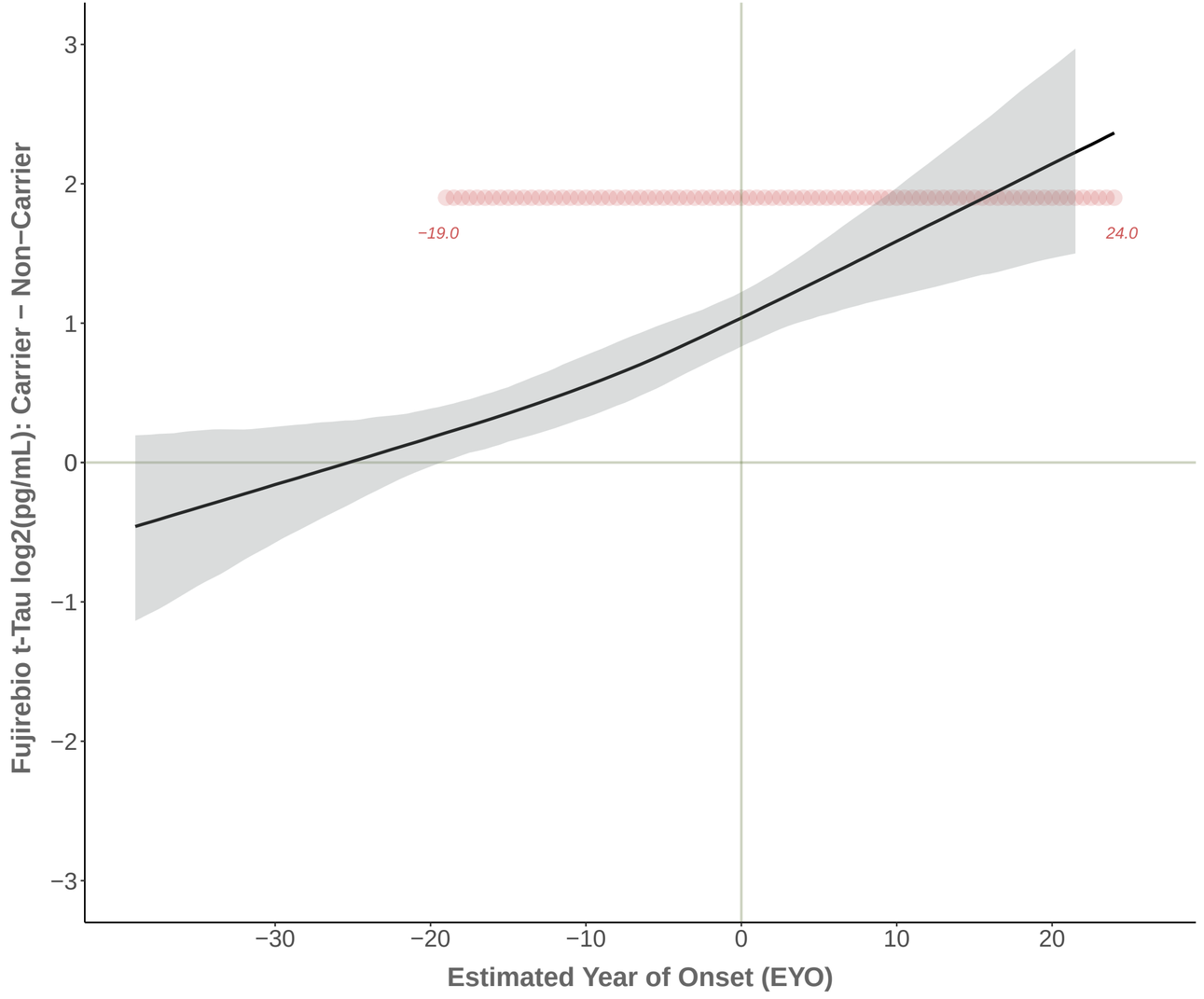
Cognitive Composite level difference in mutation carriers and non−carriers with 99% confidence interval.



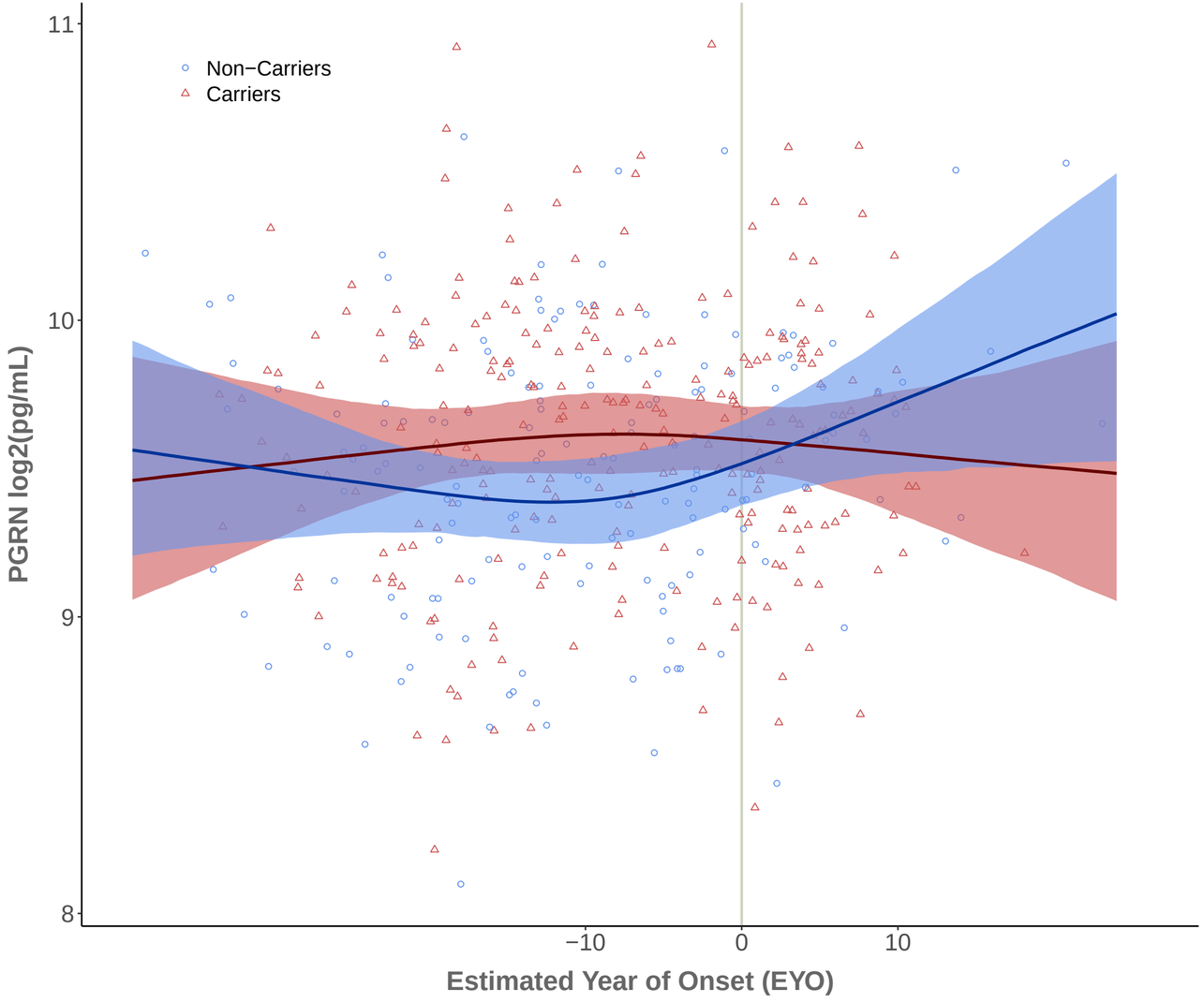
Fujirebio t-Tau level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



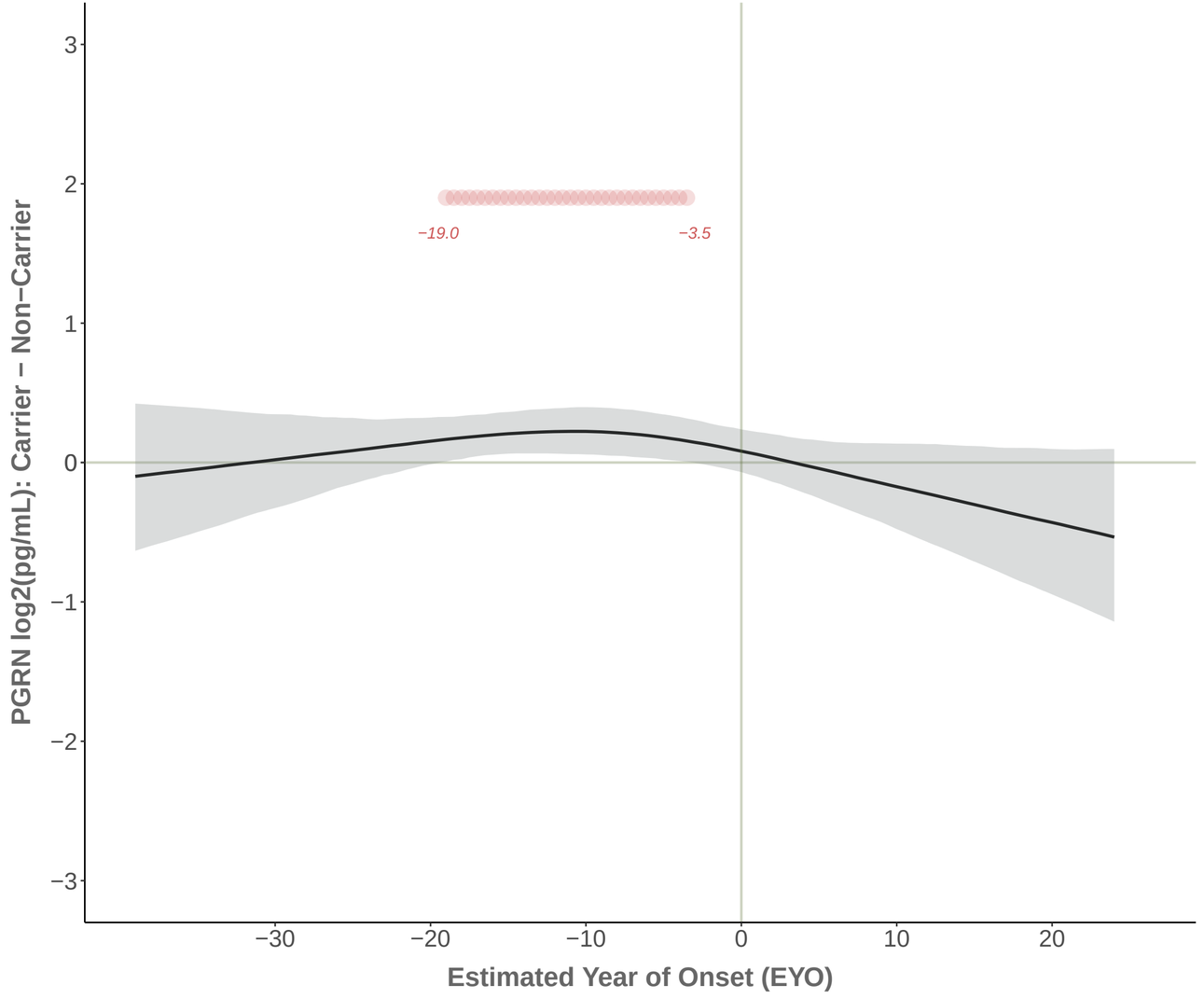
Fujirebio t-Tau level difference in mutation carriers and non−carriers with 99% confidence interval.



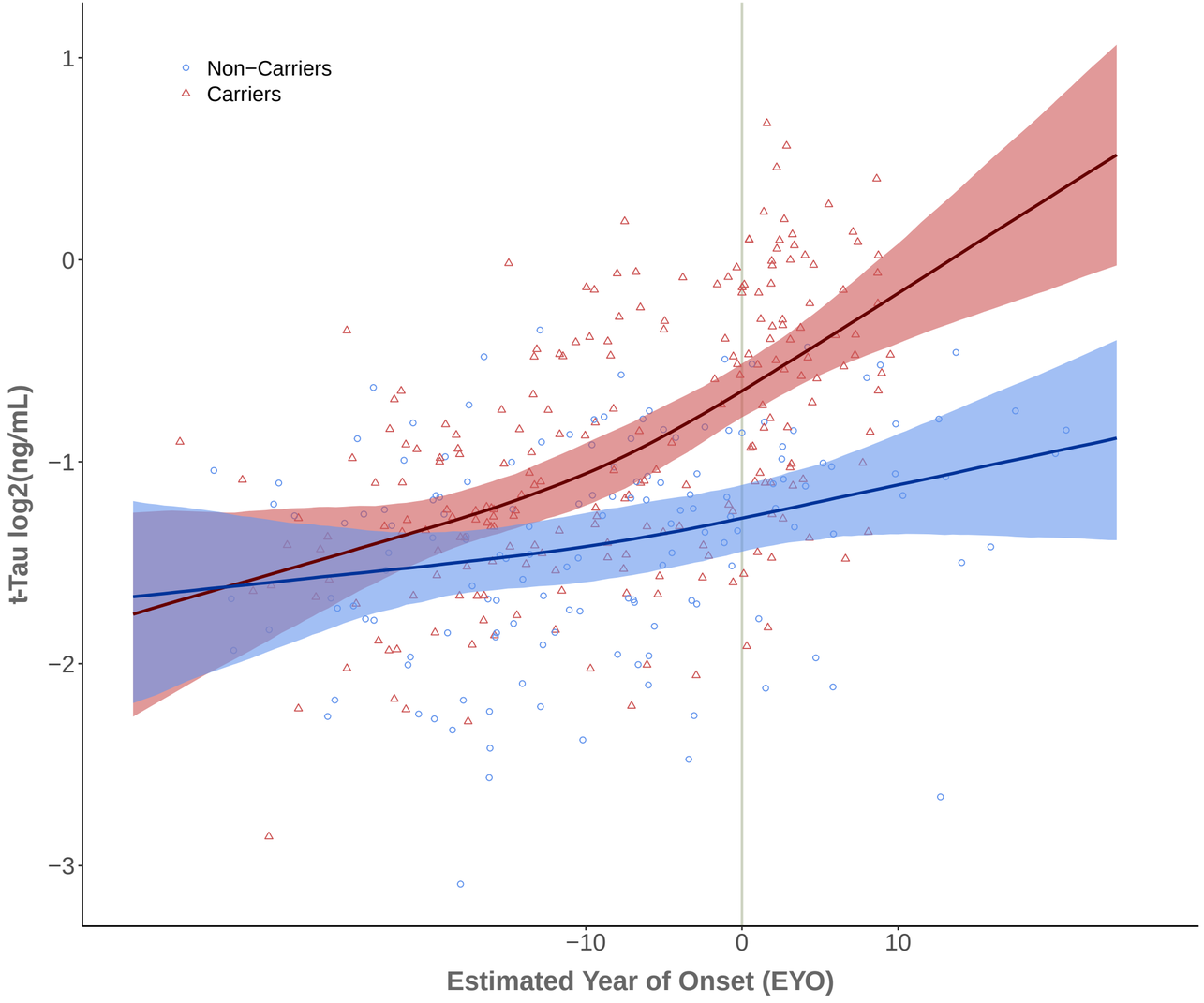
PGRN level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



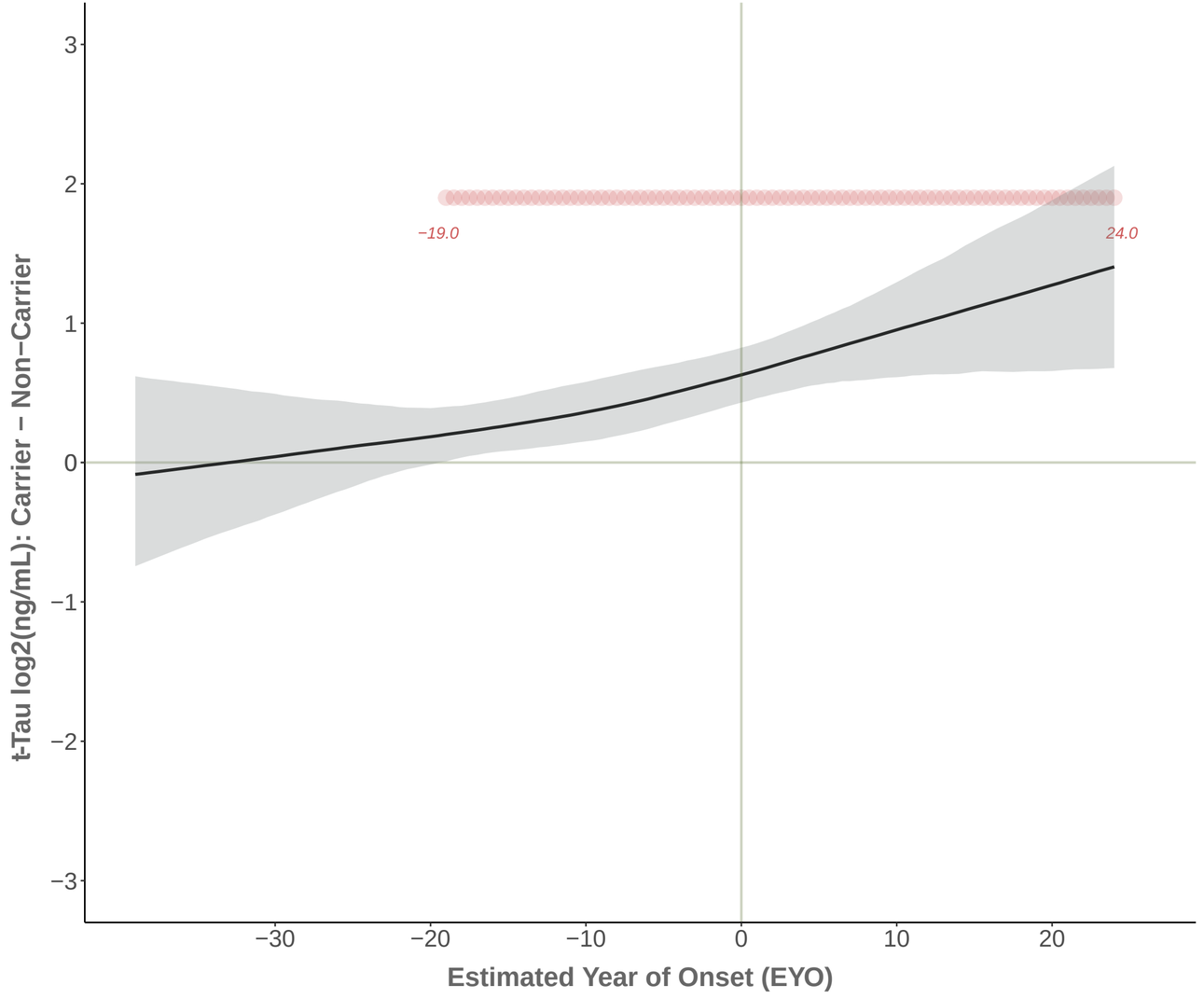
PGRN level difference in mutation carriers and non−carriers with 99% confidence interval.



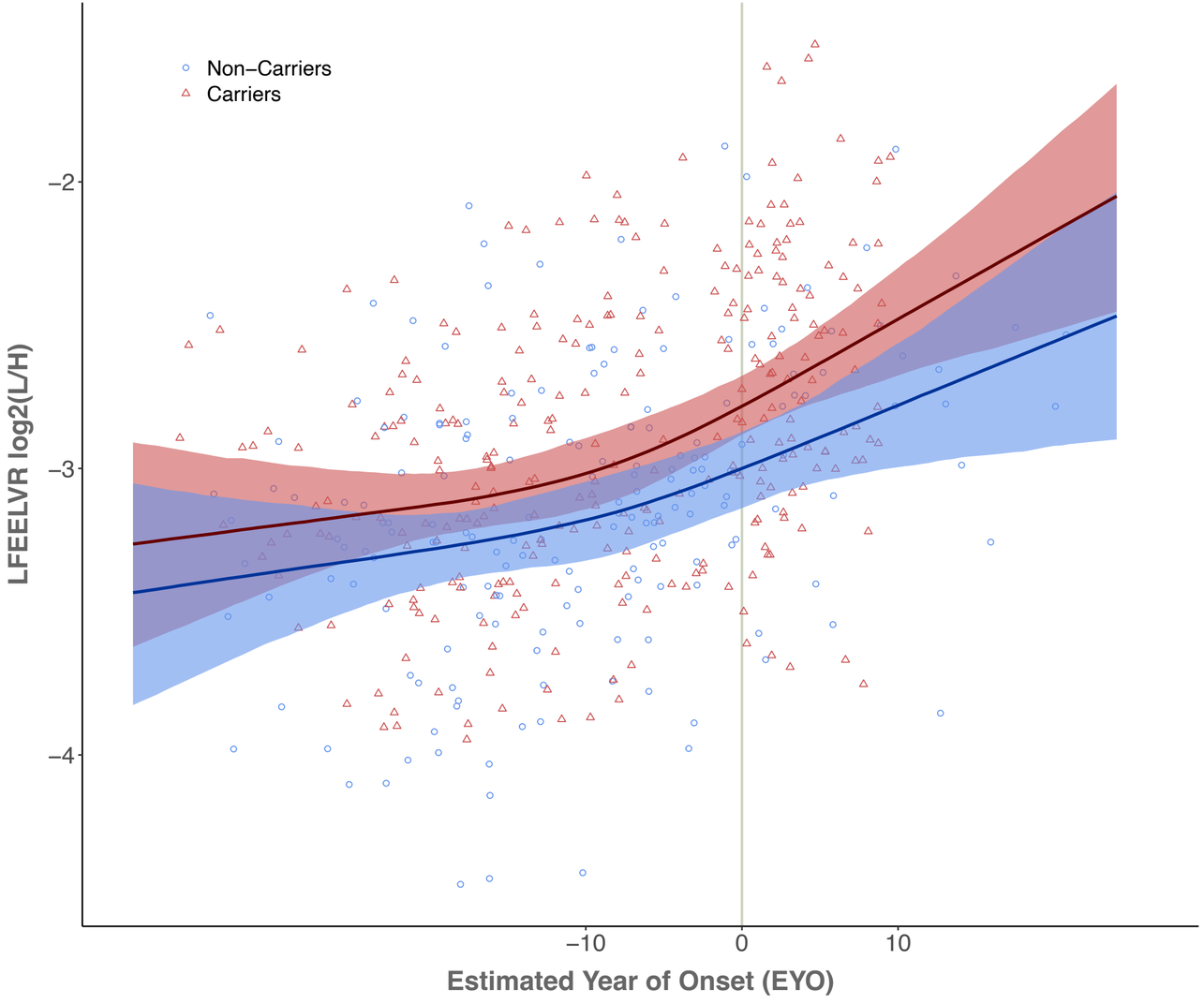
t-Tau level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



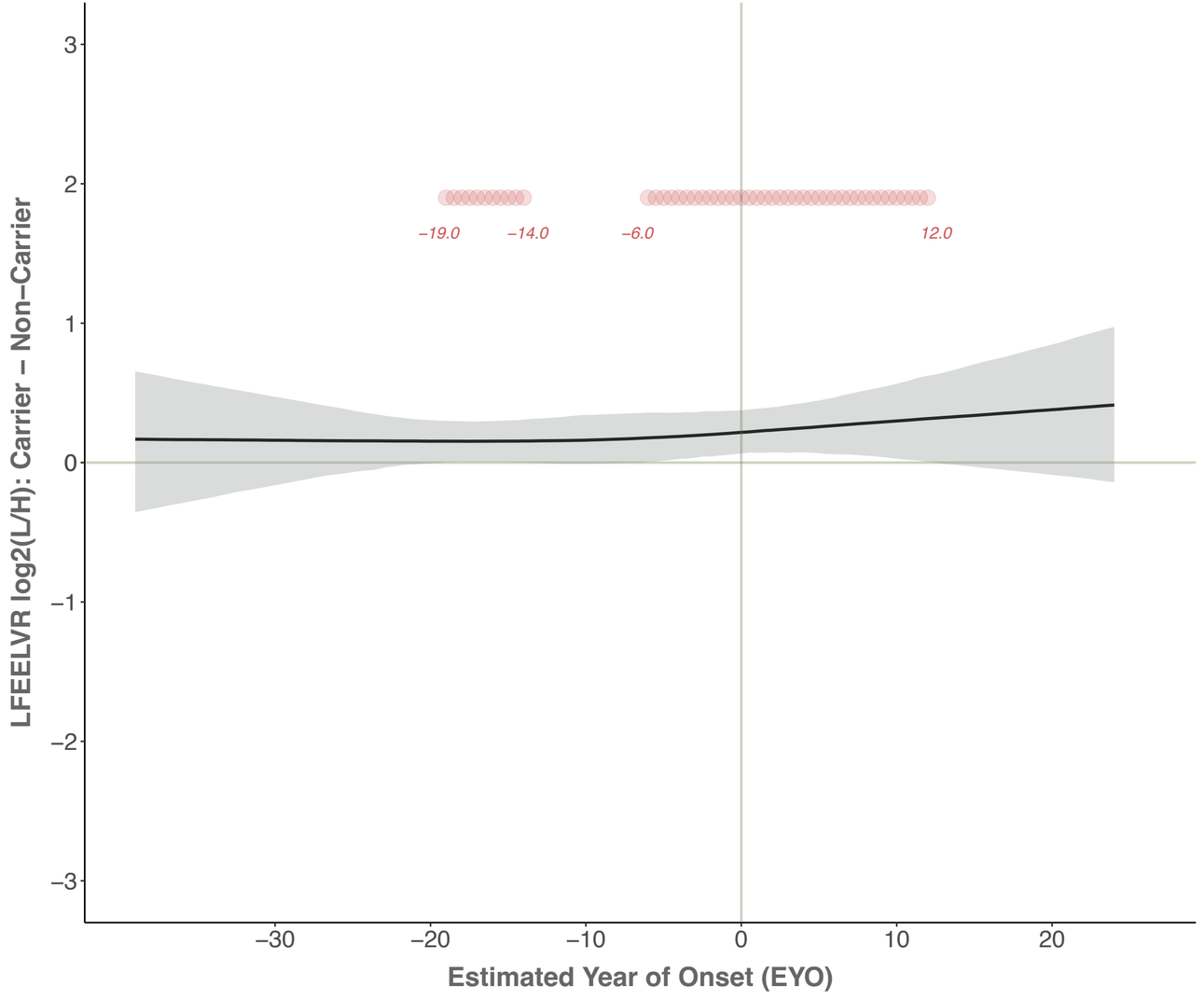
t-Tau level difference in mutation carriers and non−carriers with 99% confidence interval.



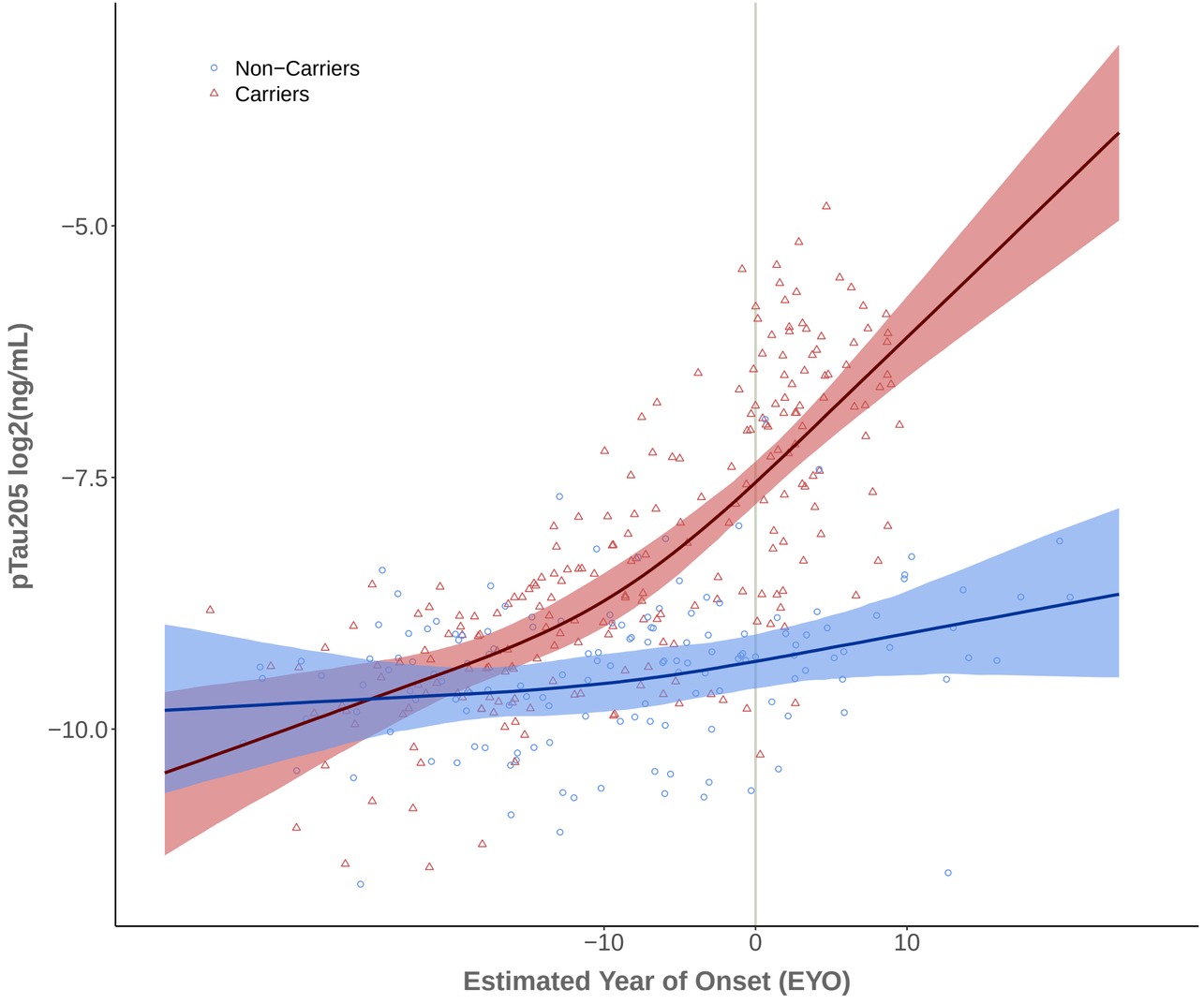
PKM2 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



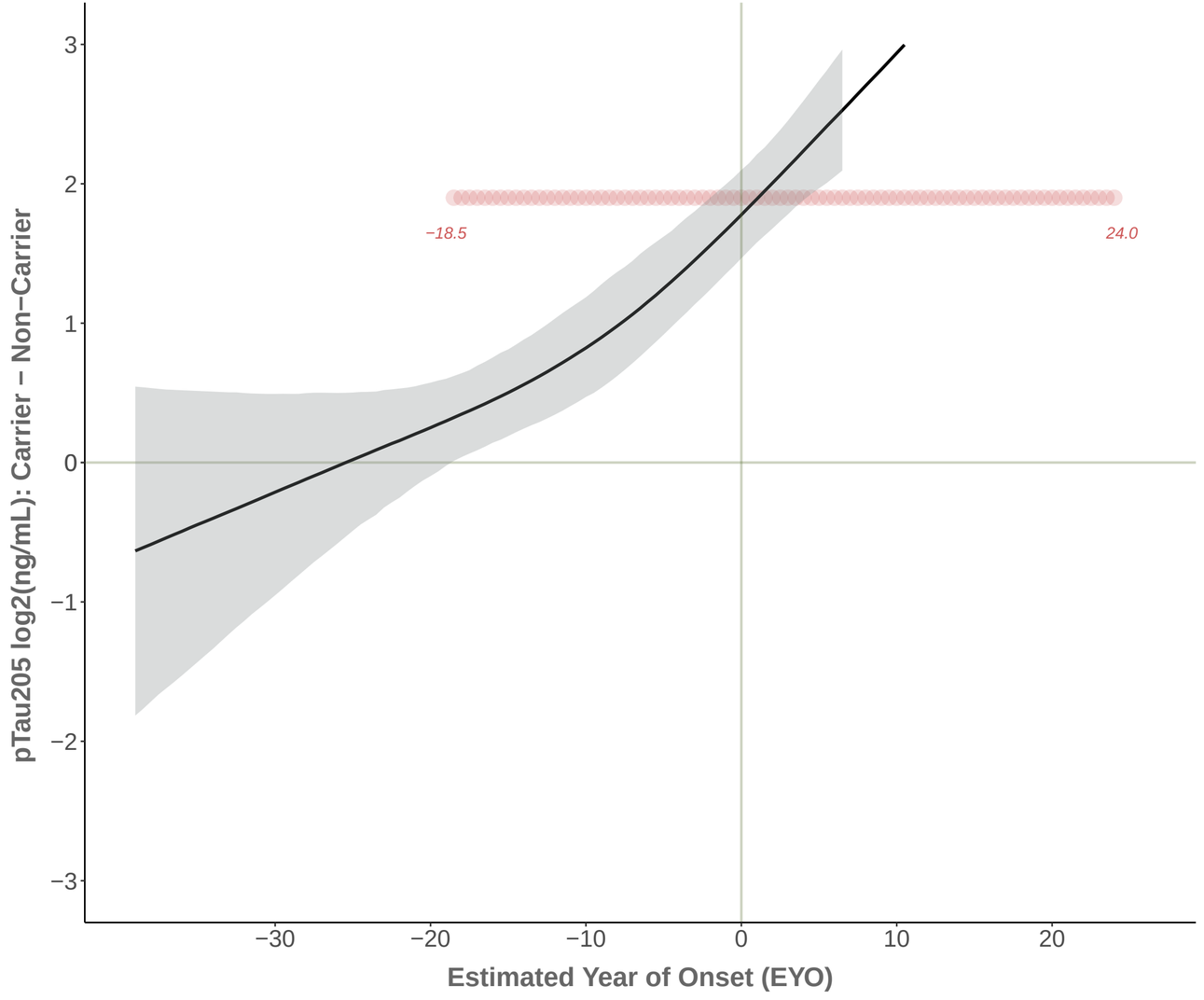
PKM2 level difference in mutation carriers and non−carriers with 99% confidence interval.



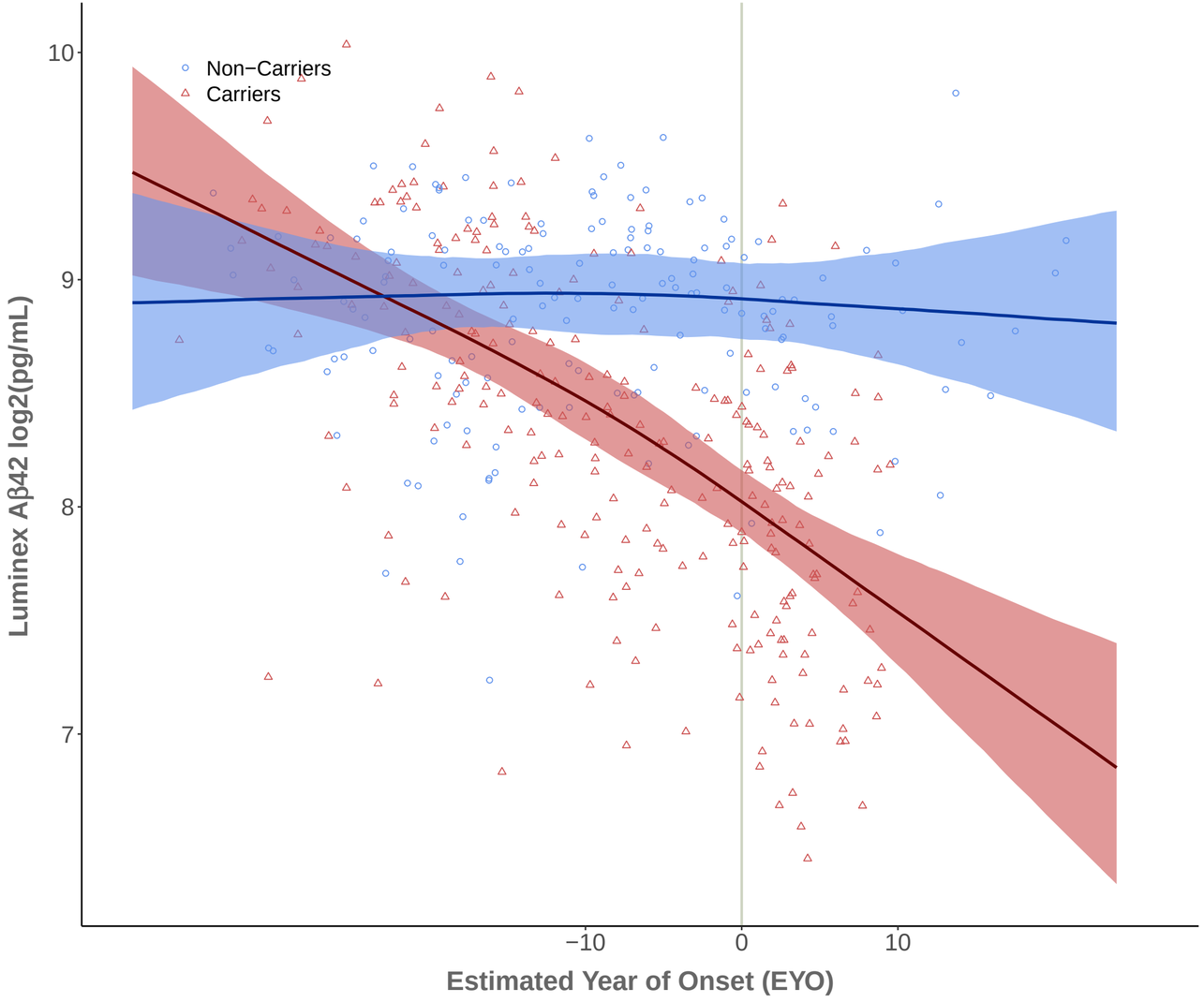
pTau205 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



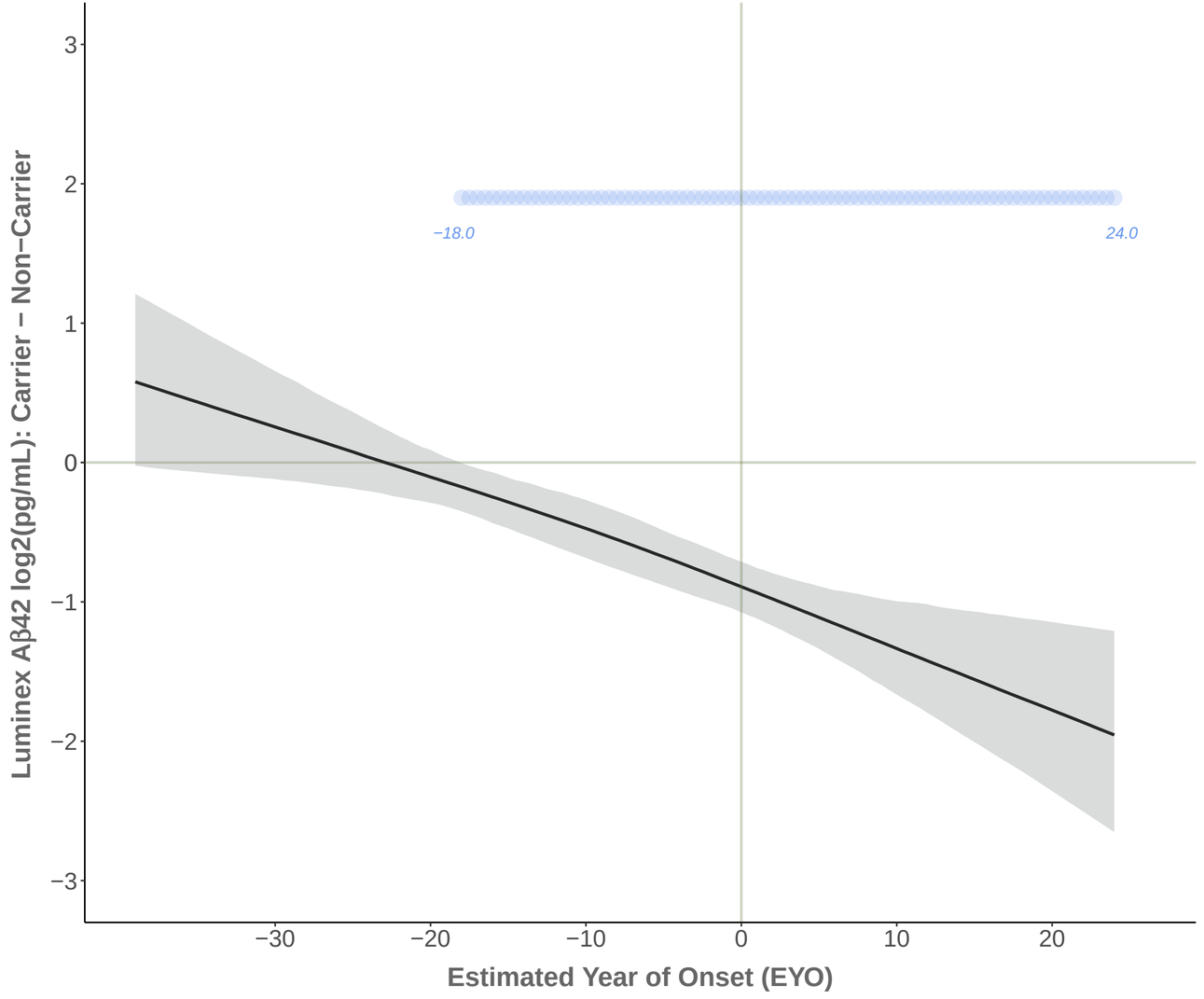
pTau205 level difference in mutation carriers and non−carriers with 99% confidence interval.



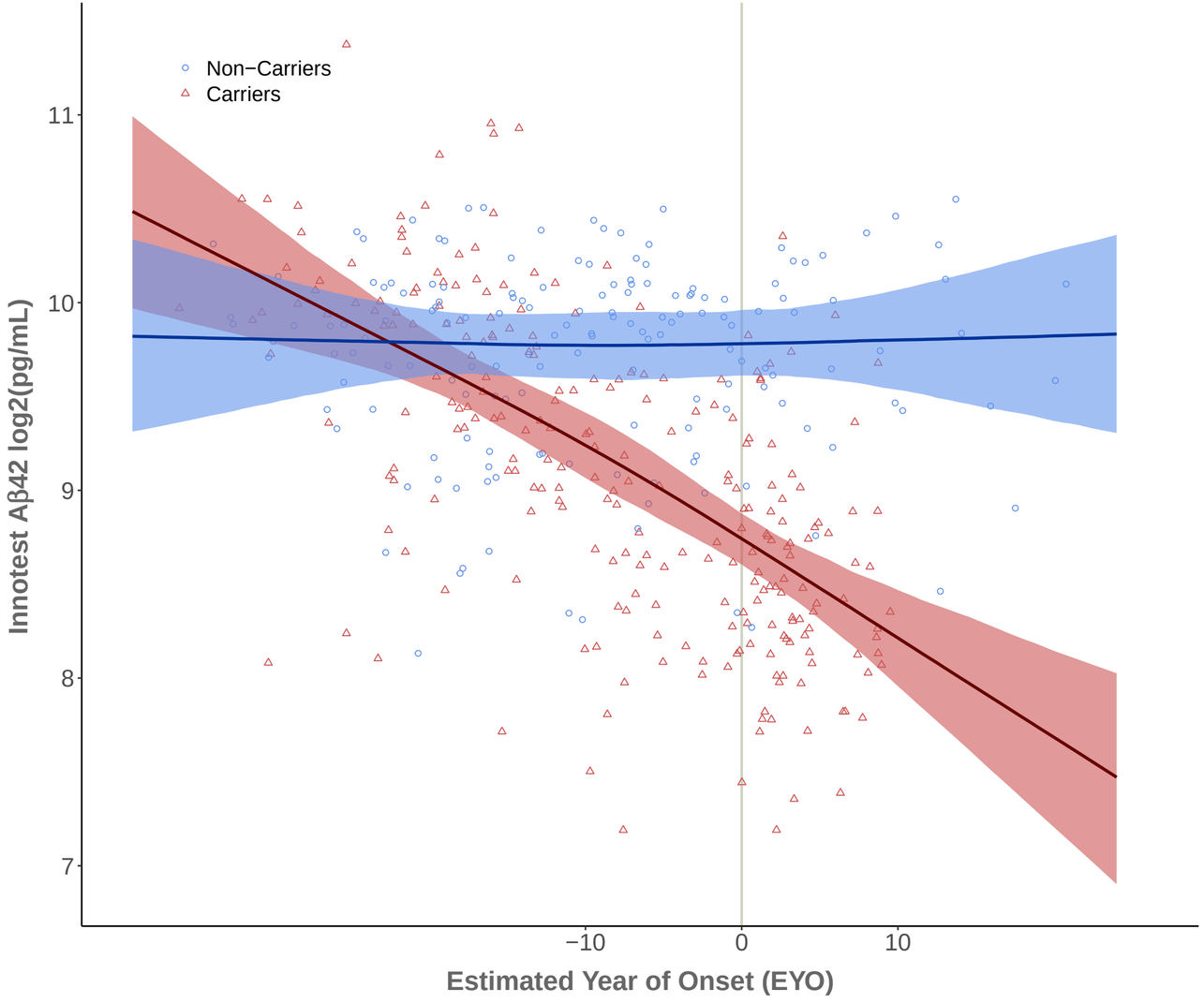
Luminex Aβ42 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



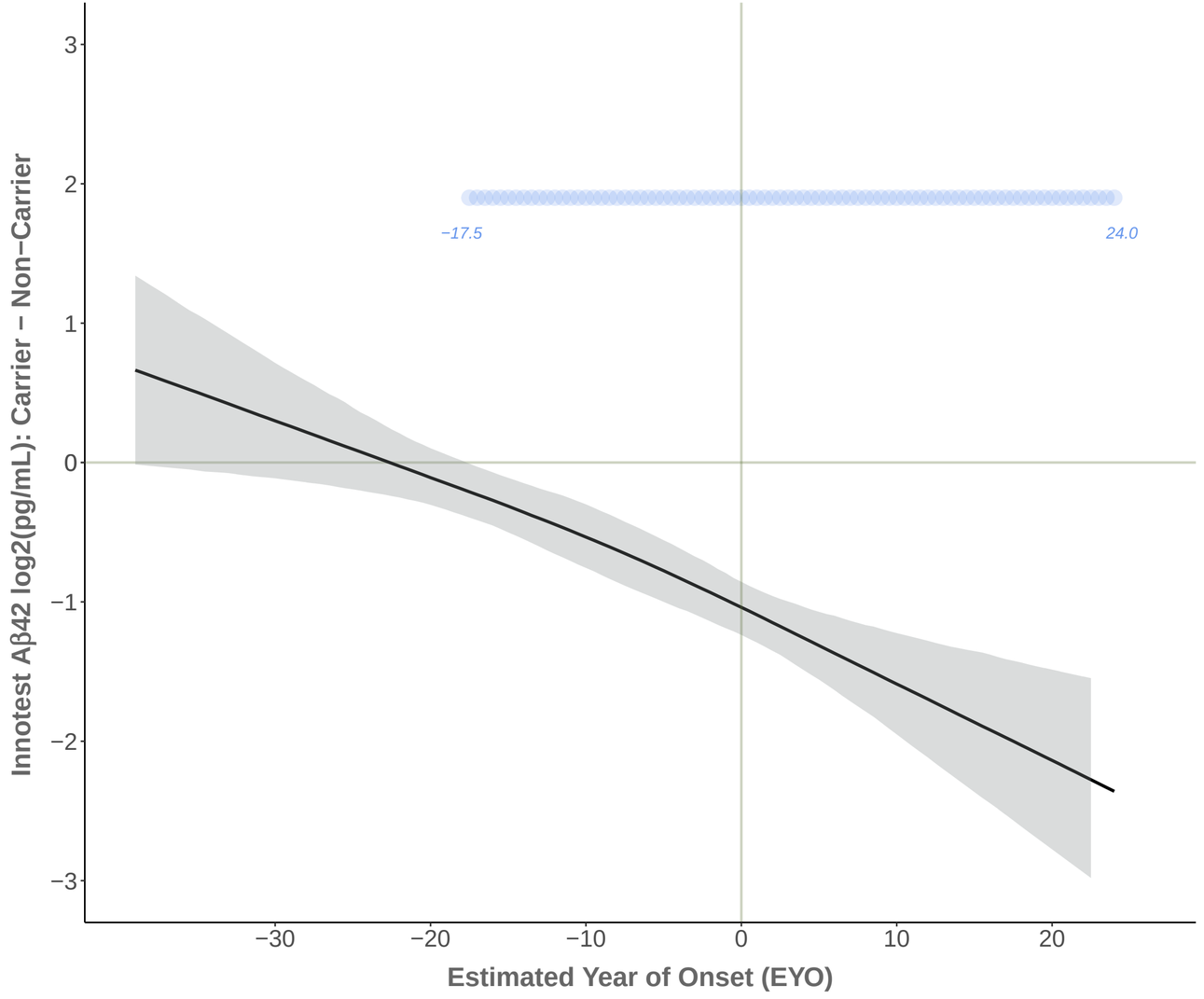
Luminex Aβ42 level difference in mutation carriers and non−carriers with 99% confidence interval.



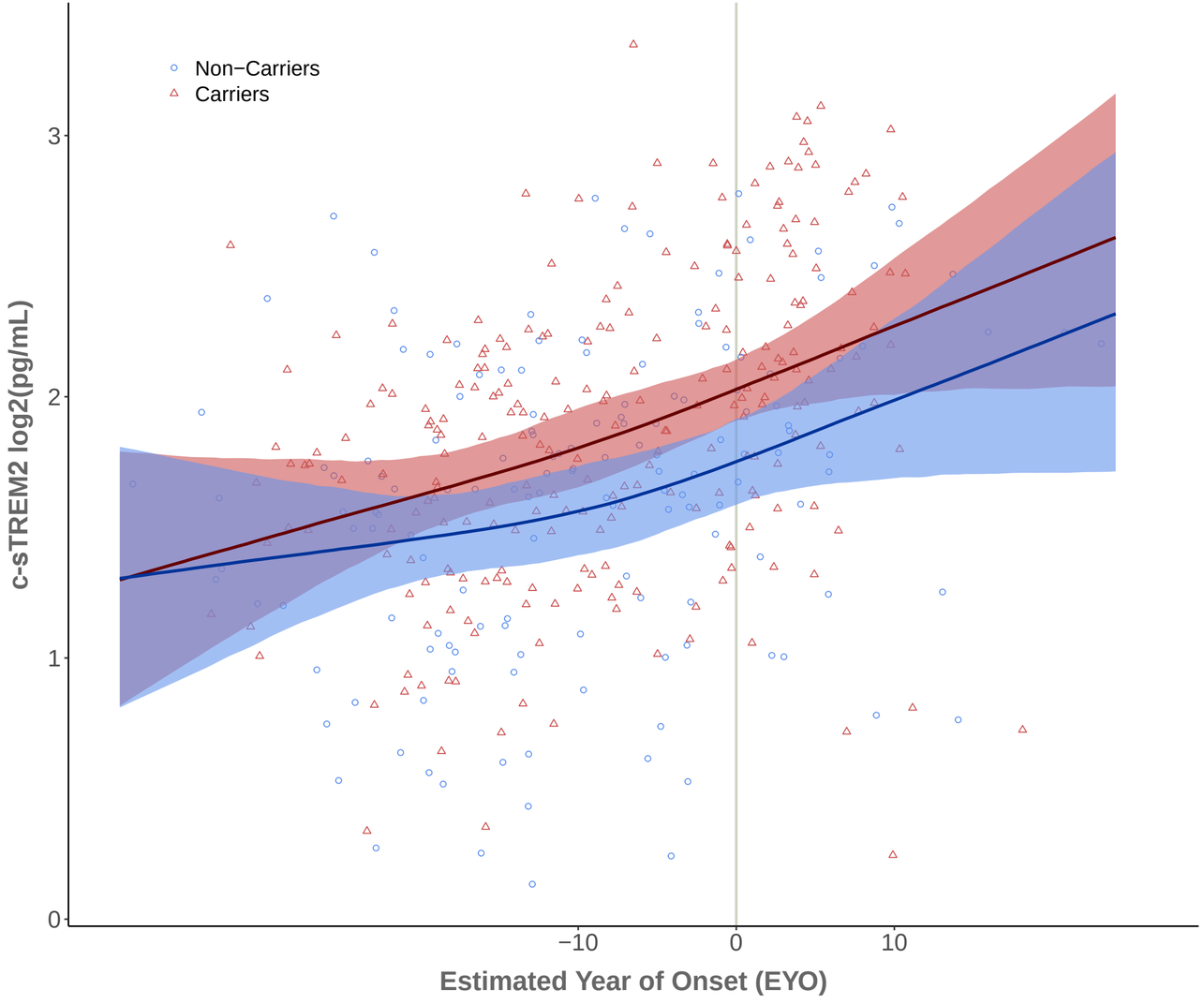
Innotest Aβ42 level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



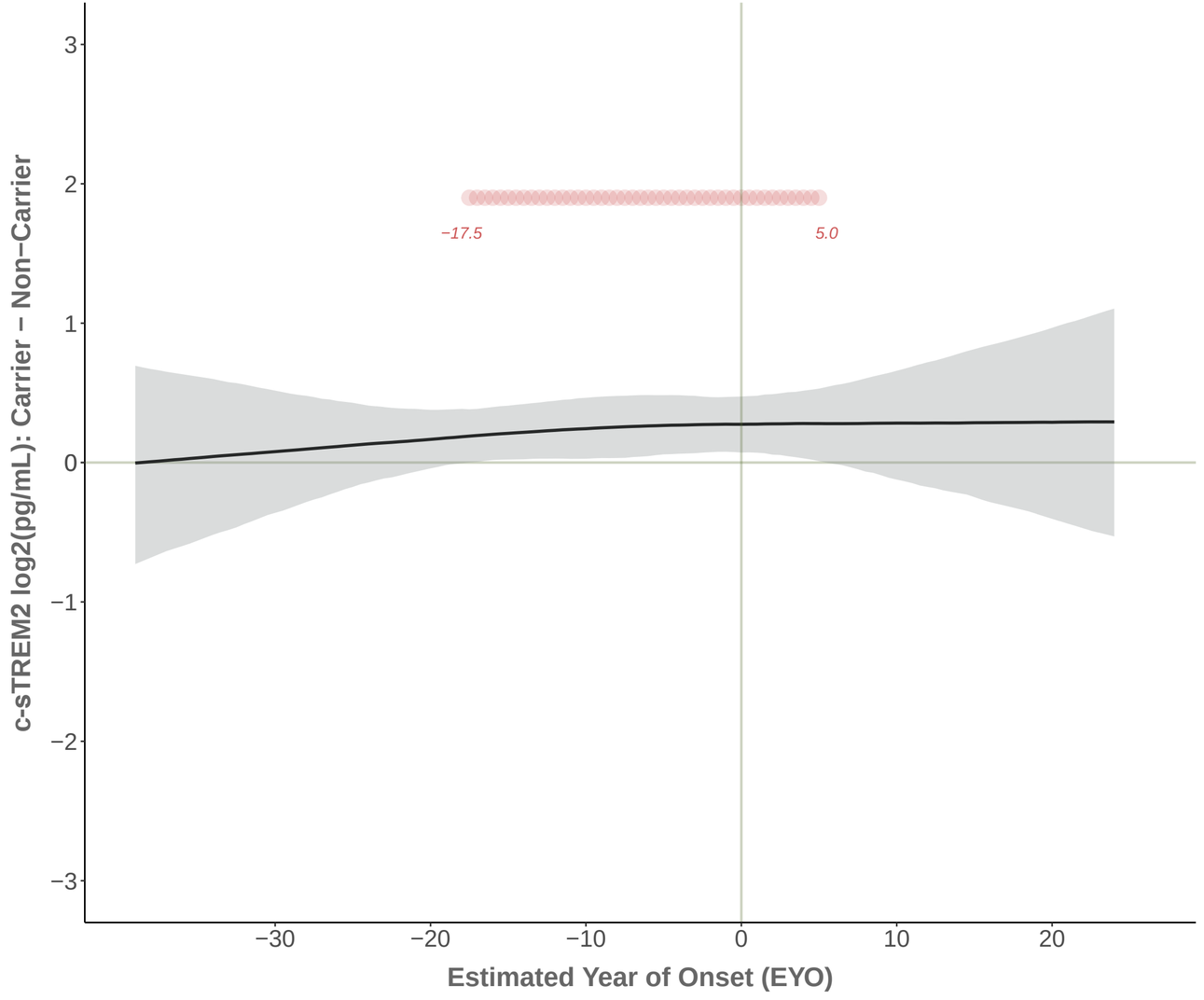
Innotest Aβ42 level difference in mutation carriers and non−carriers with 99% confidence interval.



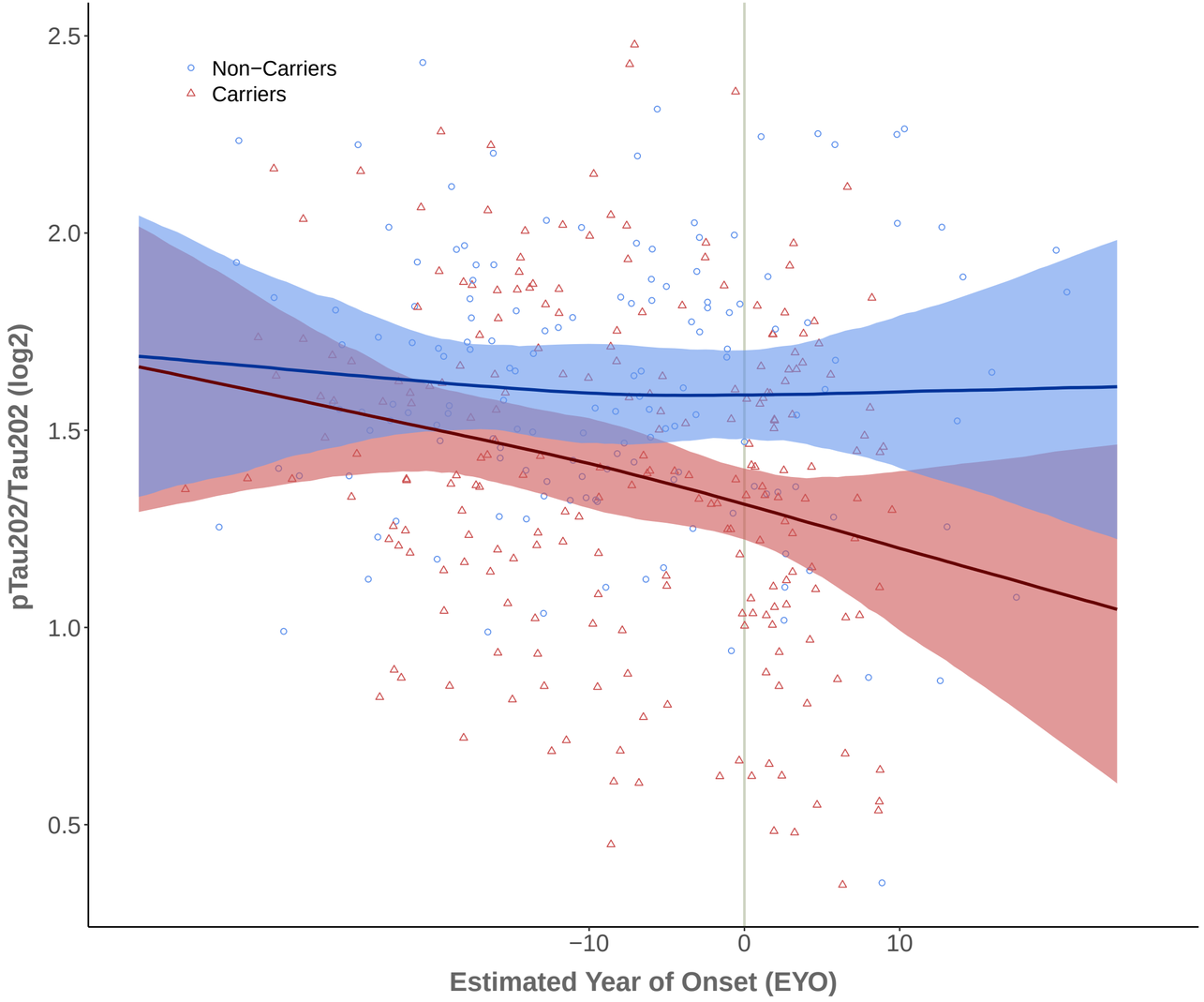
c-sTREM2 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



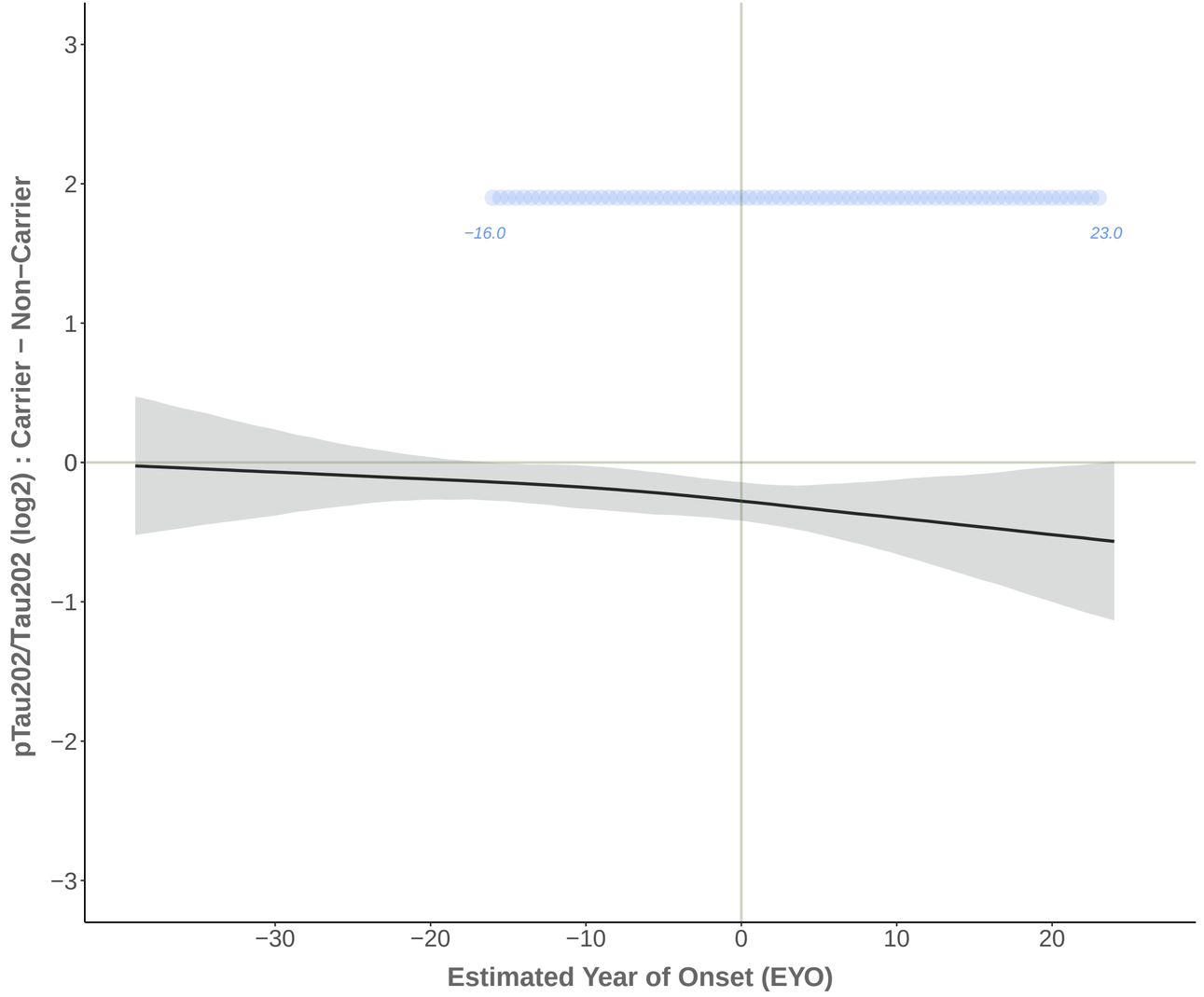
c-sTREM2 level difference in mutation carriers and non−carriers with 99% confidence interval.



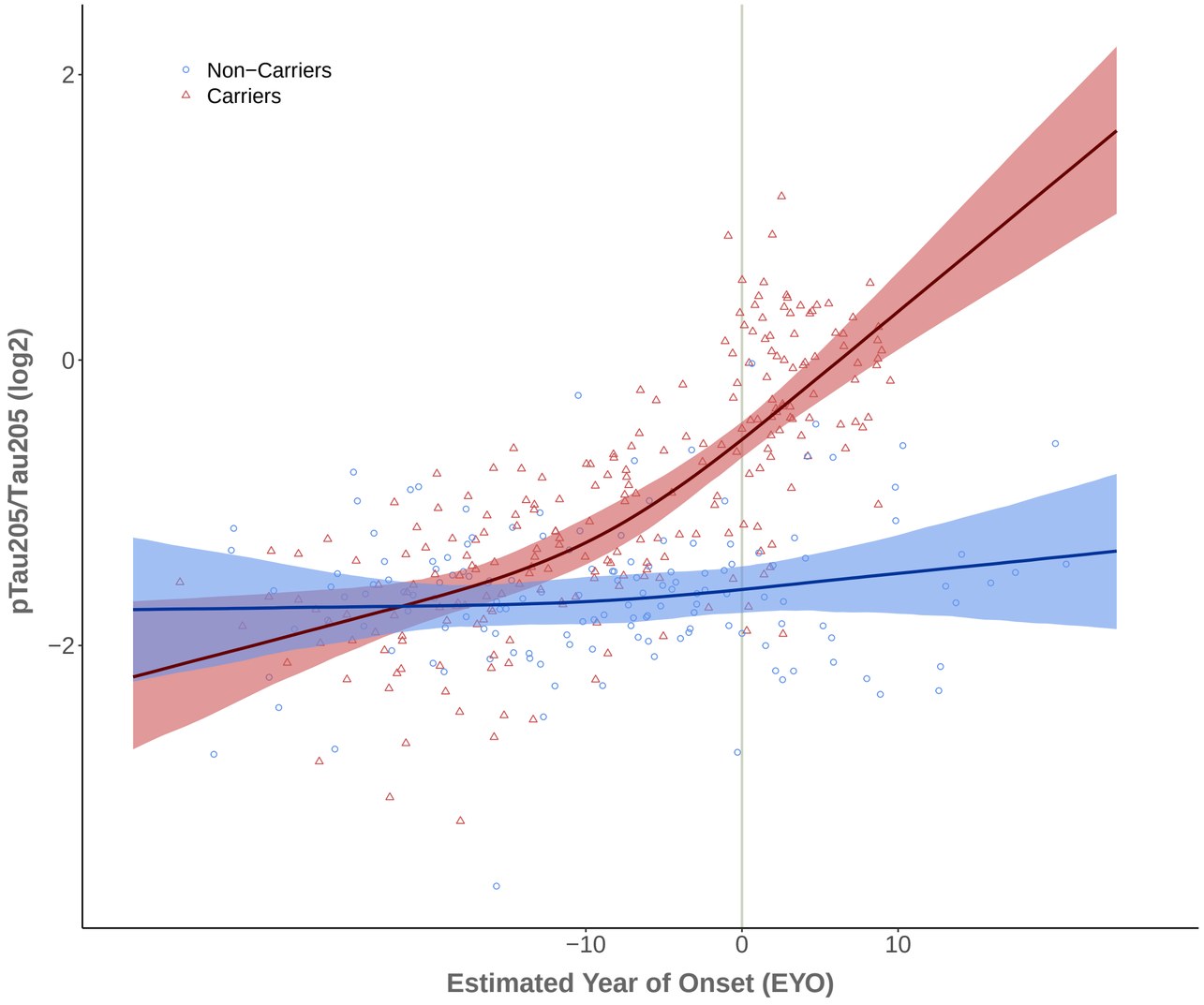
pTau202/Tau202 ratio in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



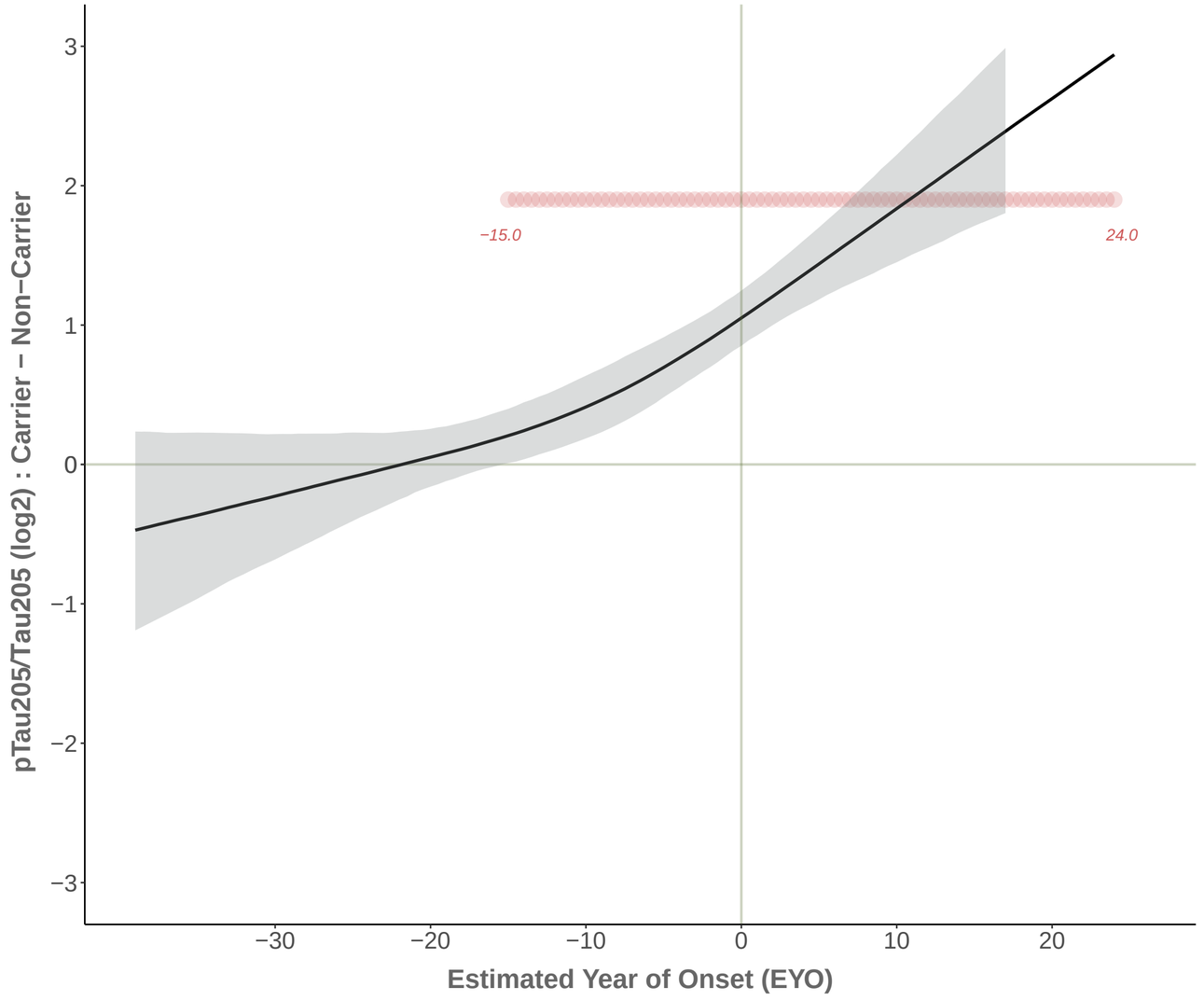
pTau202/Tau202 ratio difference in mutation carriers and non−carriers with 99% confidence interval.



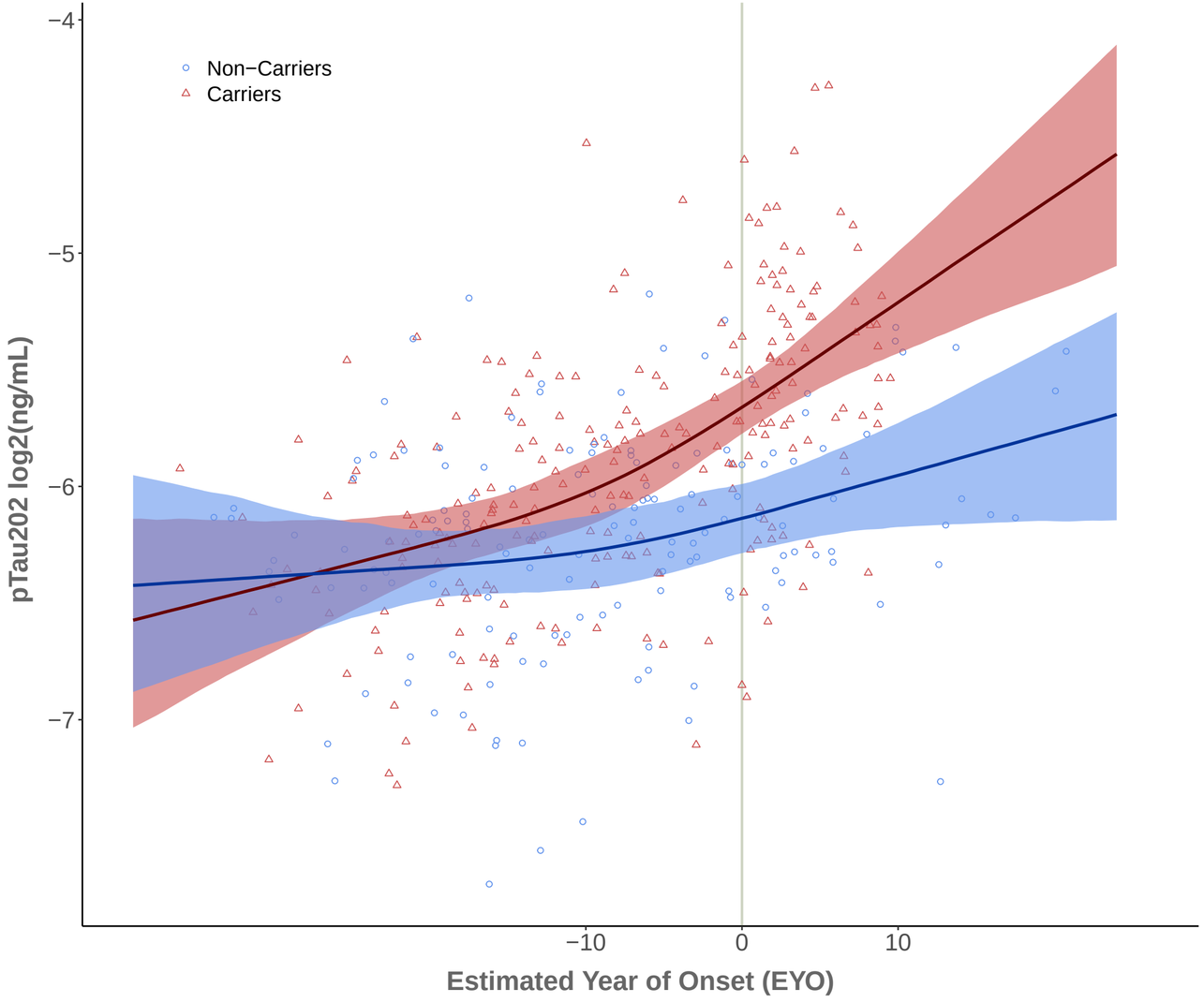
pTau205/Tau205 ratio in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



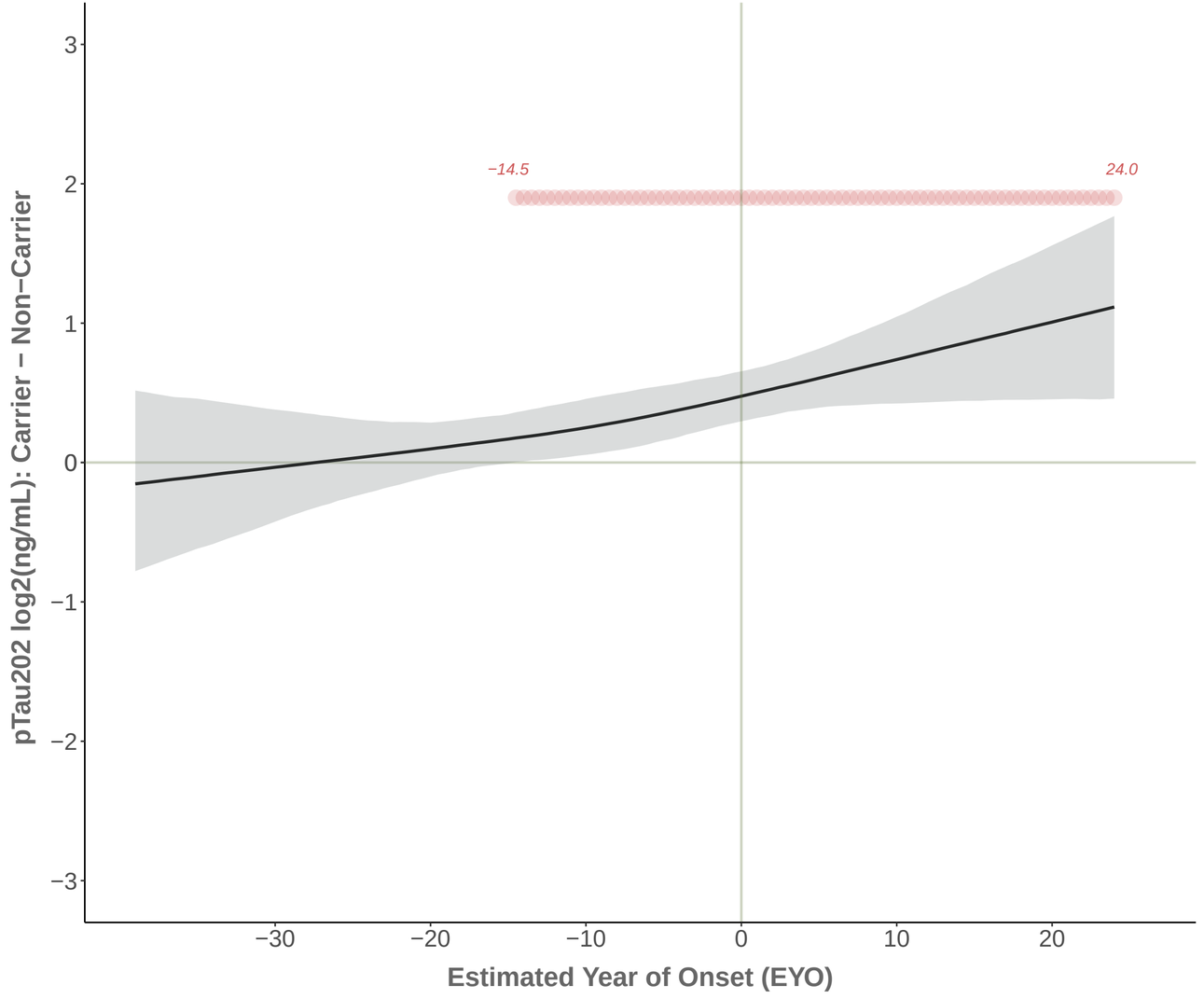
pTau205/Tau205 ratio difference in mutation carriers and non−carriers with 99% confidence interval.



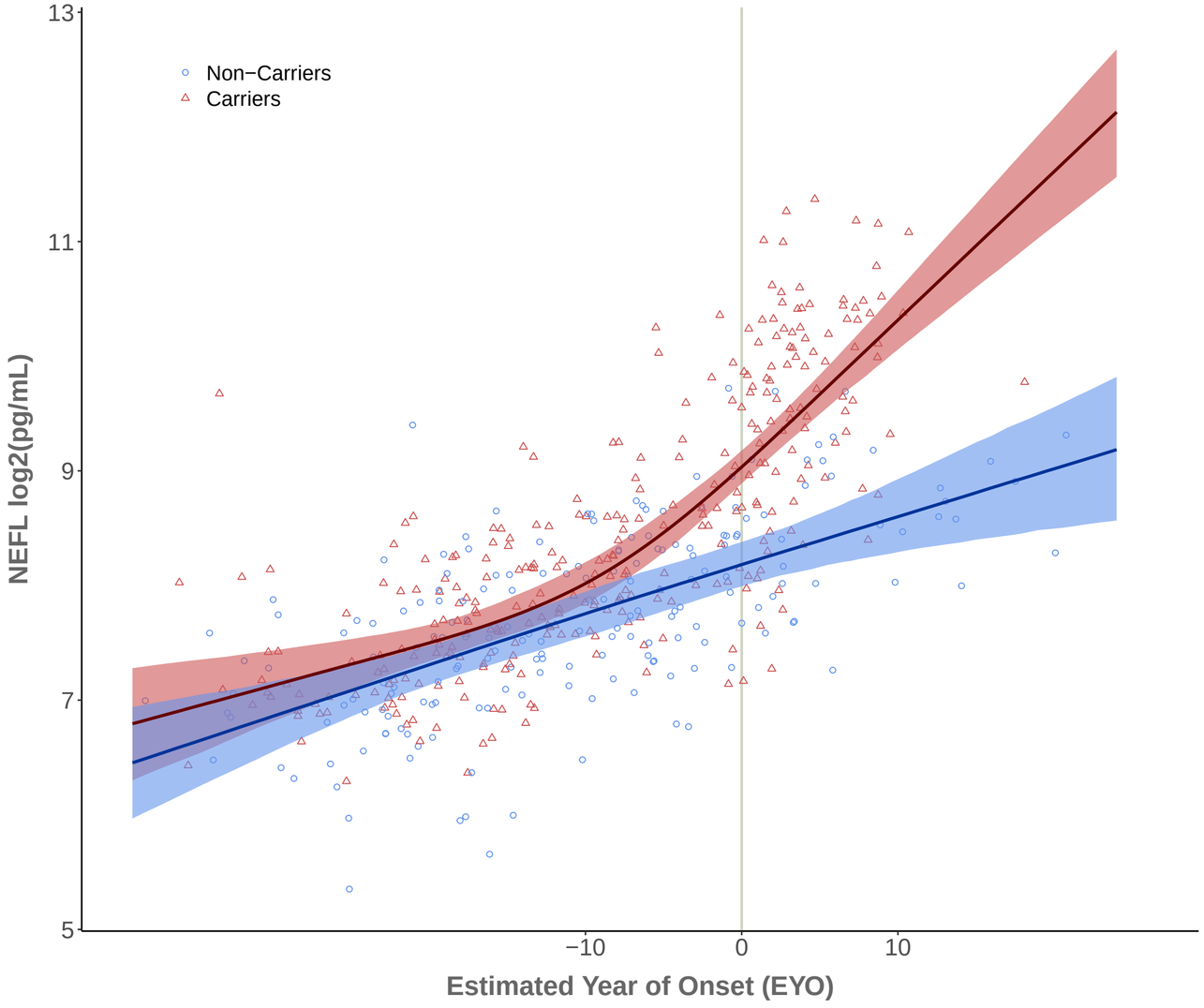
pTau202 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



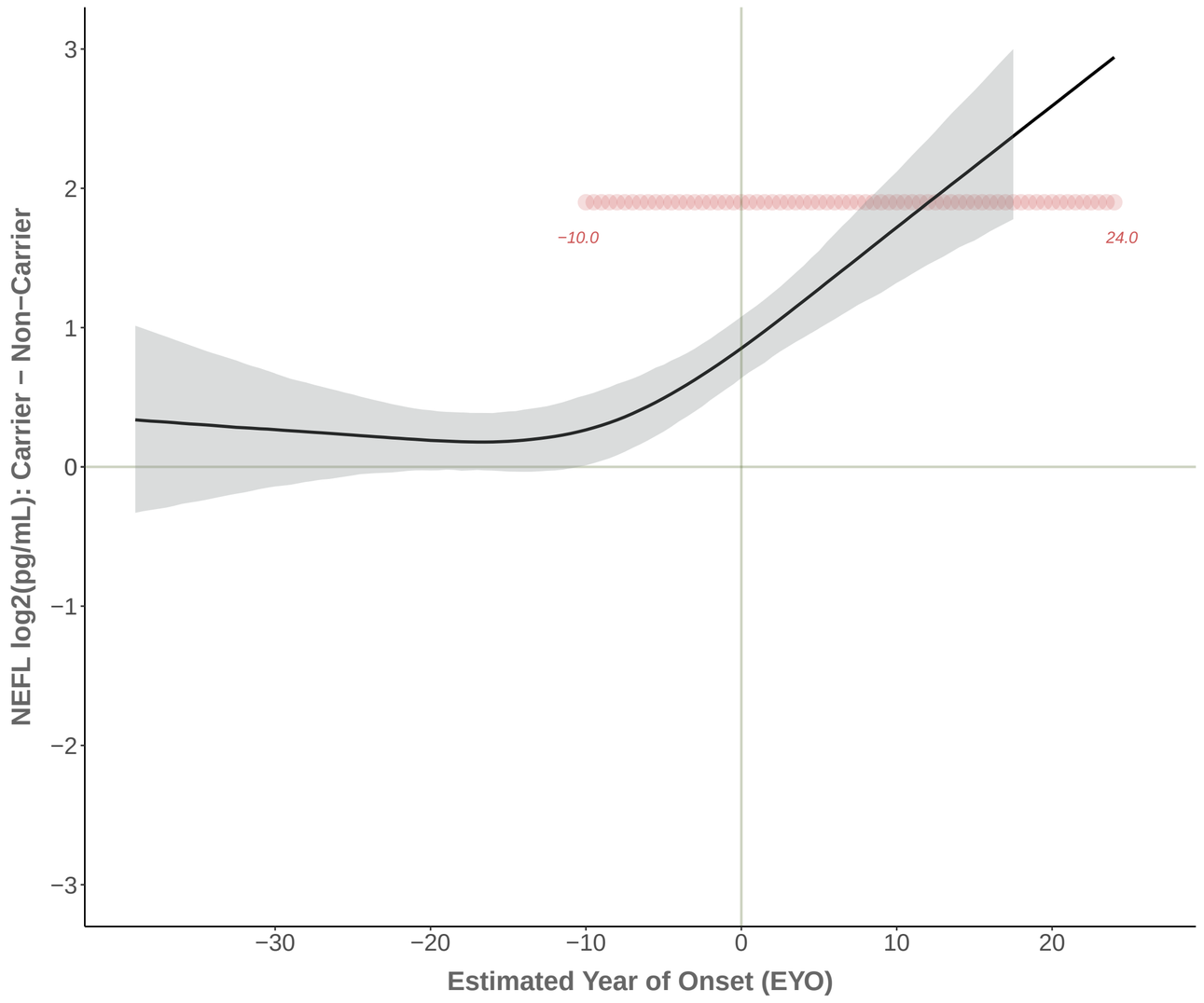
pTau202 level difference in mutation carriers and non−carriers with 99% confidence interval.



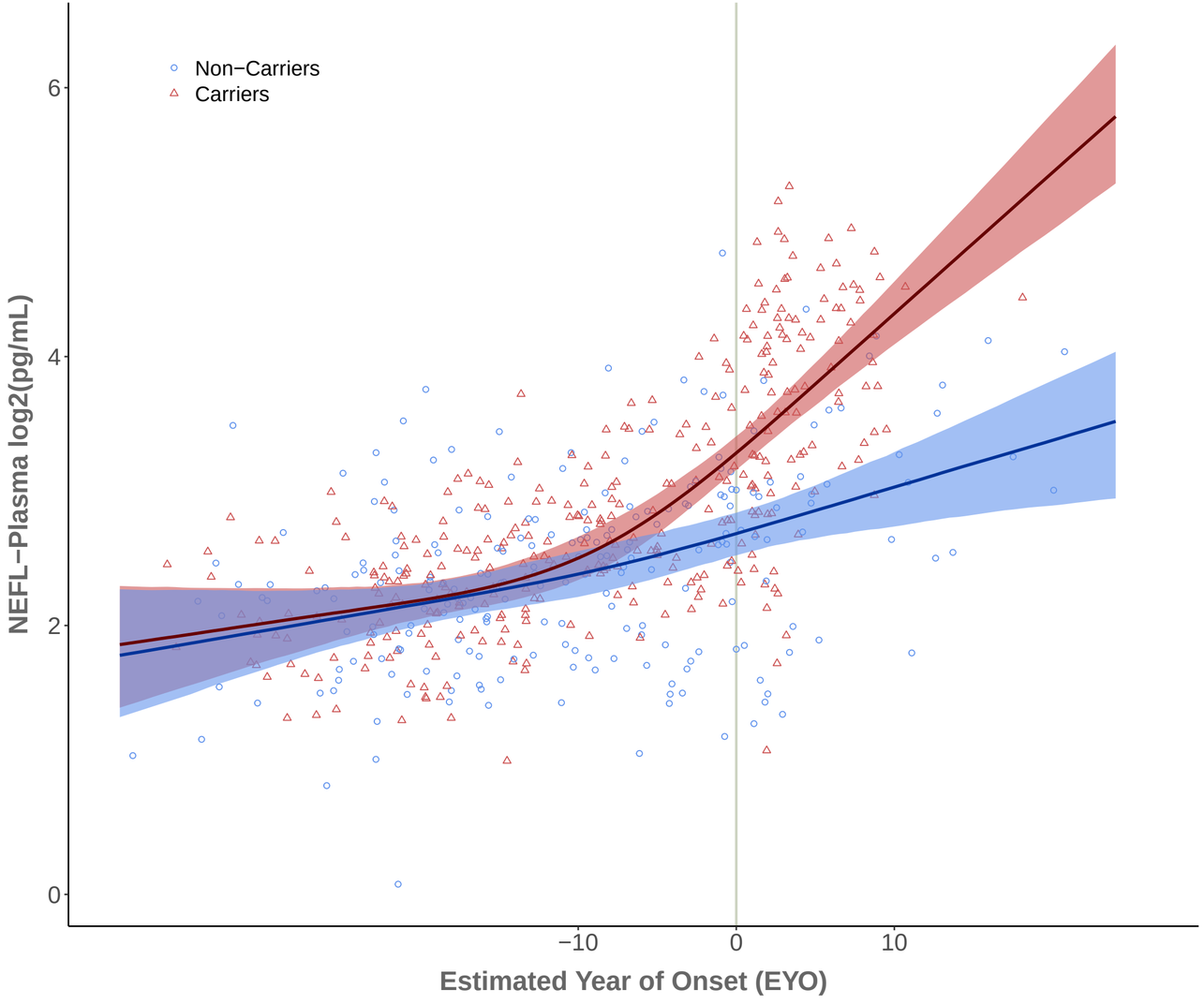
NEFL level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



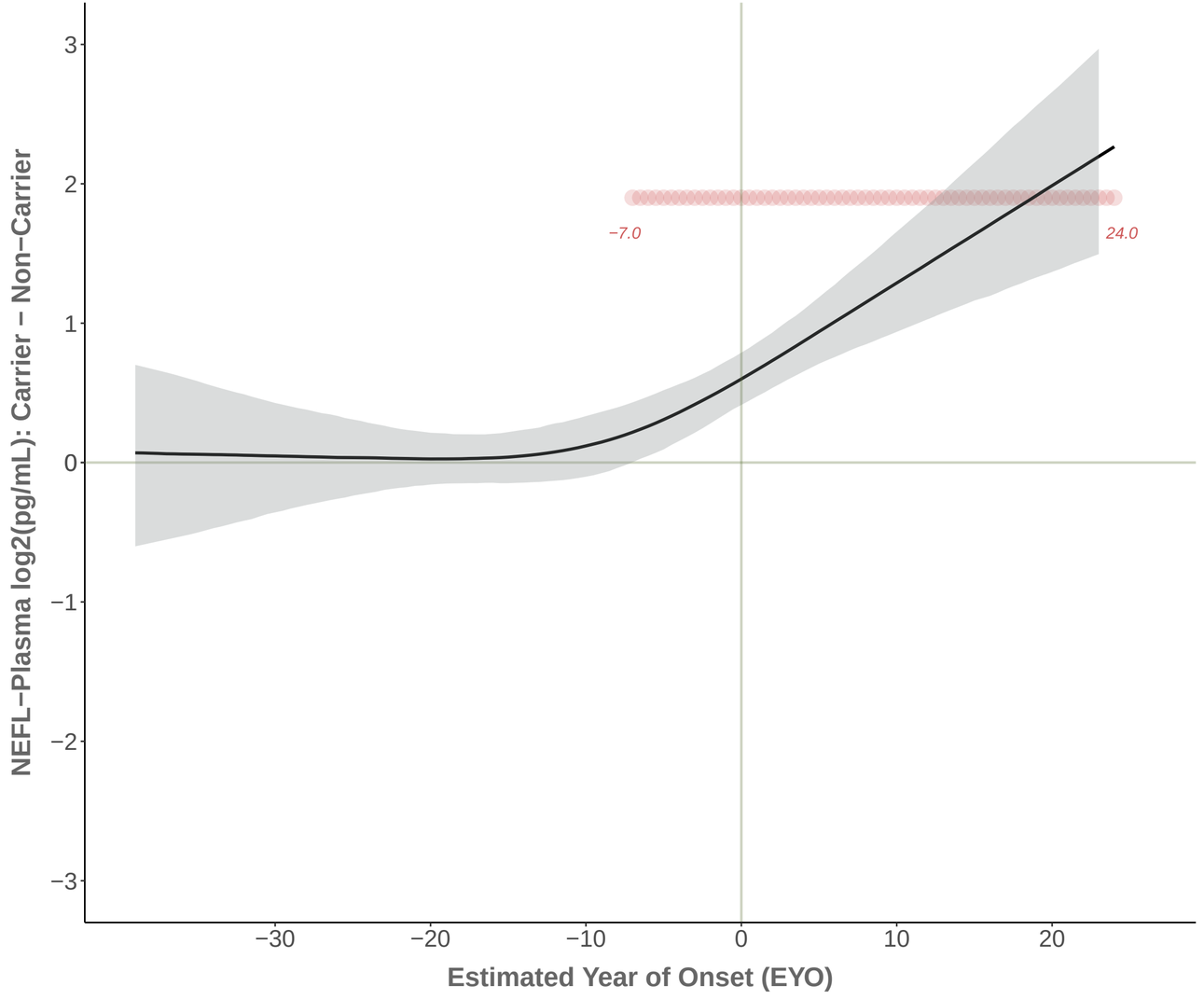
NEFL level difference in mutation carriers and non−carriers with 99% confidence interval.



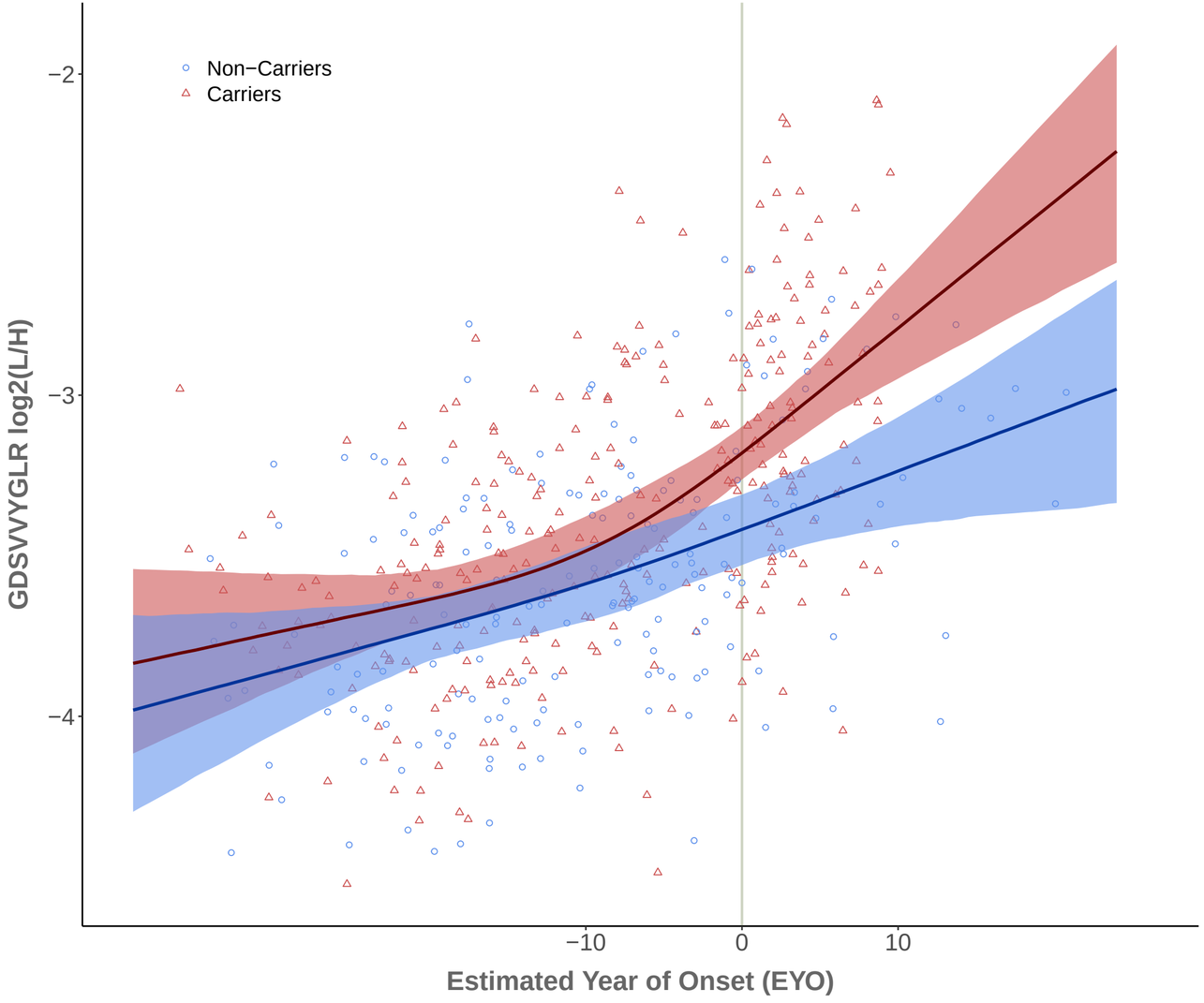
NEFL−Plasma level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



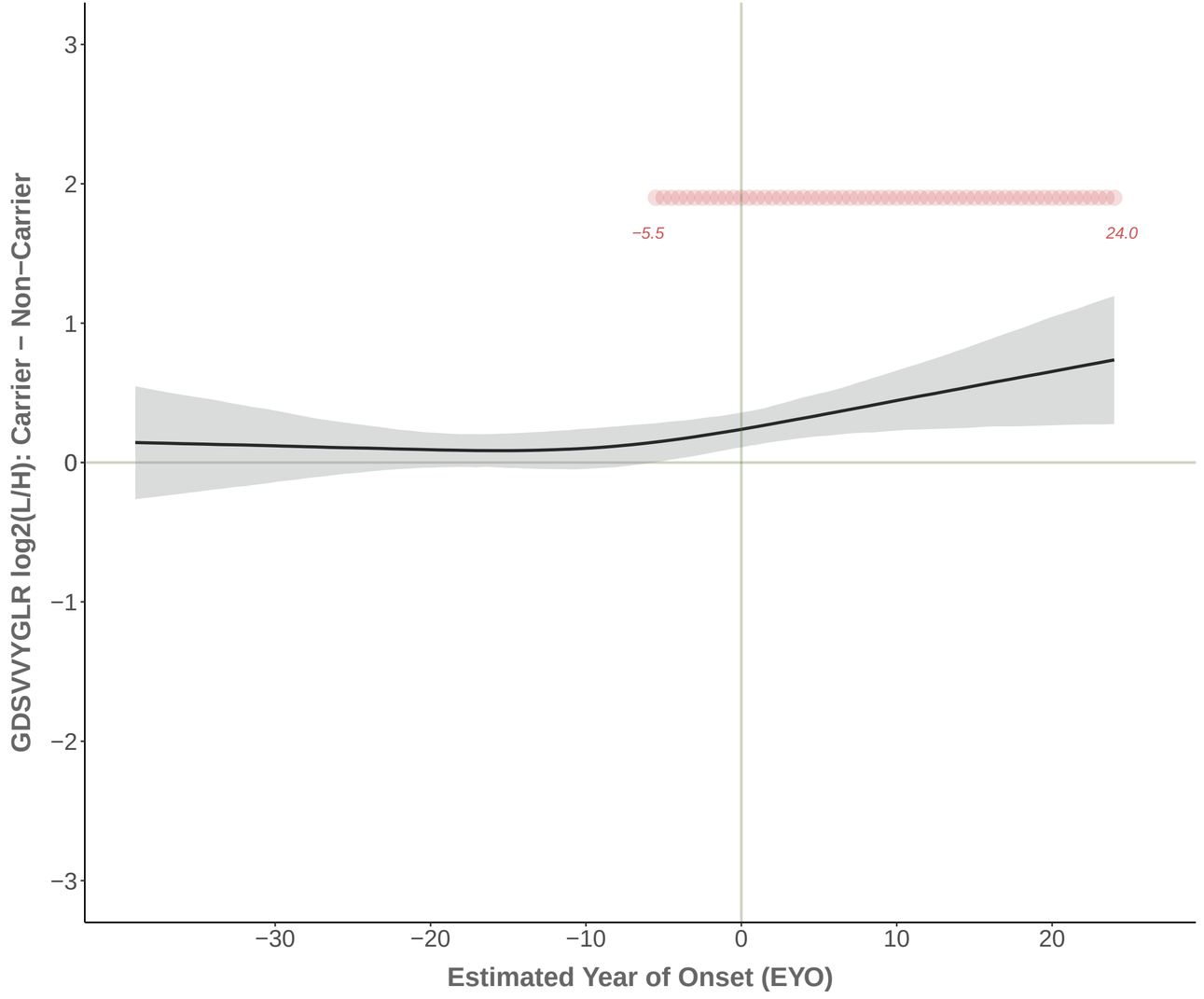
NEFL−Plasma level difference in mutation carriers and non−carriers with 99% confidence interval.



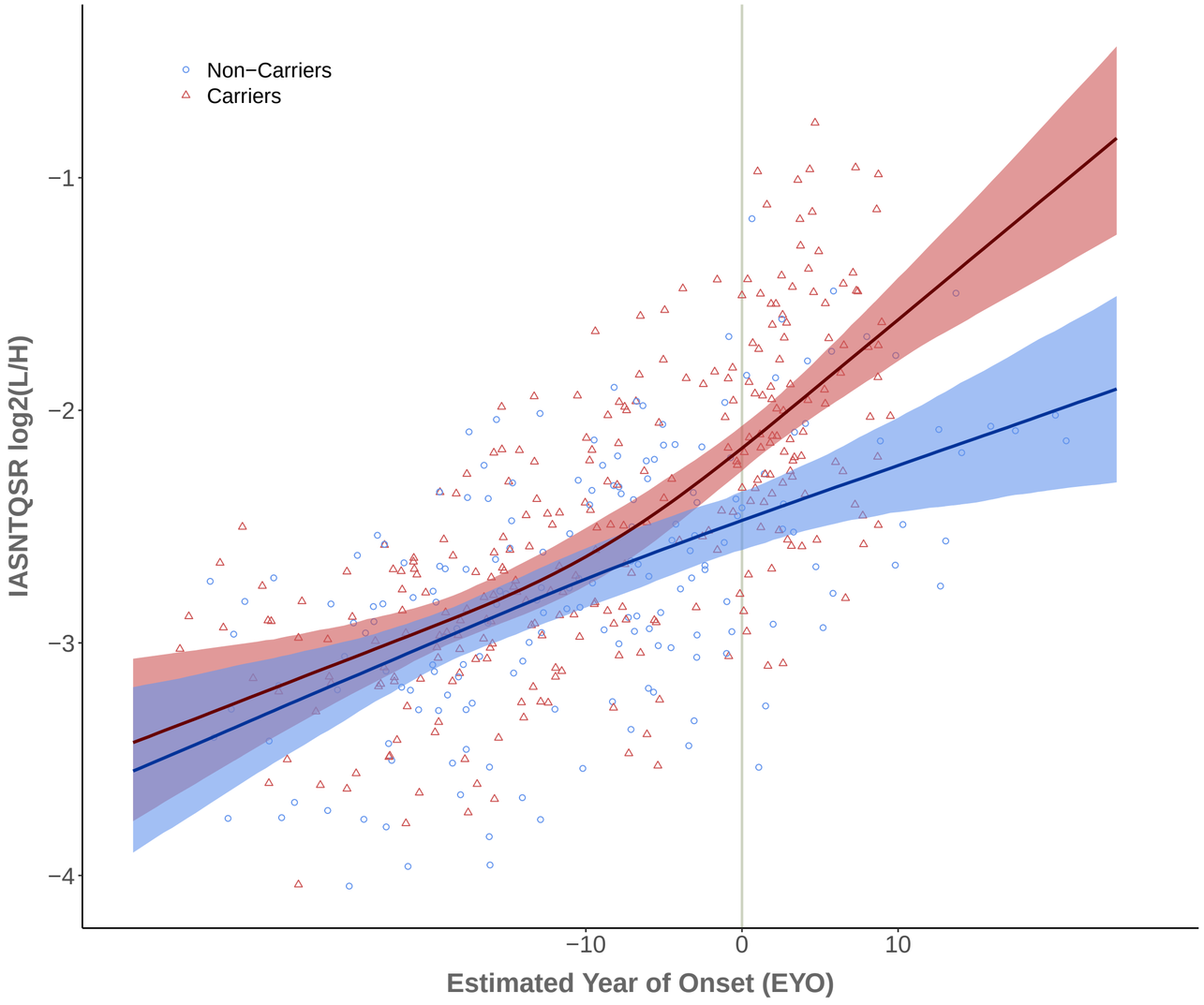
SPP1 level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



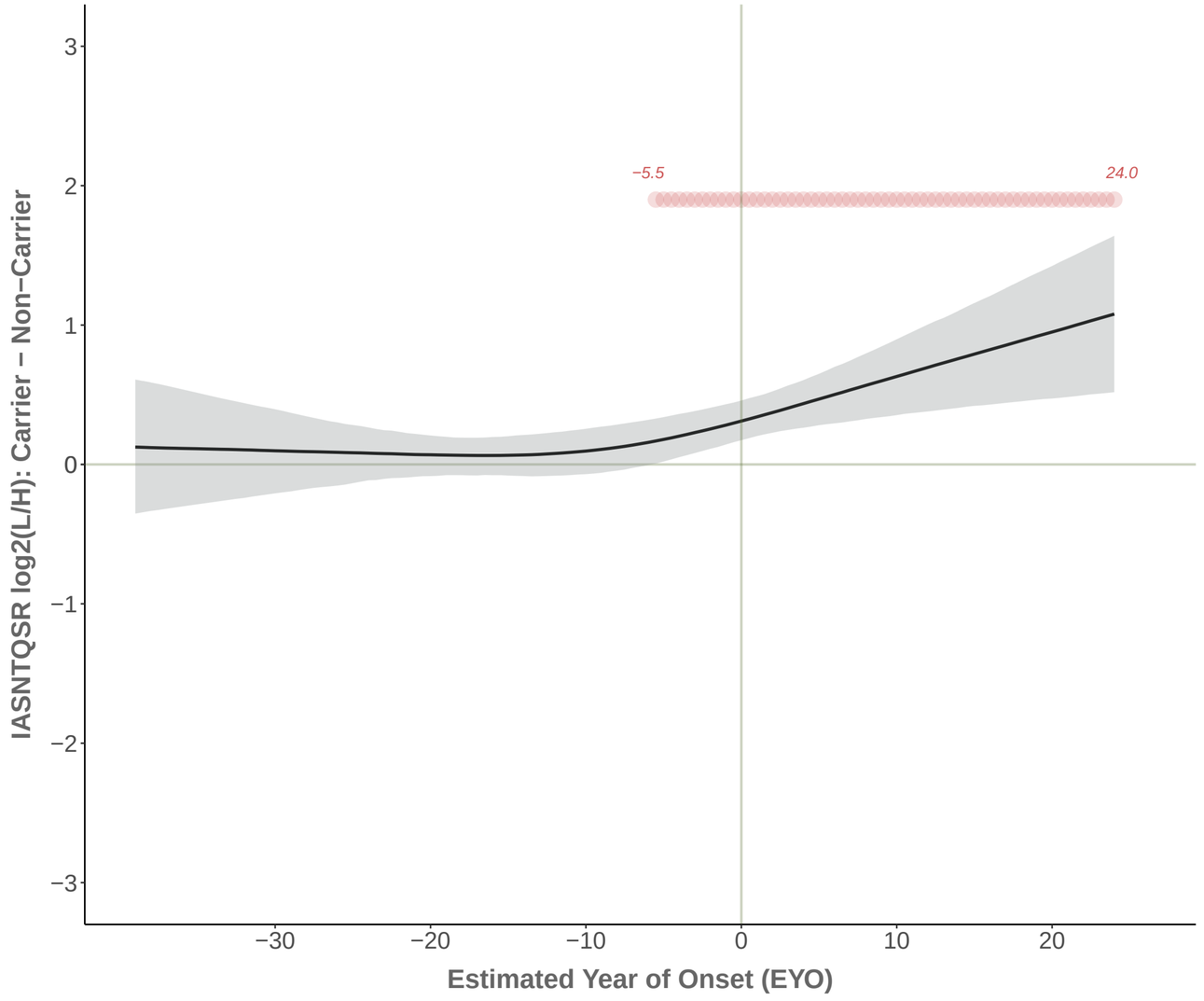
SPP1 level difference in mutation carriers and non−carriers with 99% confidence interval.



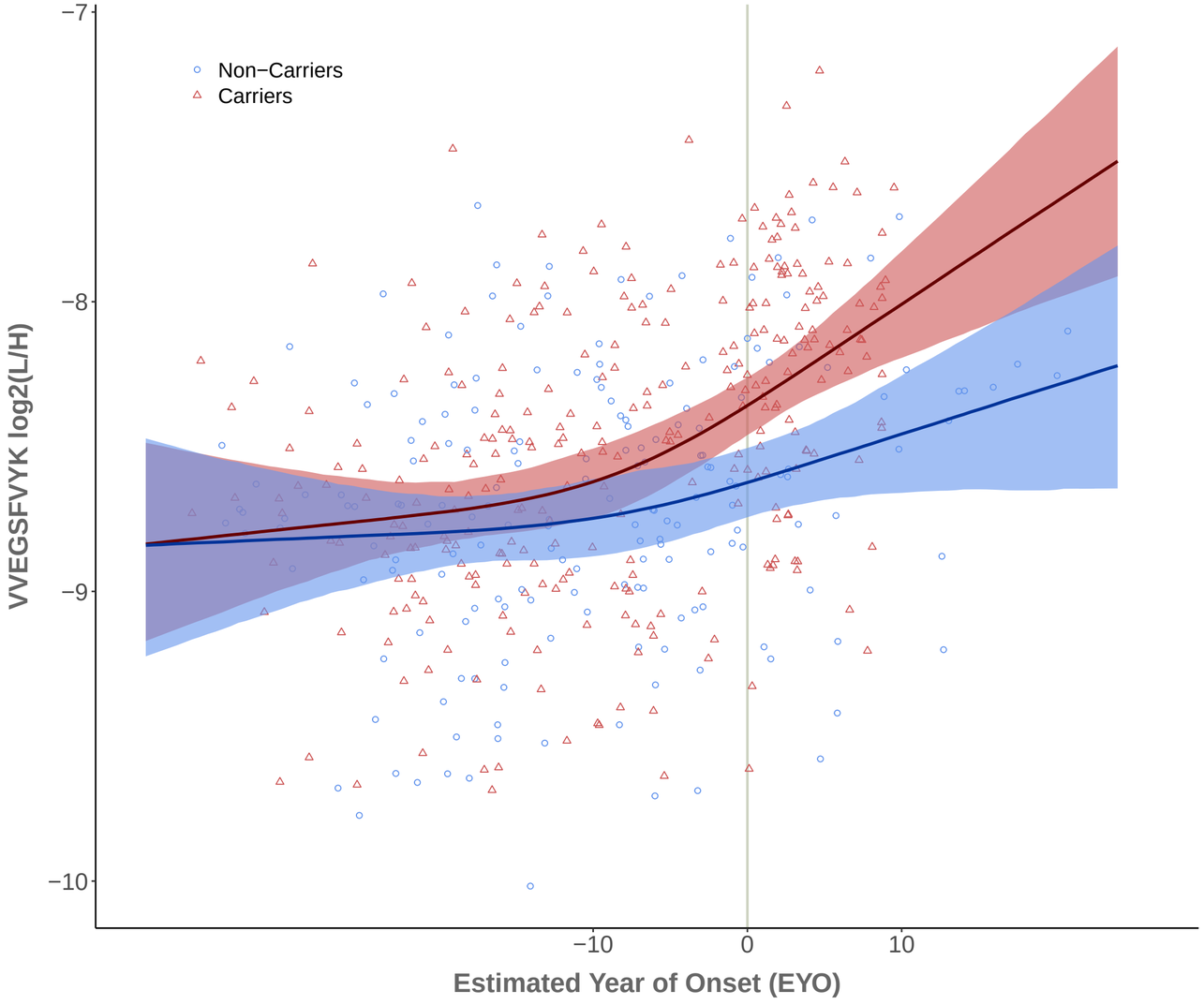
CHI3L1 level in mutation carriers and non−carriers with 99% confidence interval. 0 outliers removed for visualization purposes.



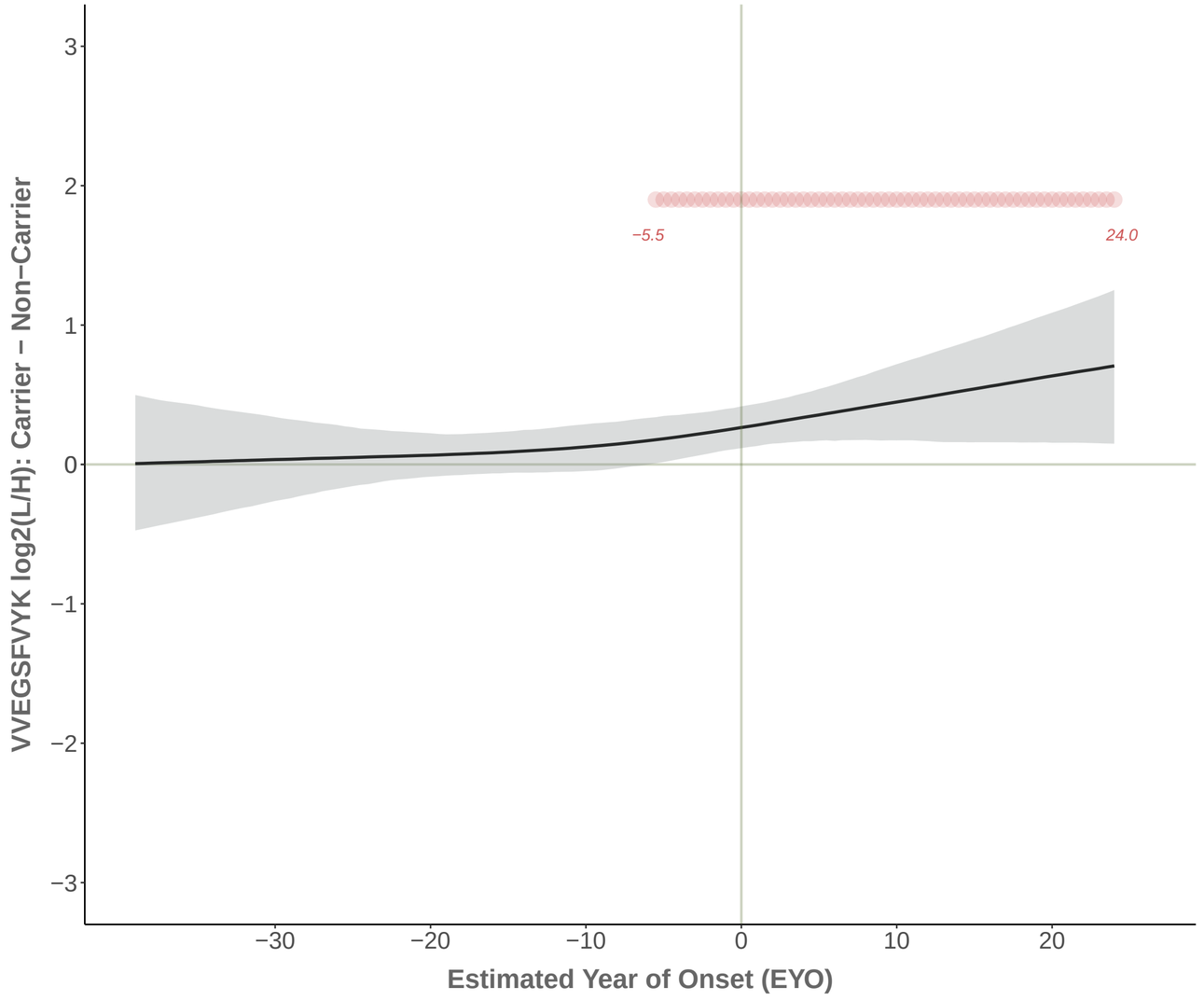
CHI3L1 level difference in mutation carriers and non−carriers with 99% confidence interval.



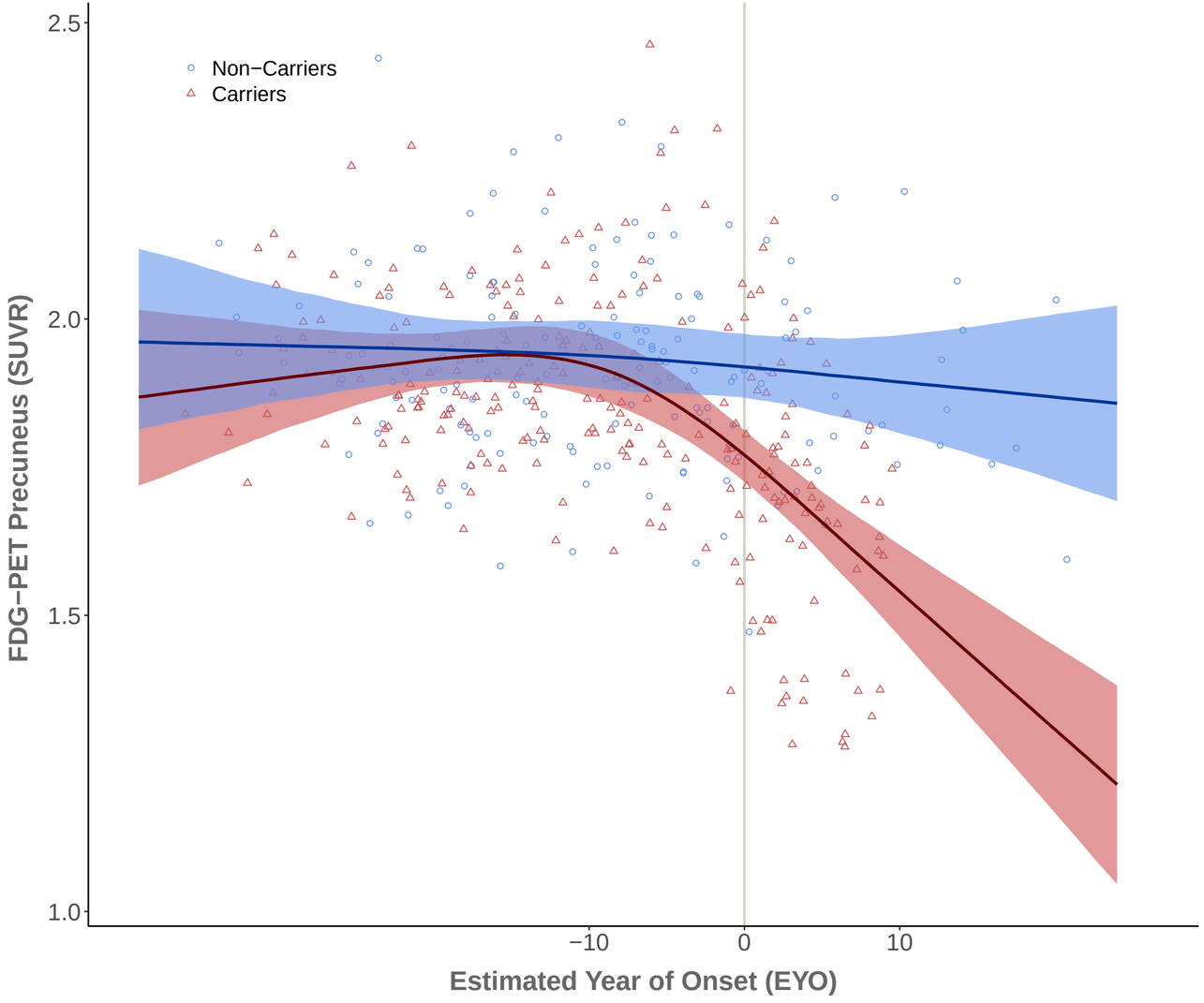
GDI1 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



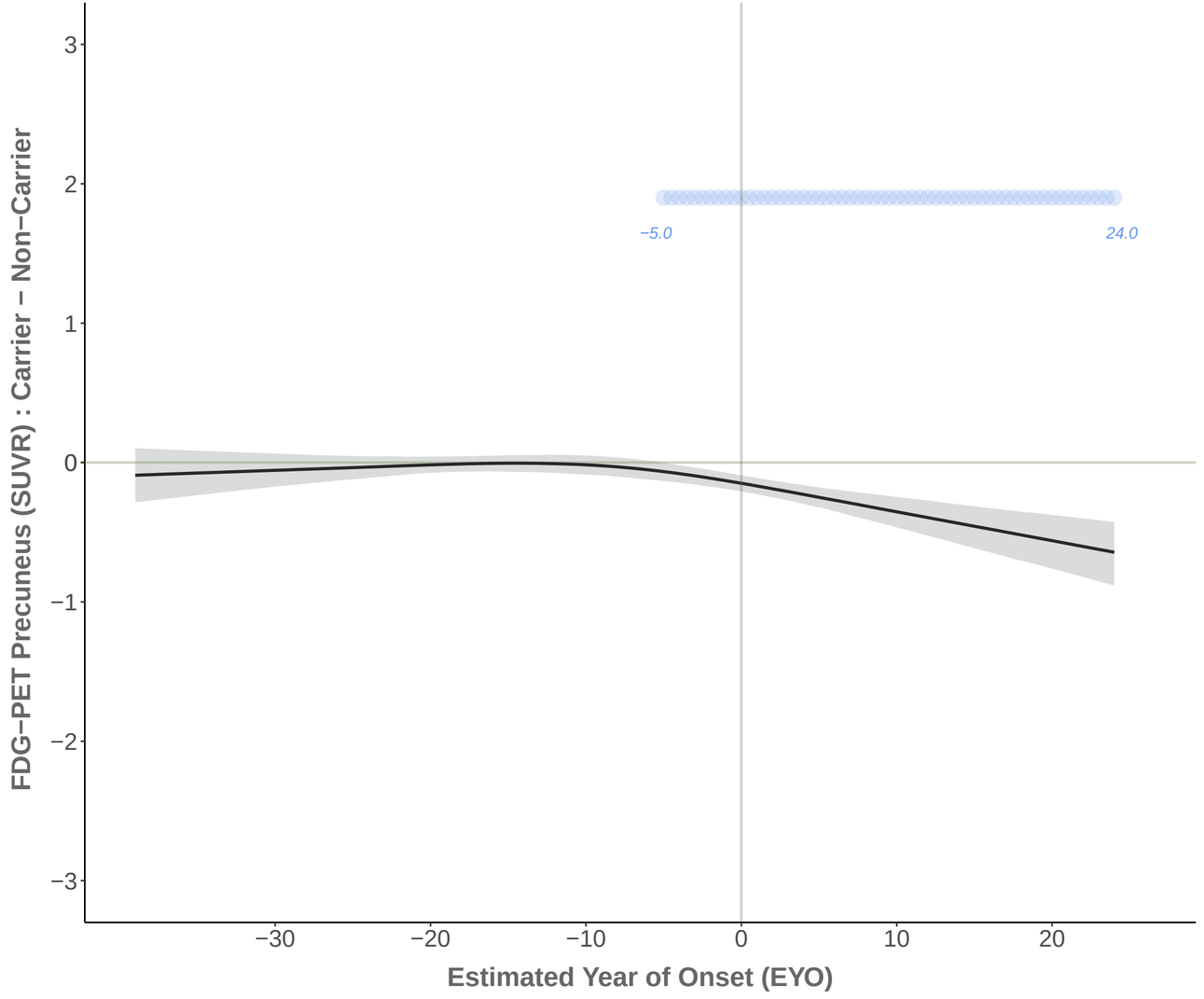
GDI1 level difference in mutation carriers and non−carriers with 99% confidence interval.



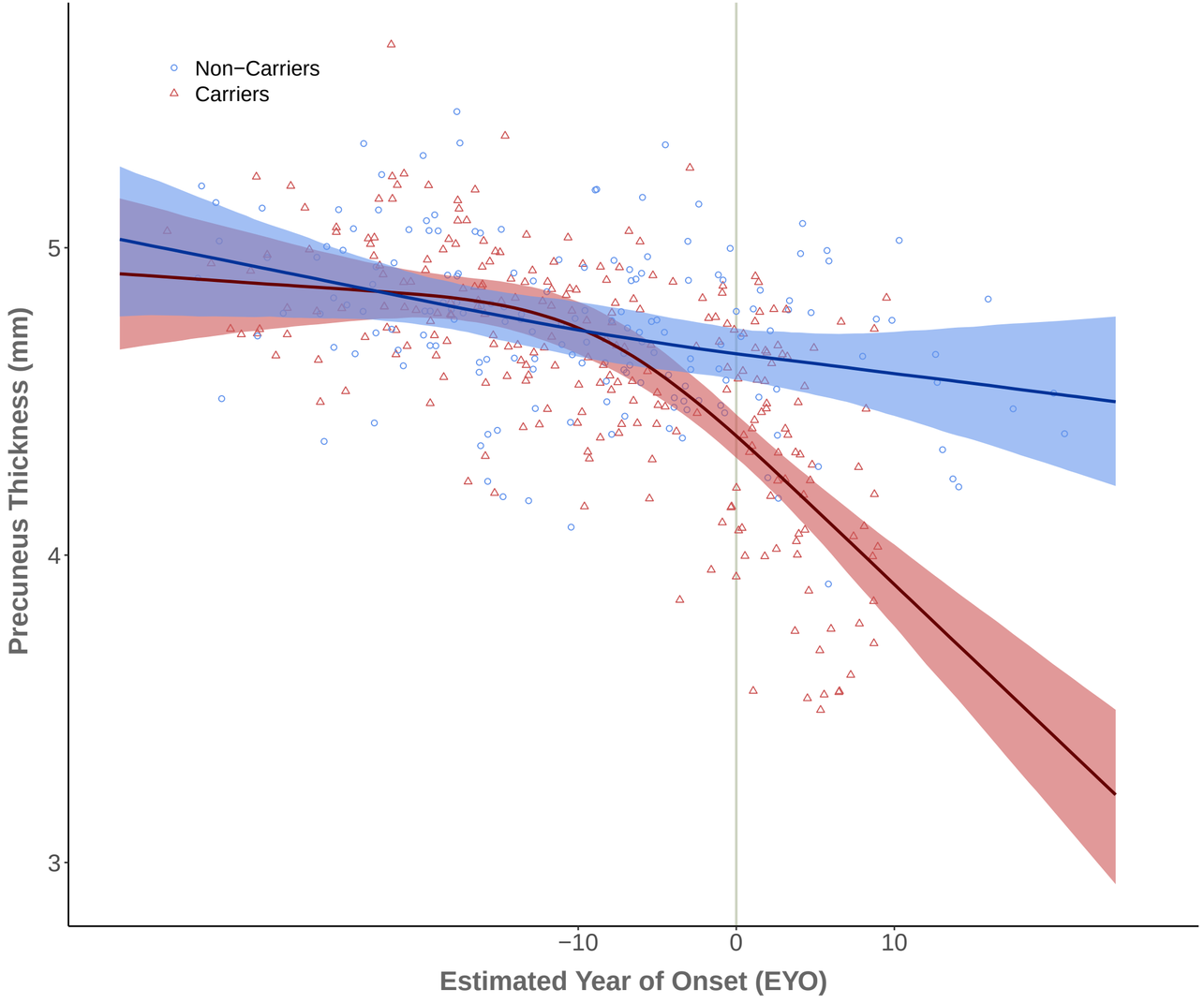
FDG−PET Precuneus SUVR in mutation carriers and non−carriers with 99% confidence interval. 5 outliers removed for visualization purposes.



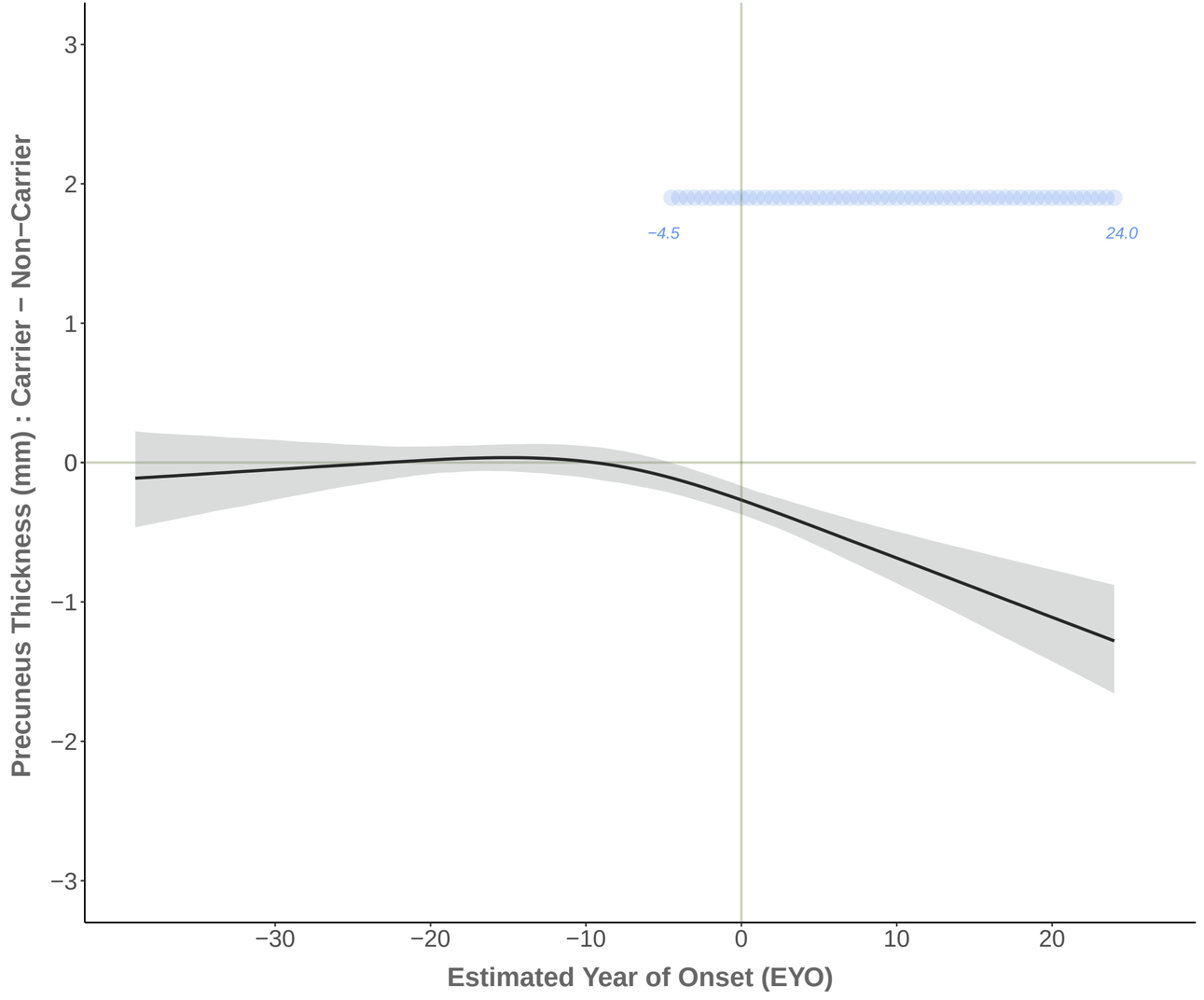
FDG−PET Precuneus SUVR difference in mutation carriers and non−carriers with 99% confidence interval.



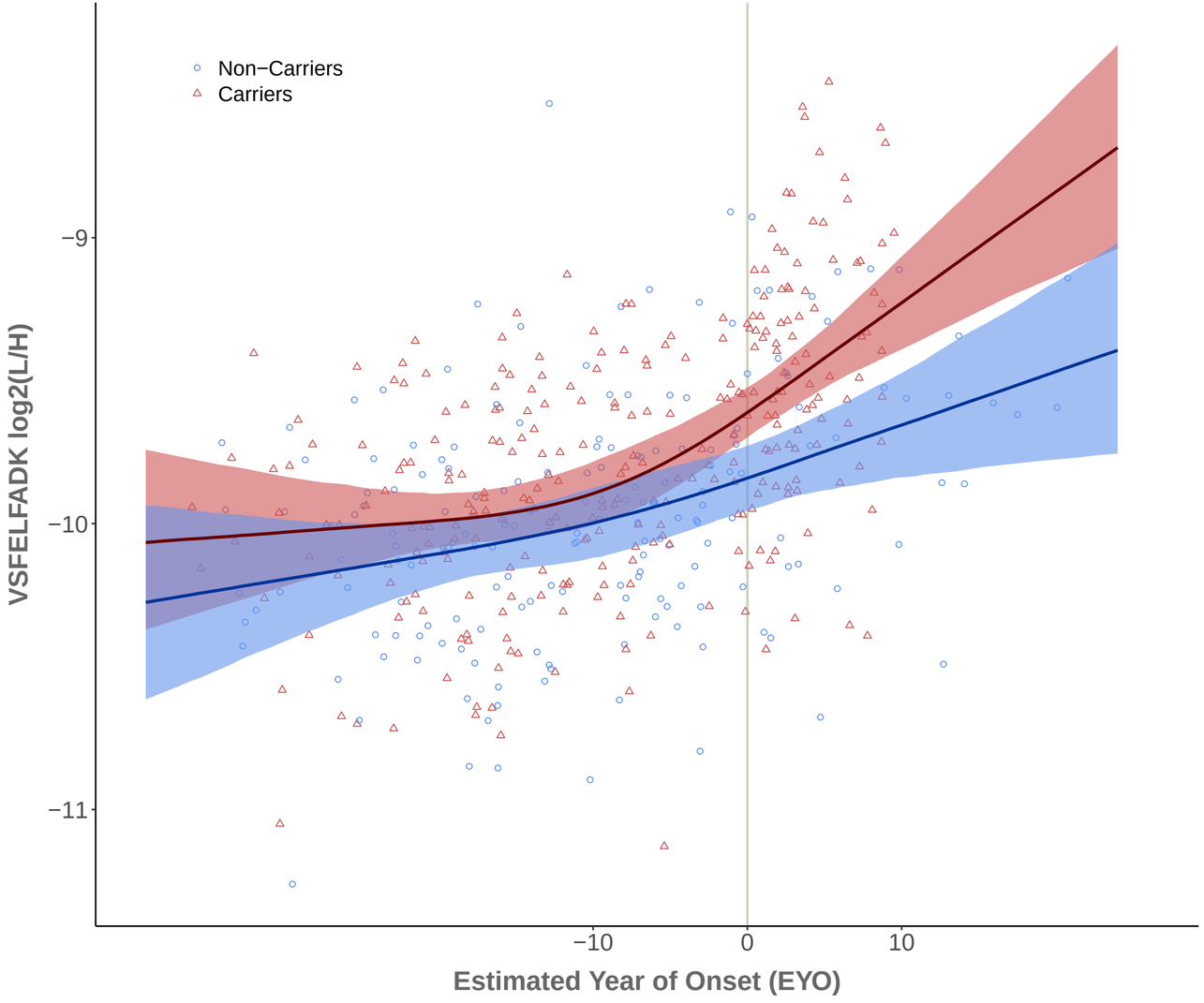
Precuneus Thickness in mutation carriers and non−carriers with 99% confidence interval. 7 outliers removed for visualization purposes.



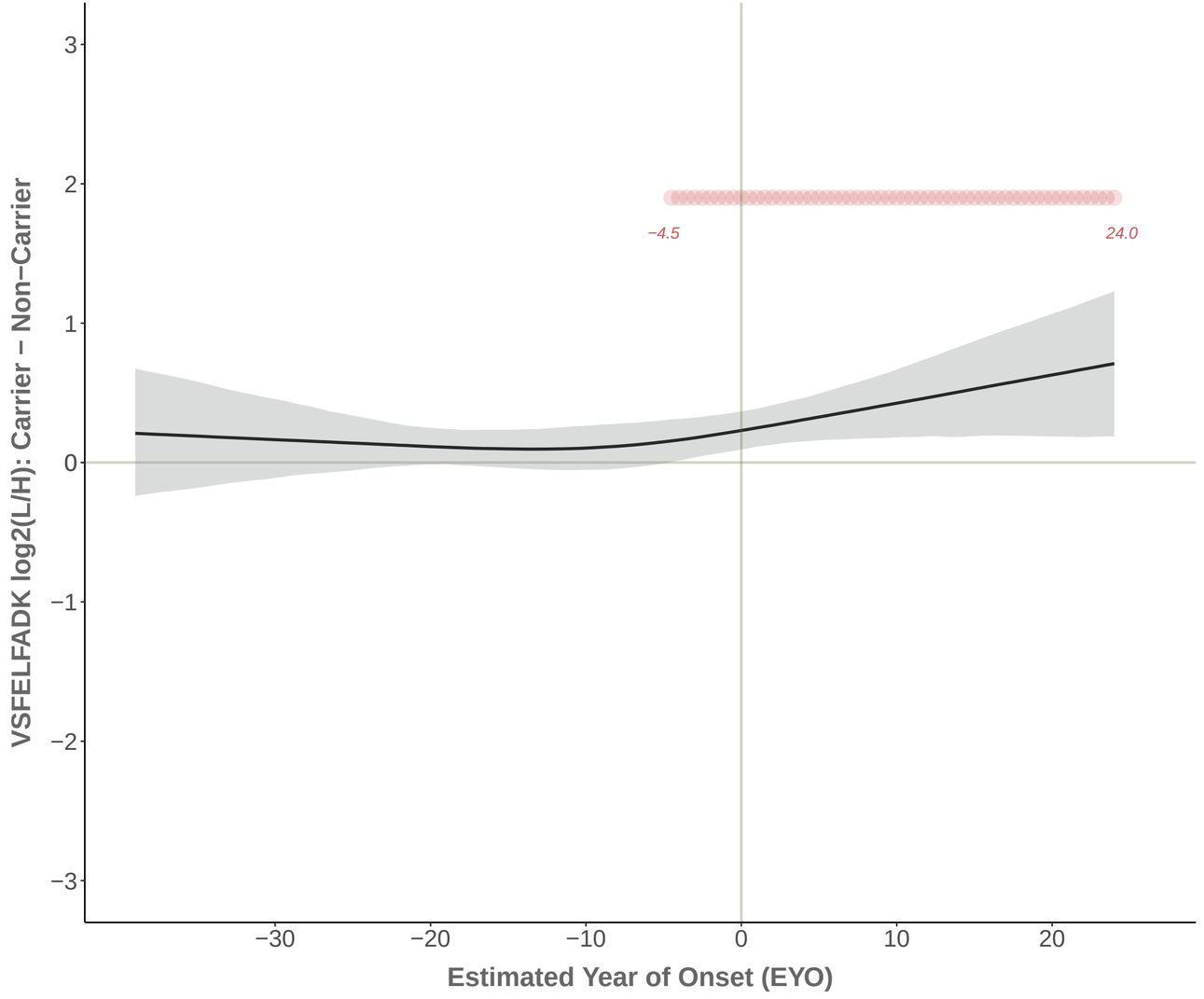
Precuneus Thickness difference in mutation carriers and non−carriers with 99% confidence interval.



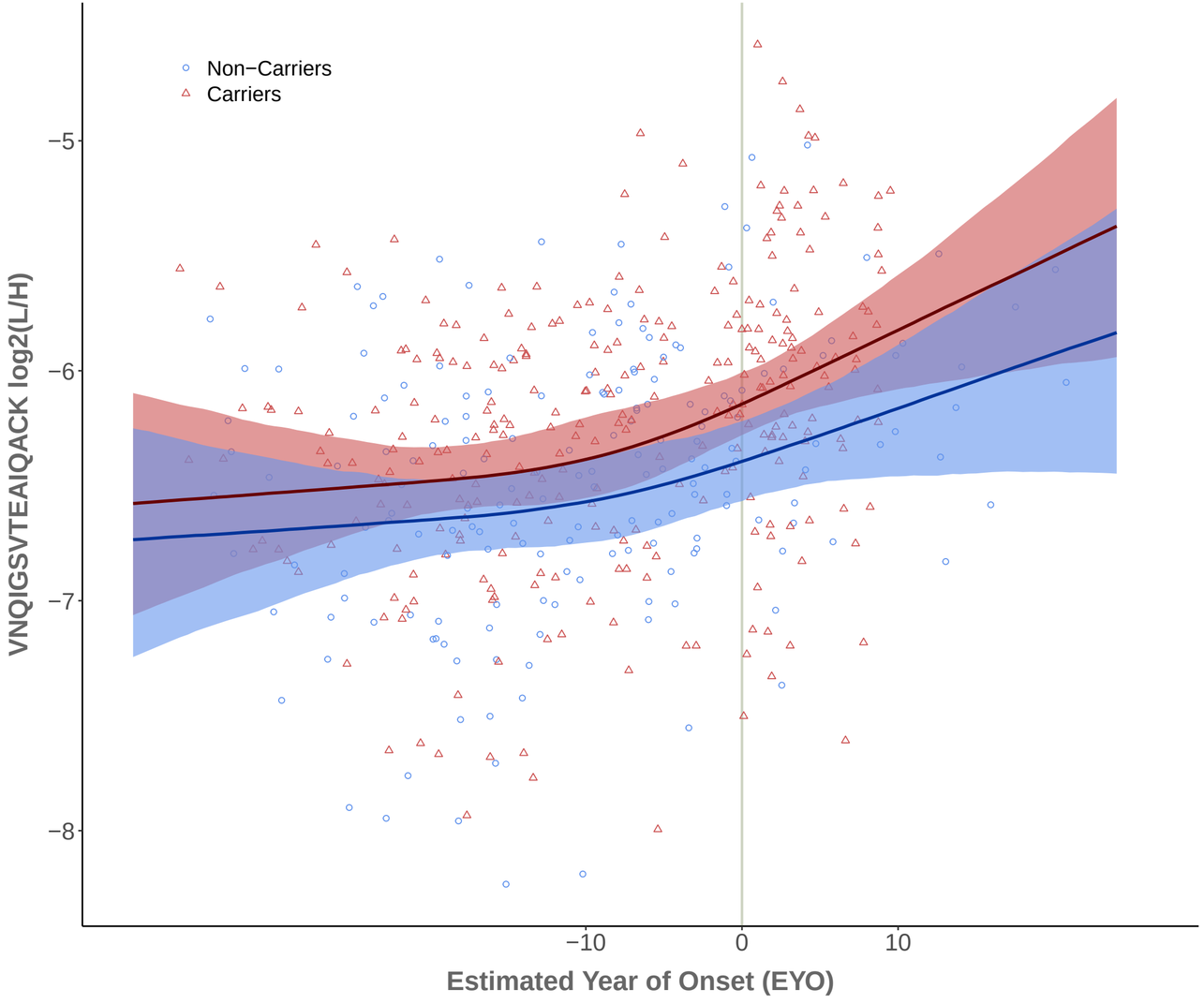
PPIA level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



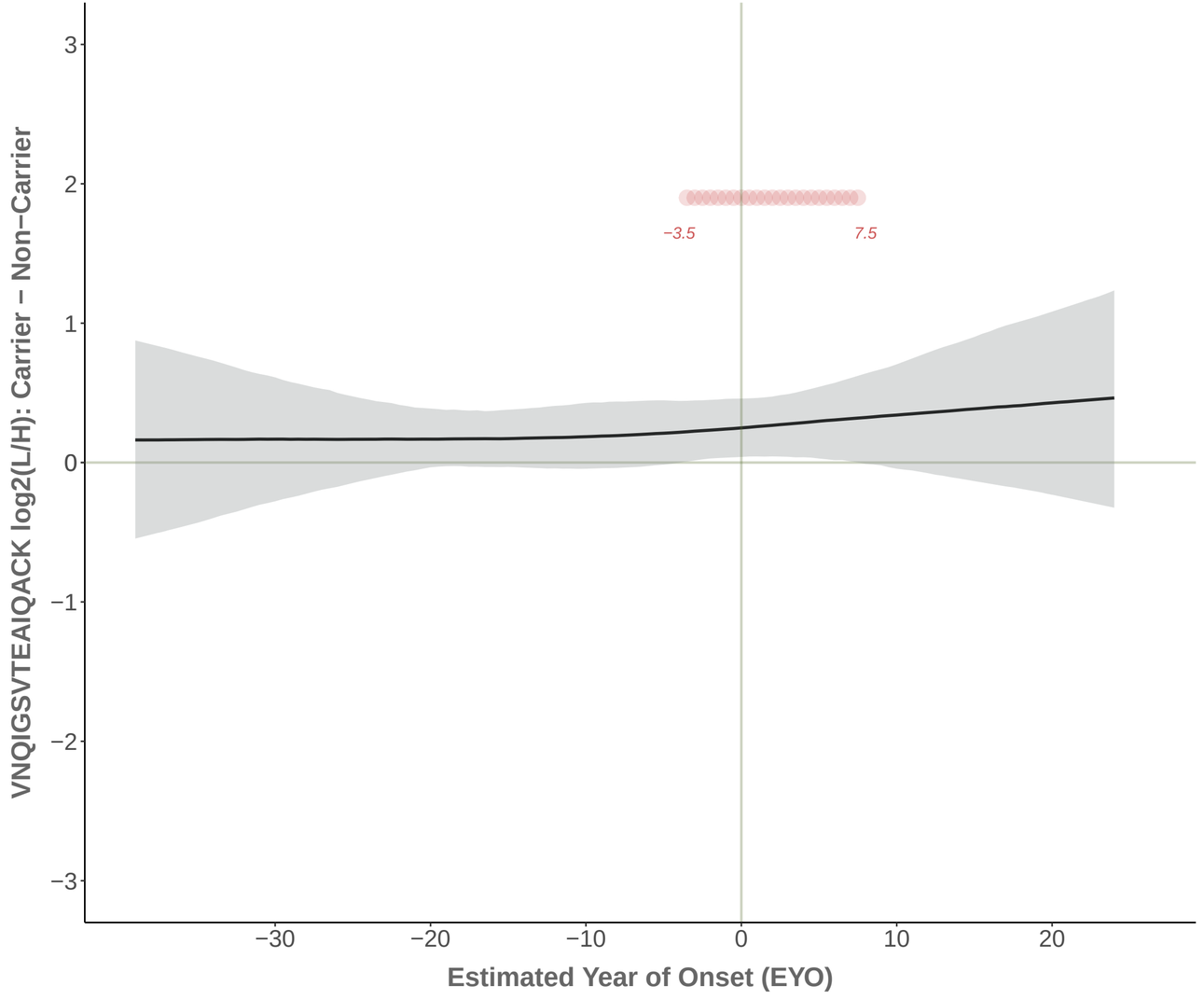
PPIA level difference in mutation carriers and non−carriers with 99% confidence interval.



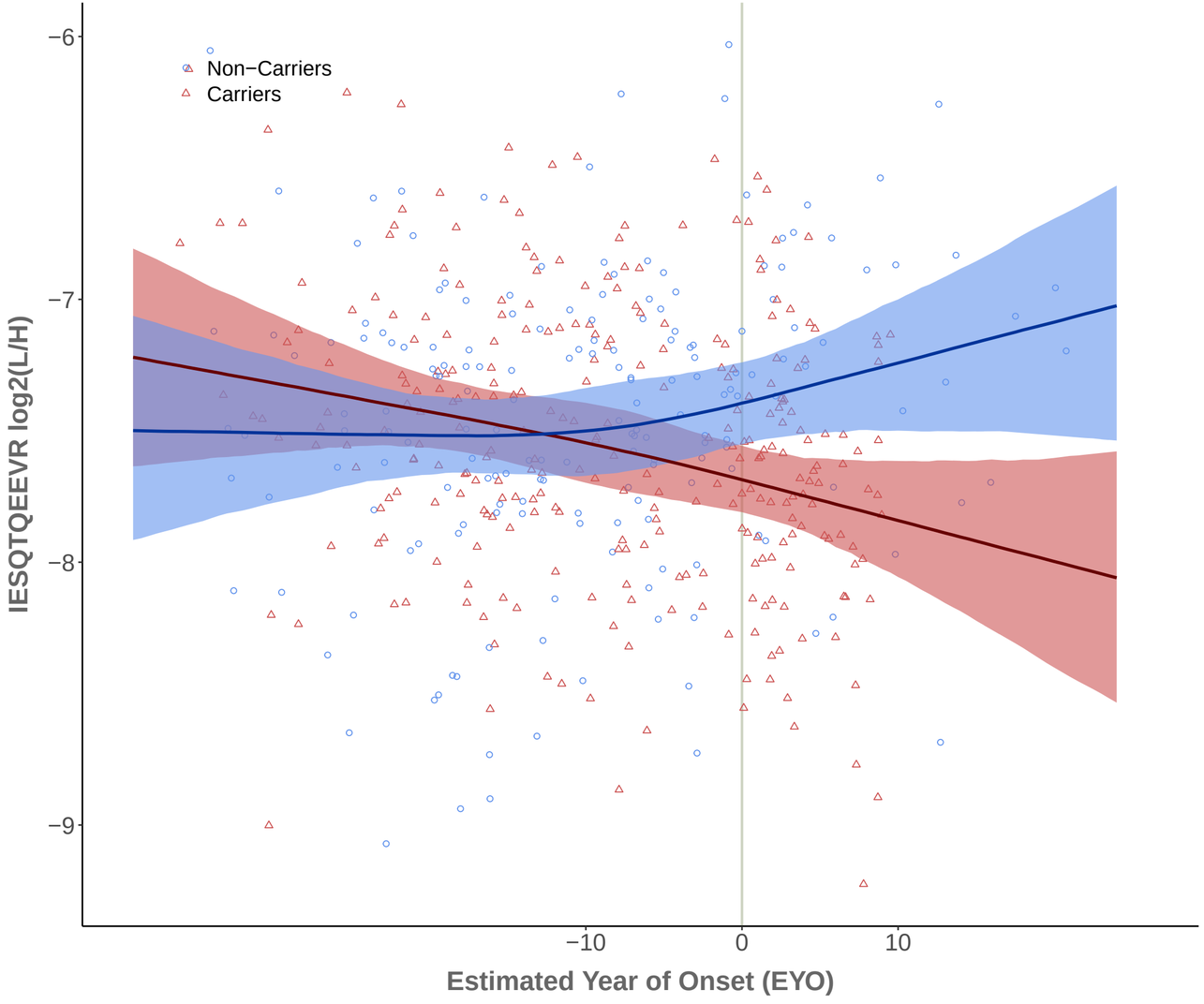
ENO2 level in mutation carriers and non−carriers with 99% confidence interval. 6 outliers removed for visualization purposes.



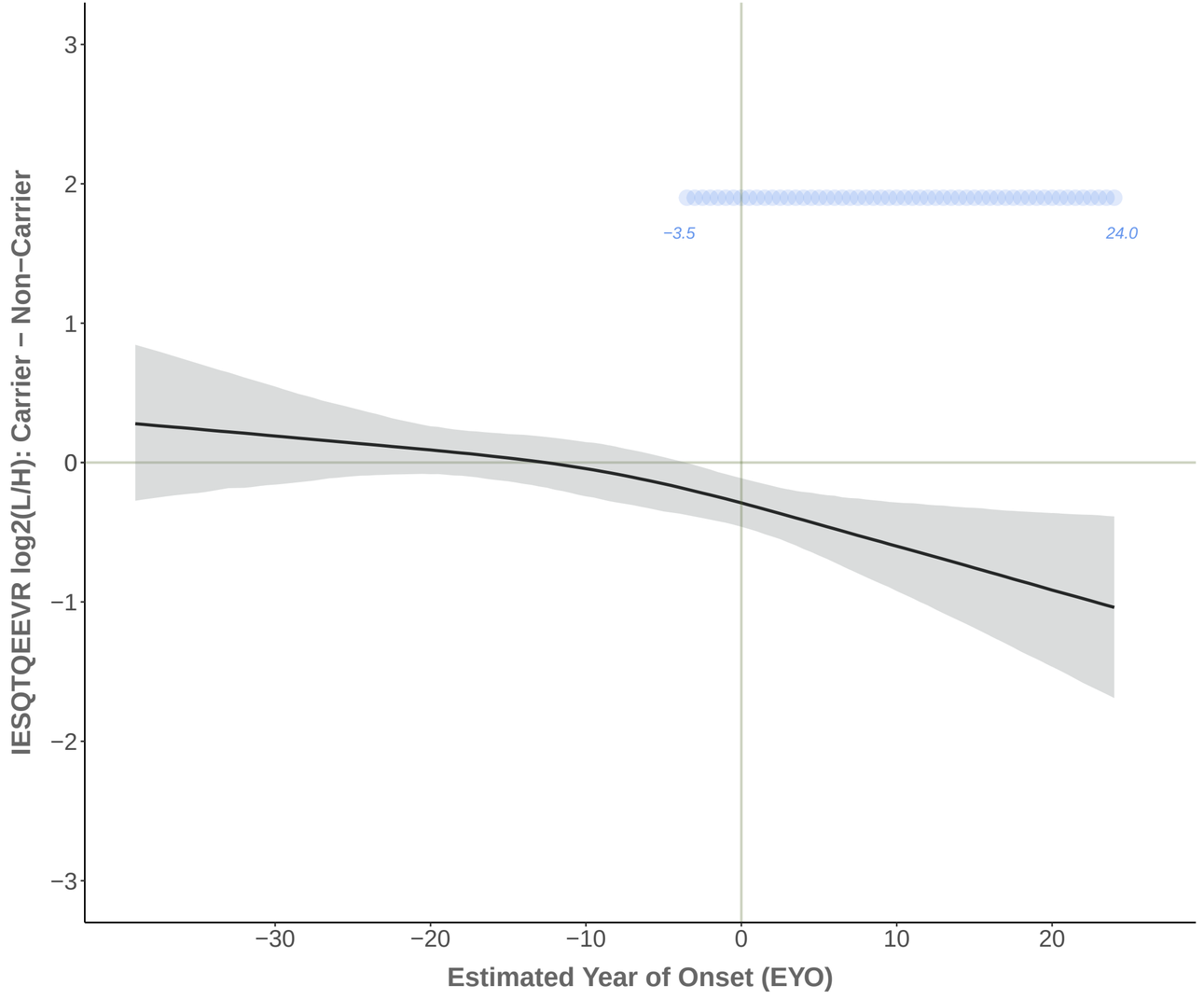
ENO2 level difference in mutation carriers and non−carriers with 99% confidence interval.



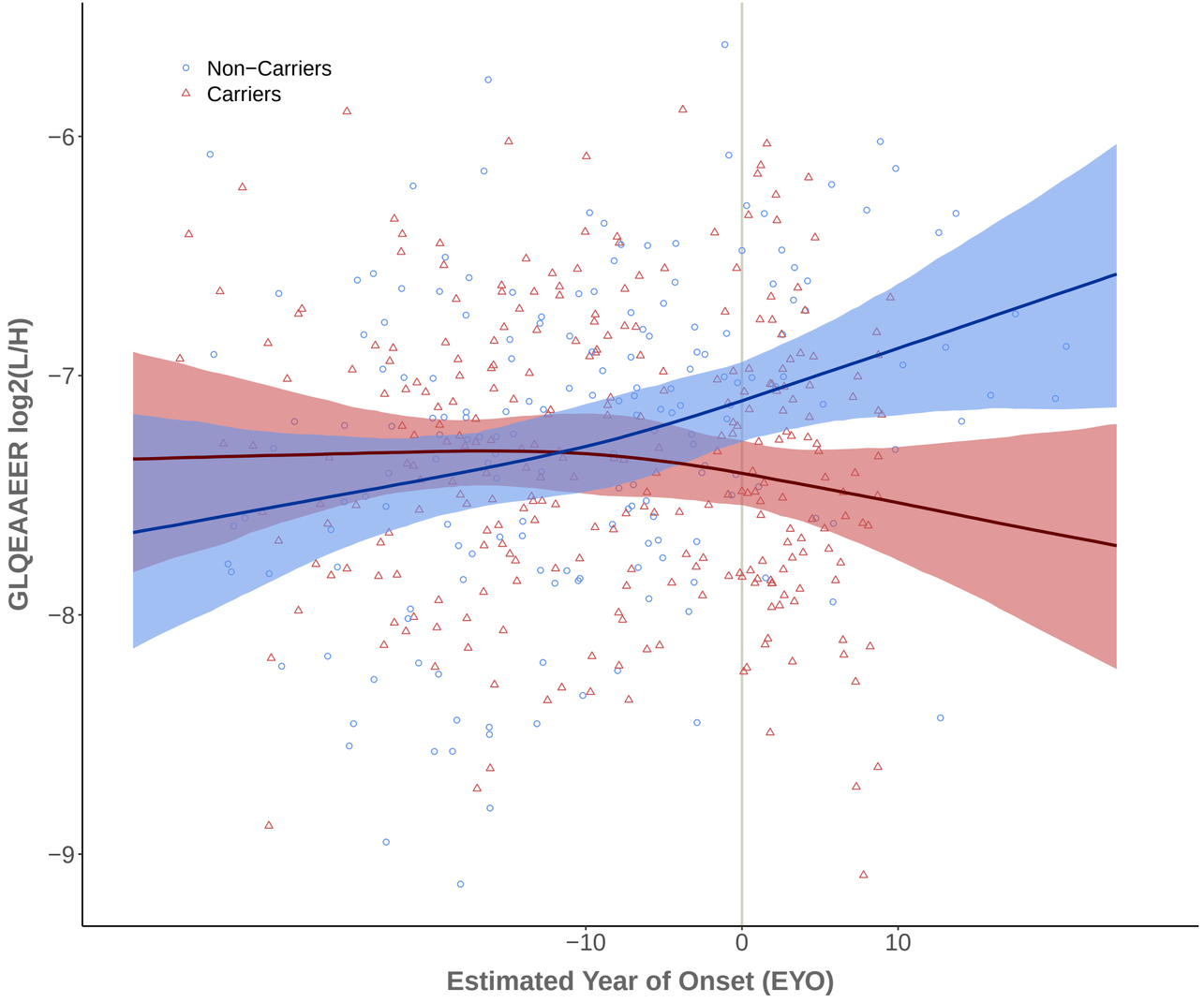
SCG2 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



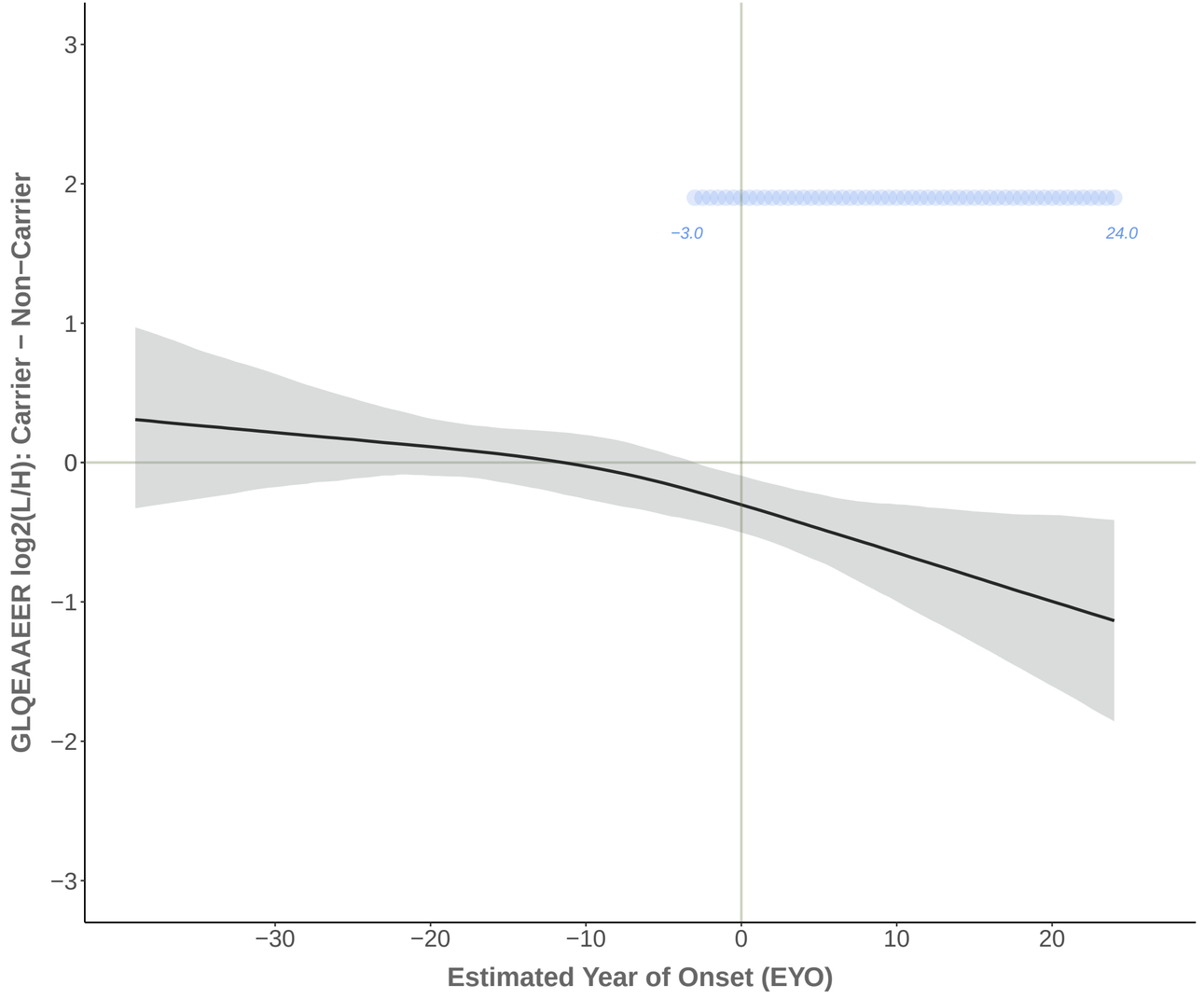
SCG2 level difference in mutation carriers and non−carriers with 99% confidence interval.



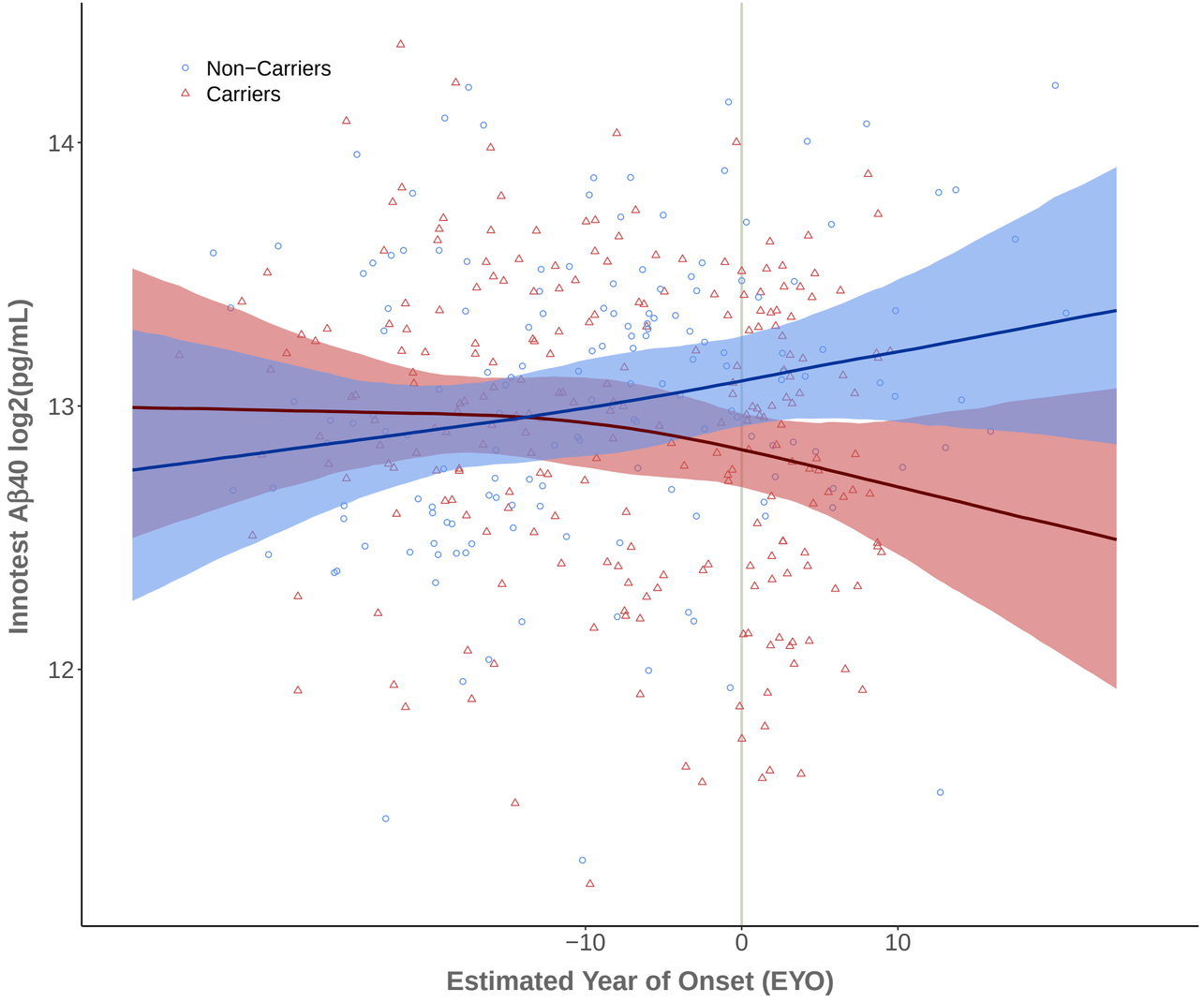
VGF level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



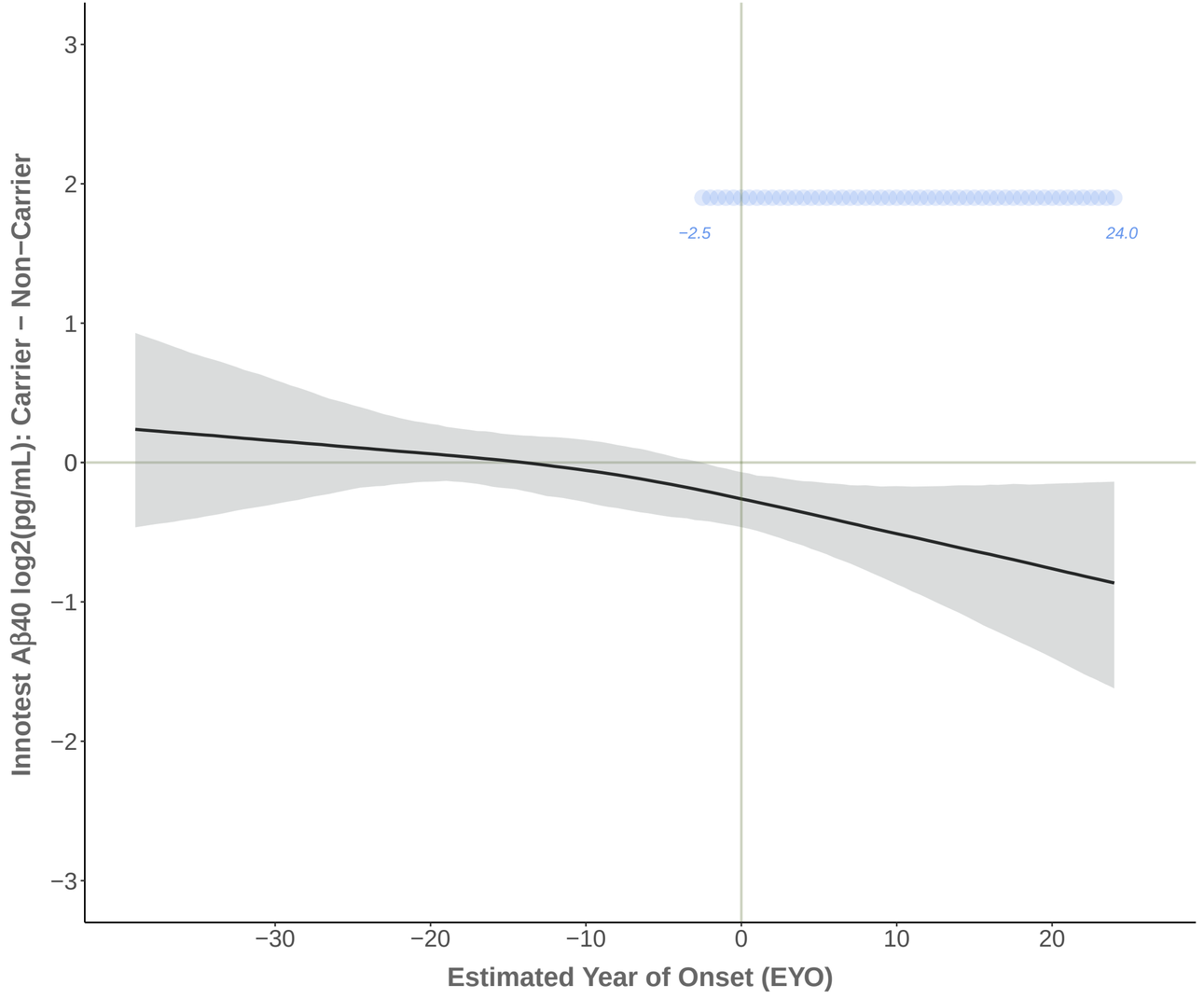
VGF level difference in mutation carriers and non−carriers with 99% confidence interval.



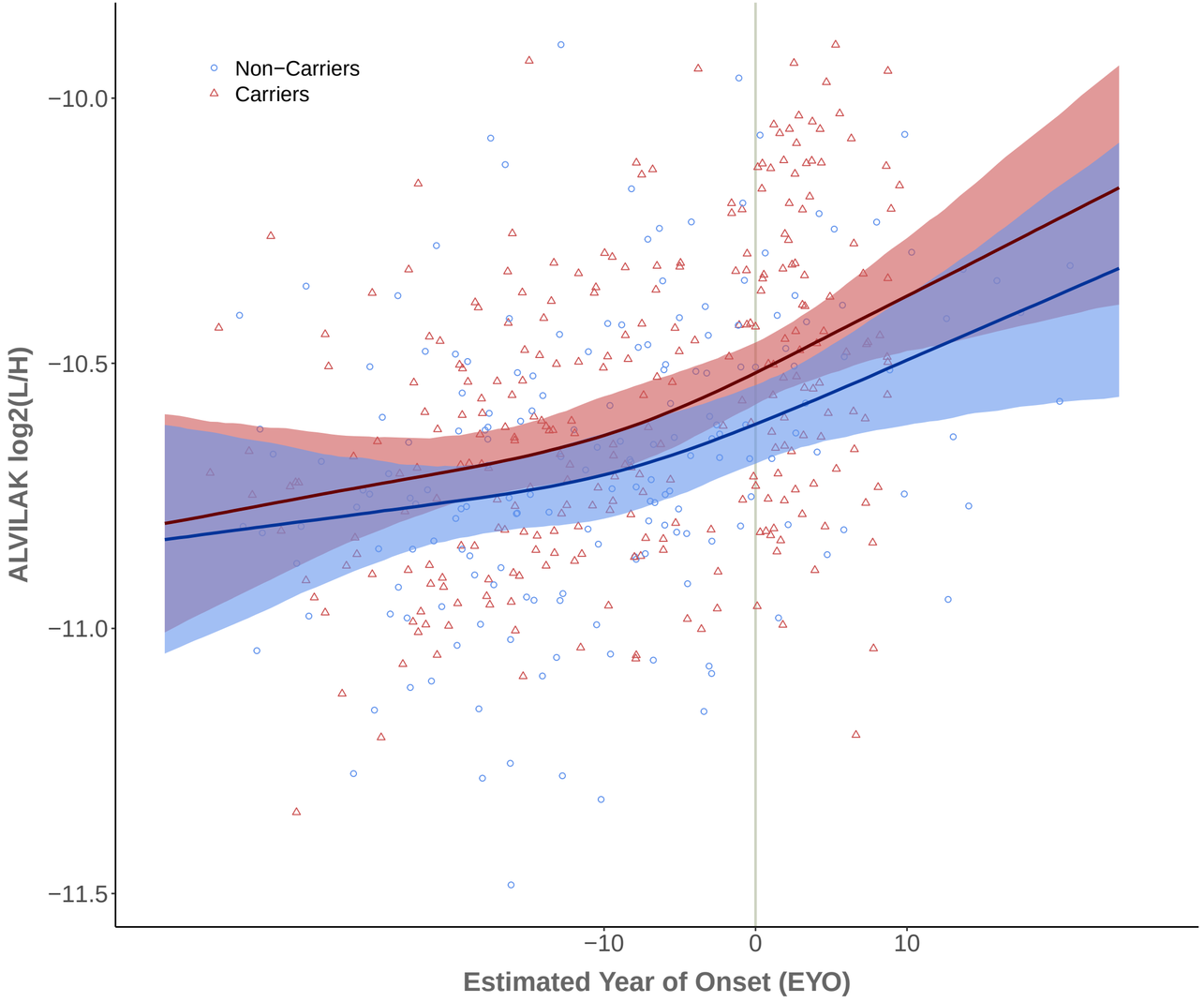
Innotest Aβ40 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



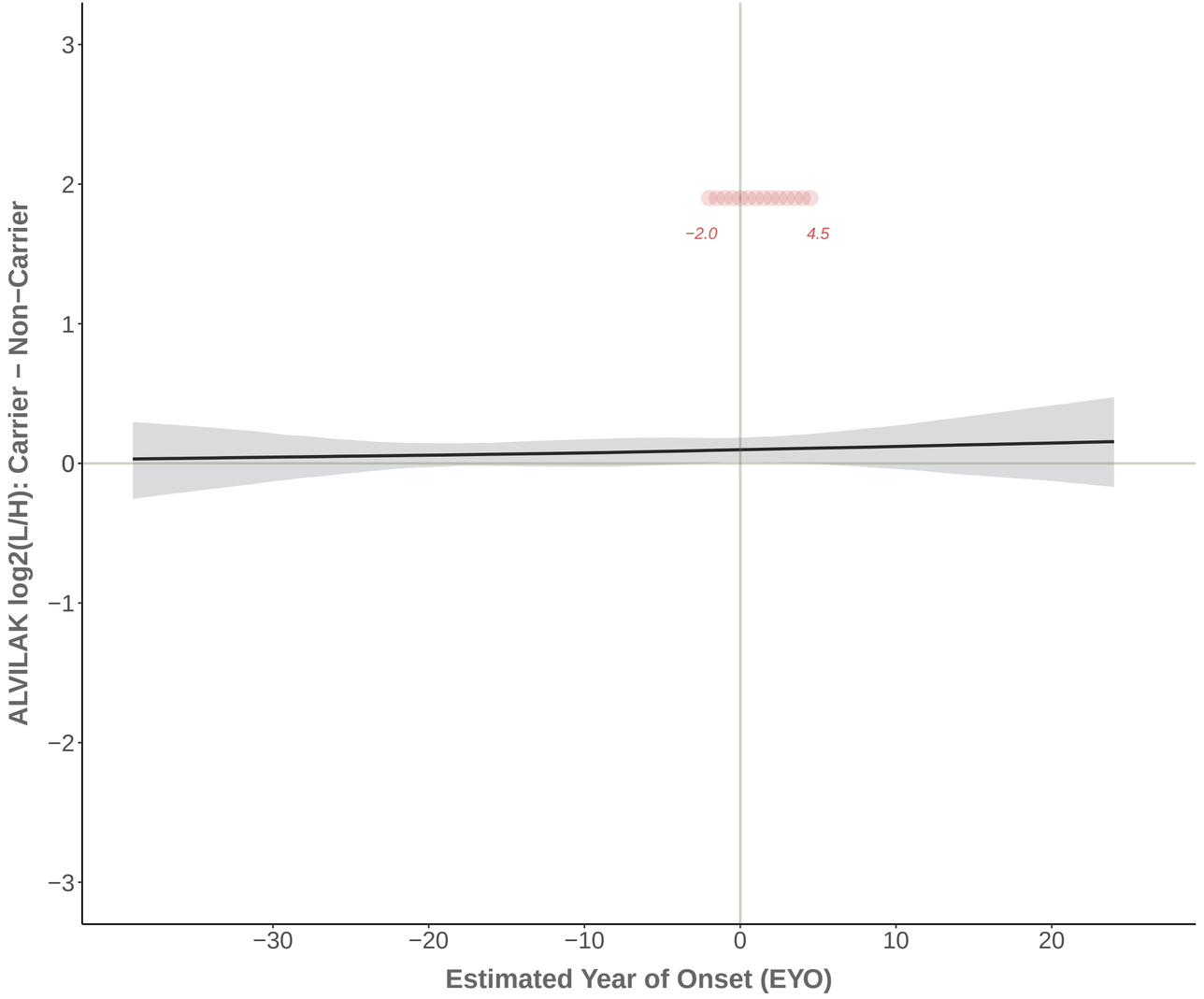
Innotest Aβ40 level difference in mutation carriers and non−carriers with 99% confidence interval.



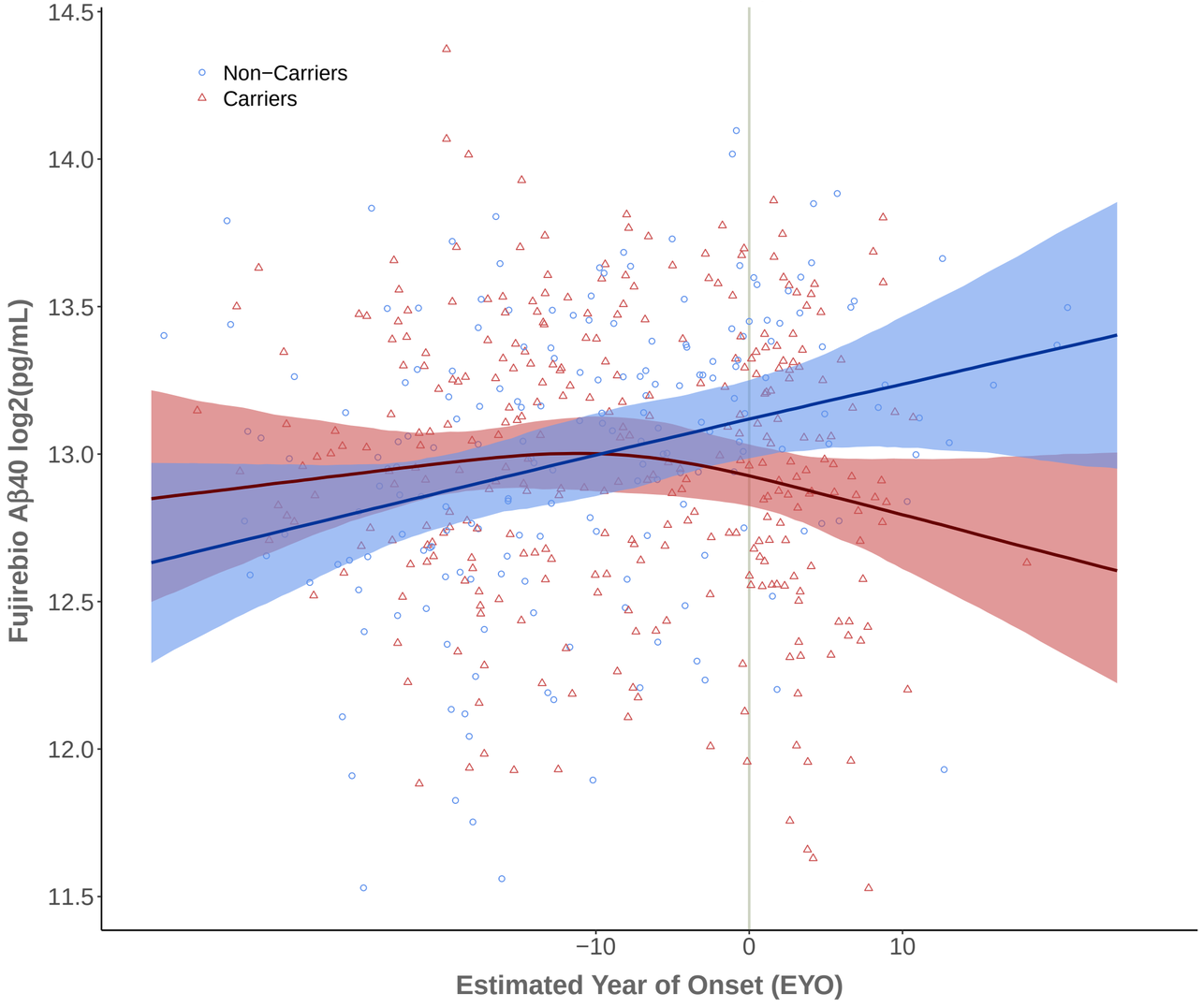
PARK7 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



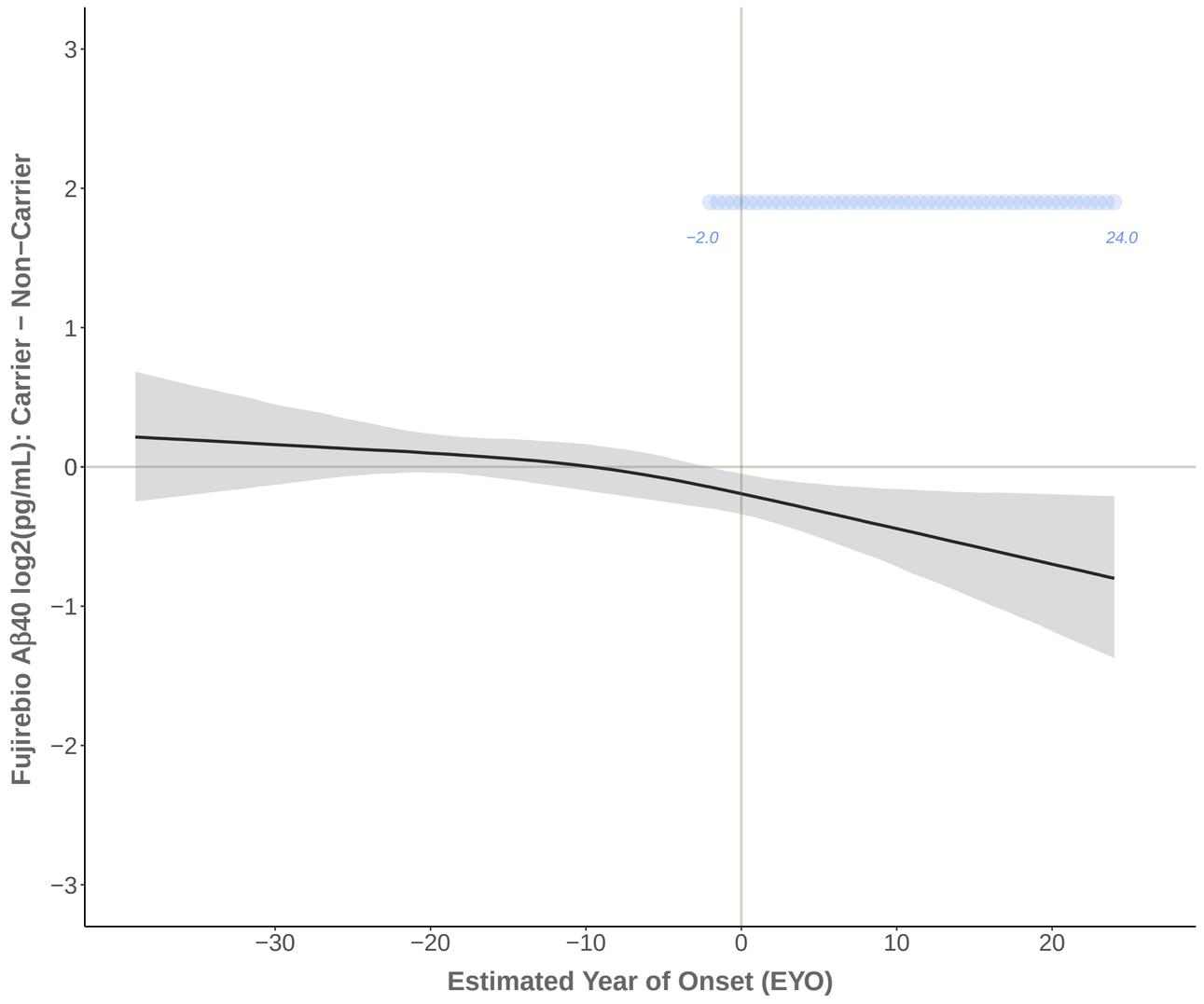
PARK7 level difference in mutation carriers and non−carriers with 99% confidence interval.



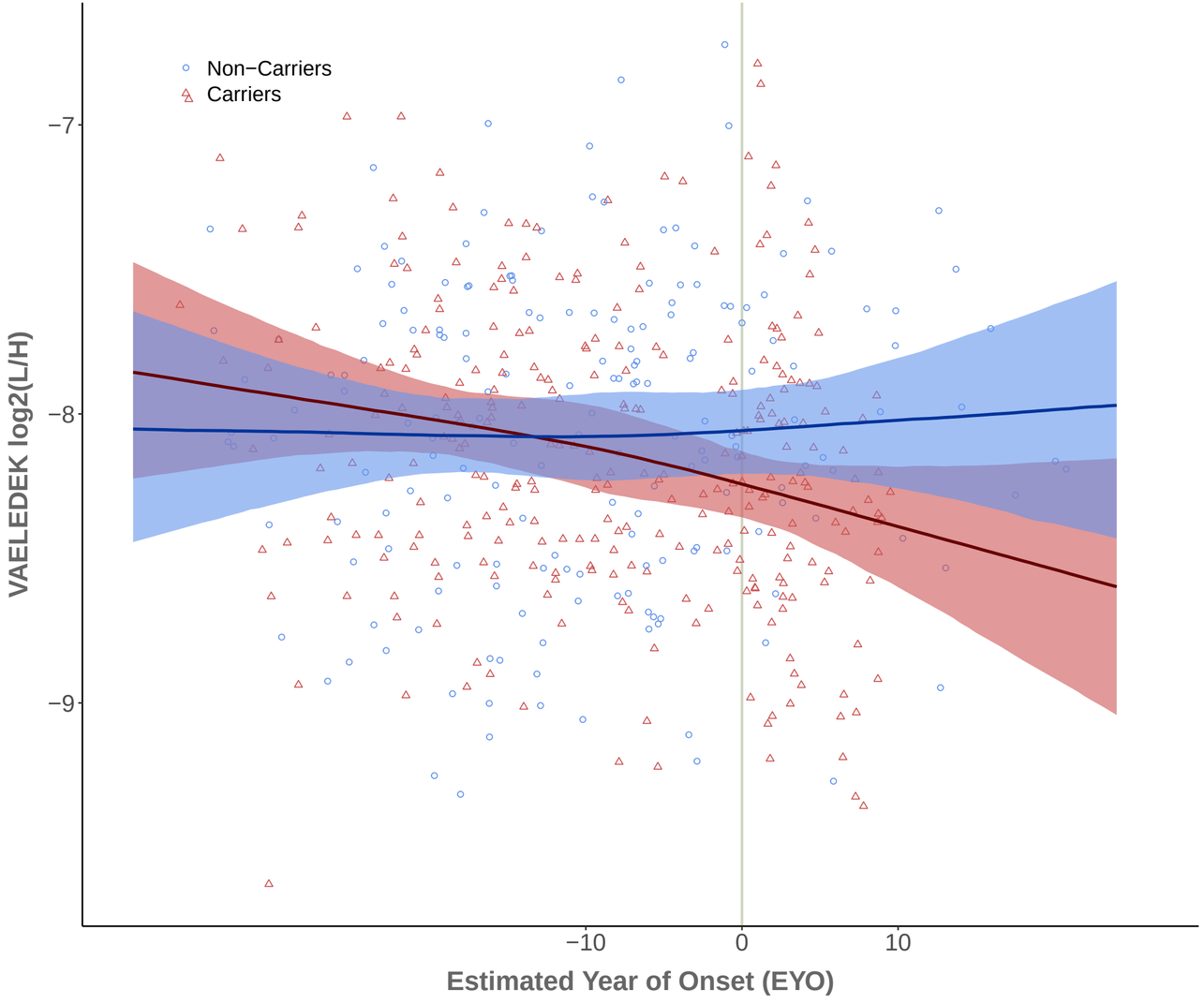
Fujirebio Aβ40 level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



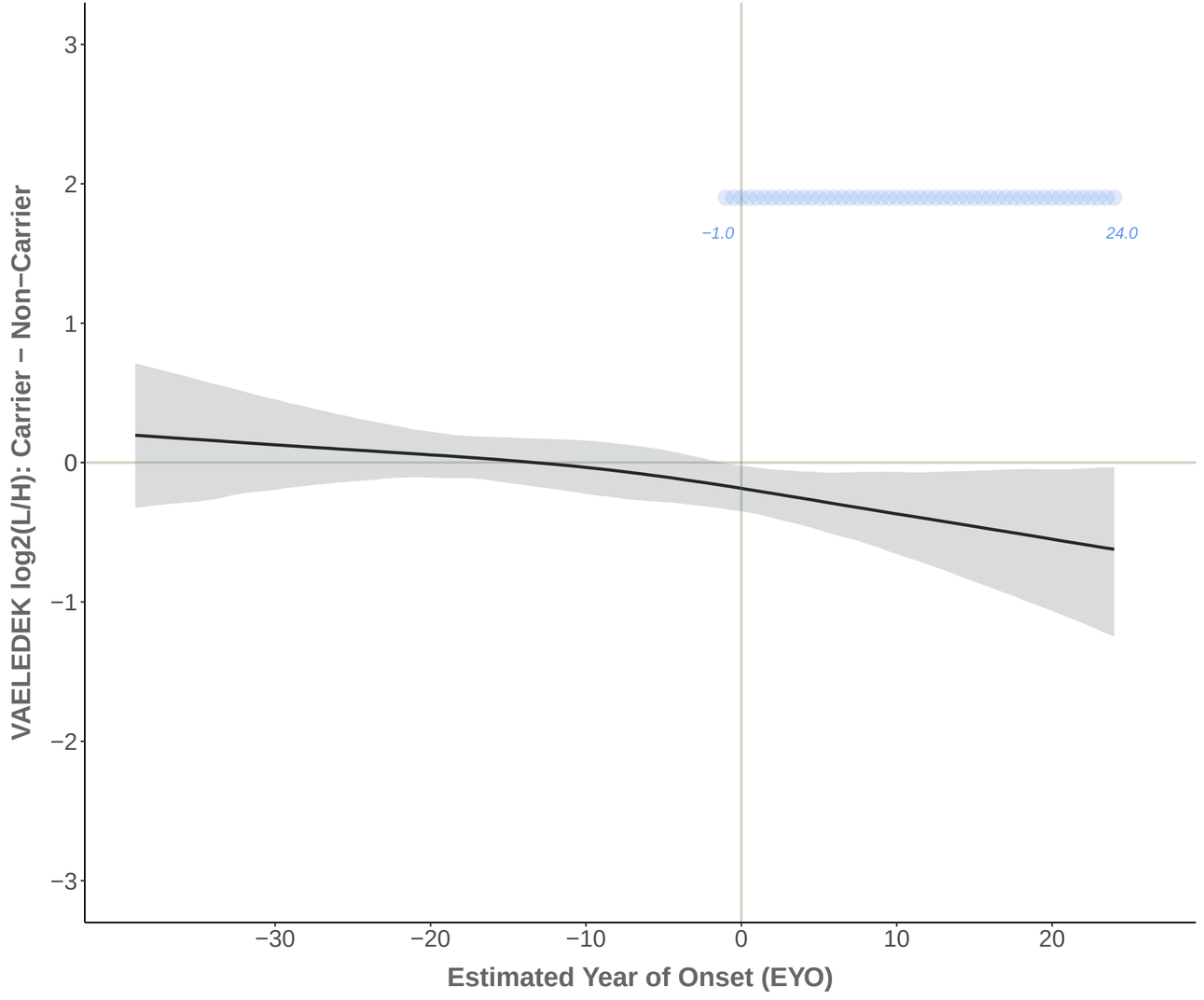
Fujirebio Aβ40 level difference in mutation carriers and non−carriers with 99% confidence interval.



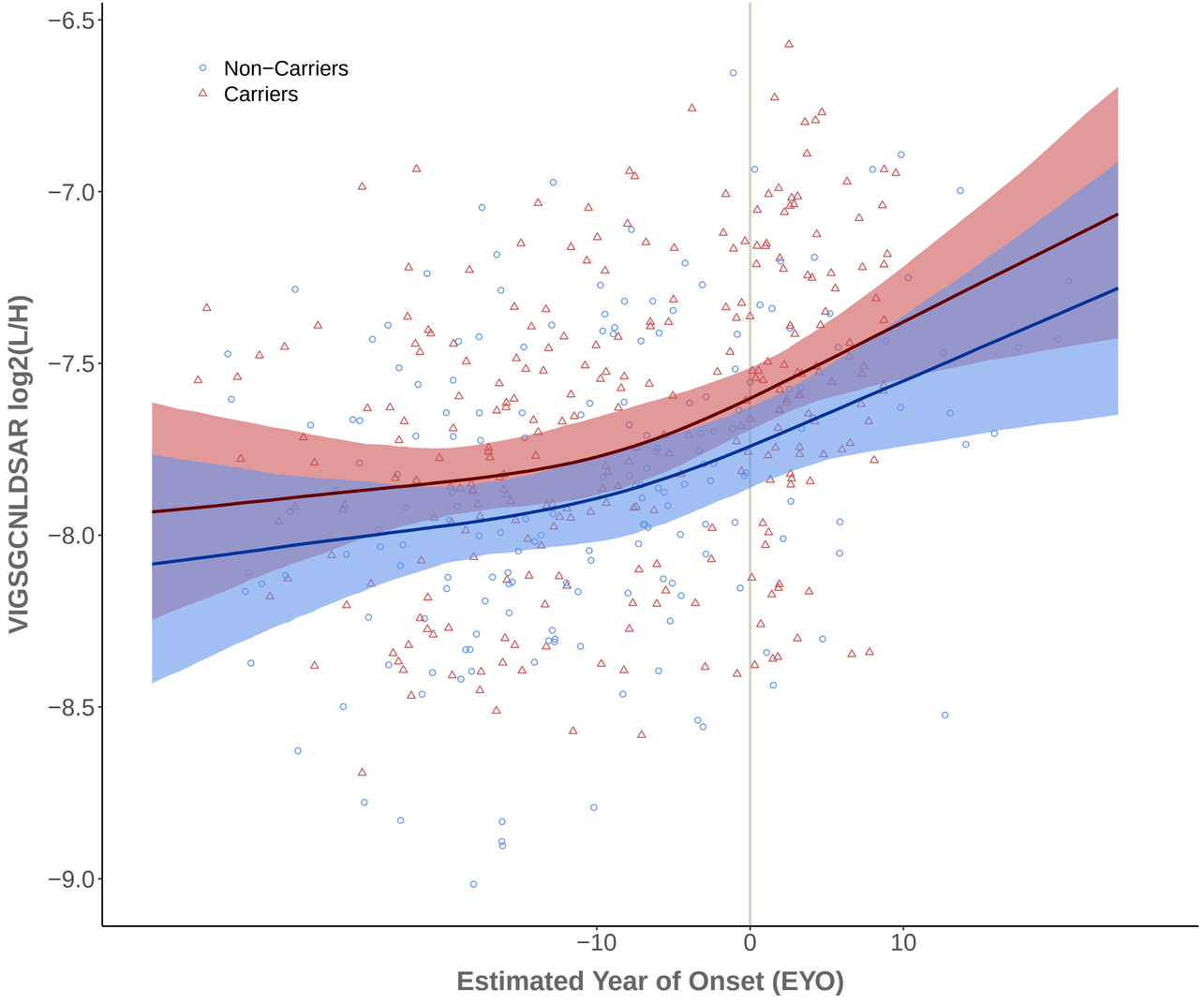
NPTX2 level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



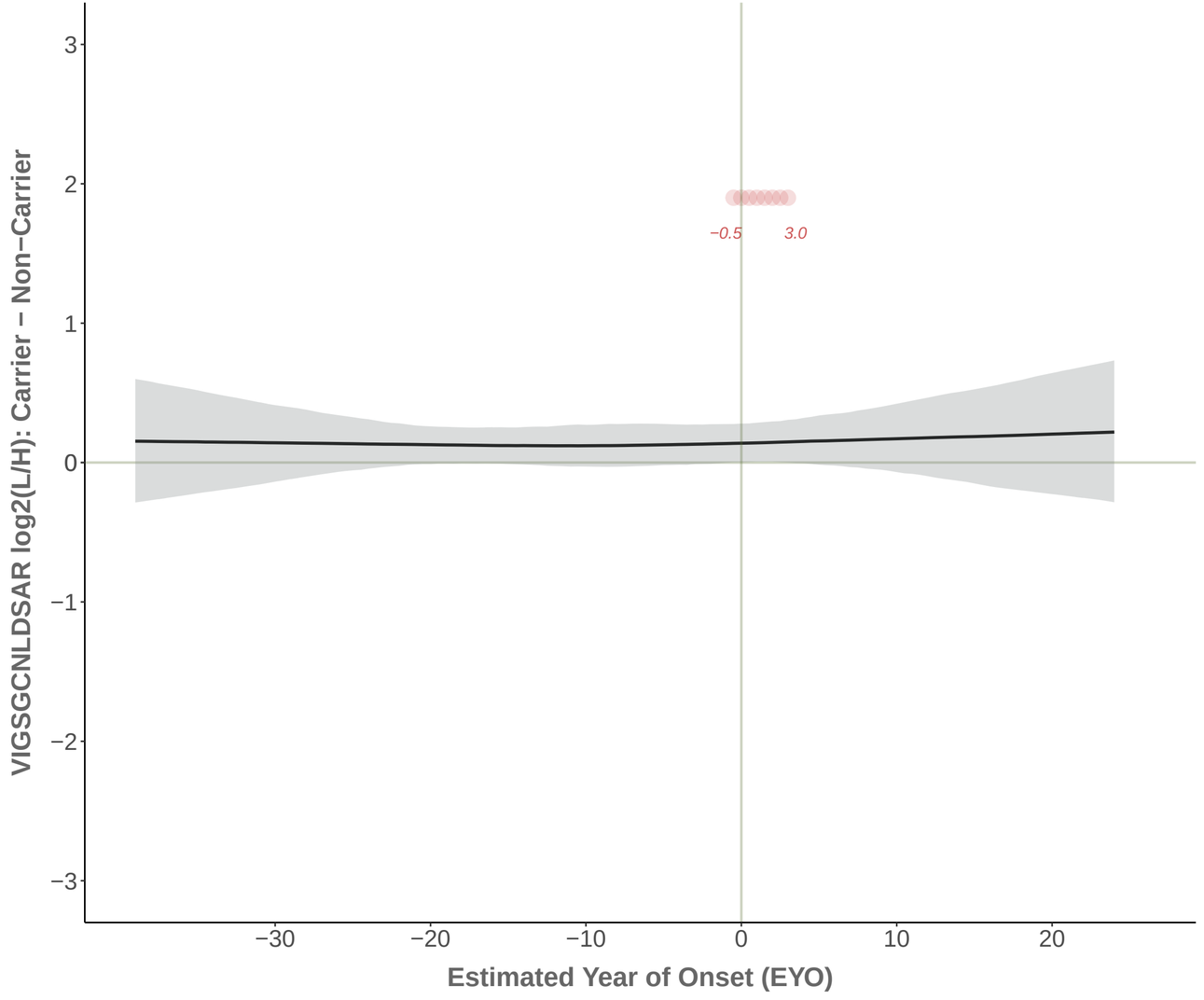
NPTX2 level difference in mutation carriers and non−carriers with 99% confidence interval.



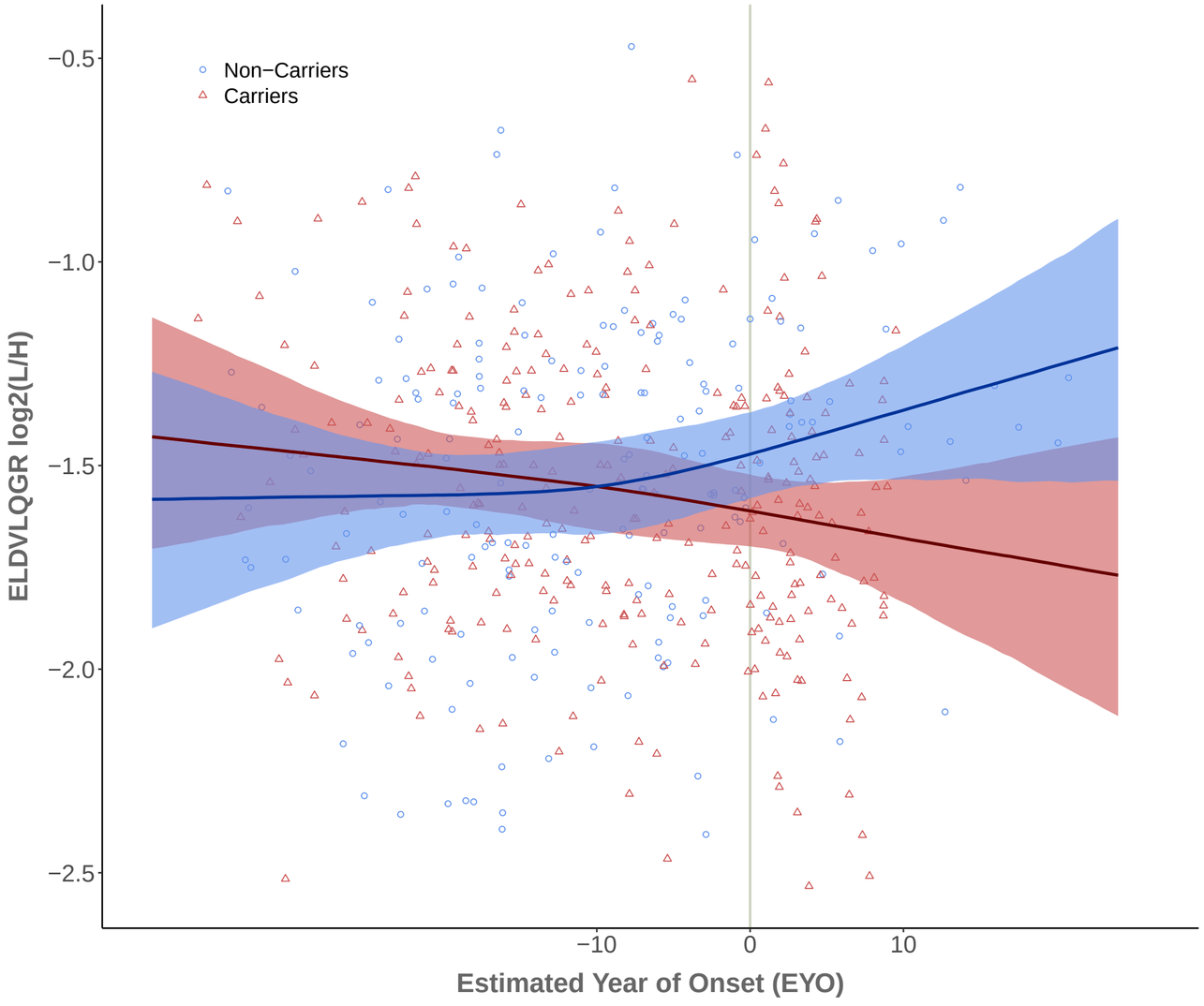
LDHC level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



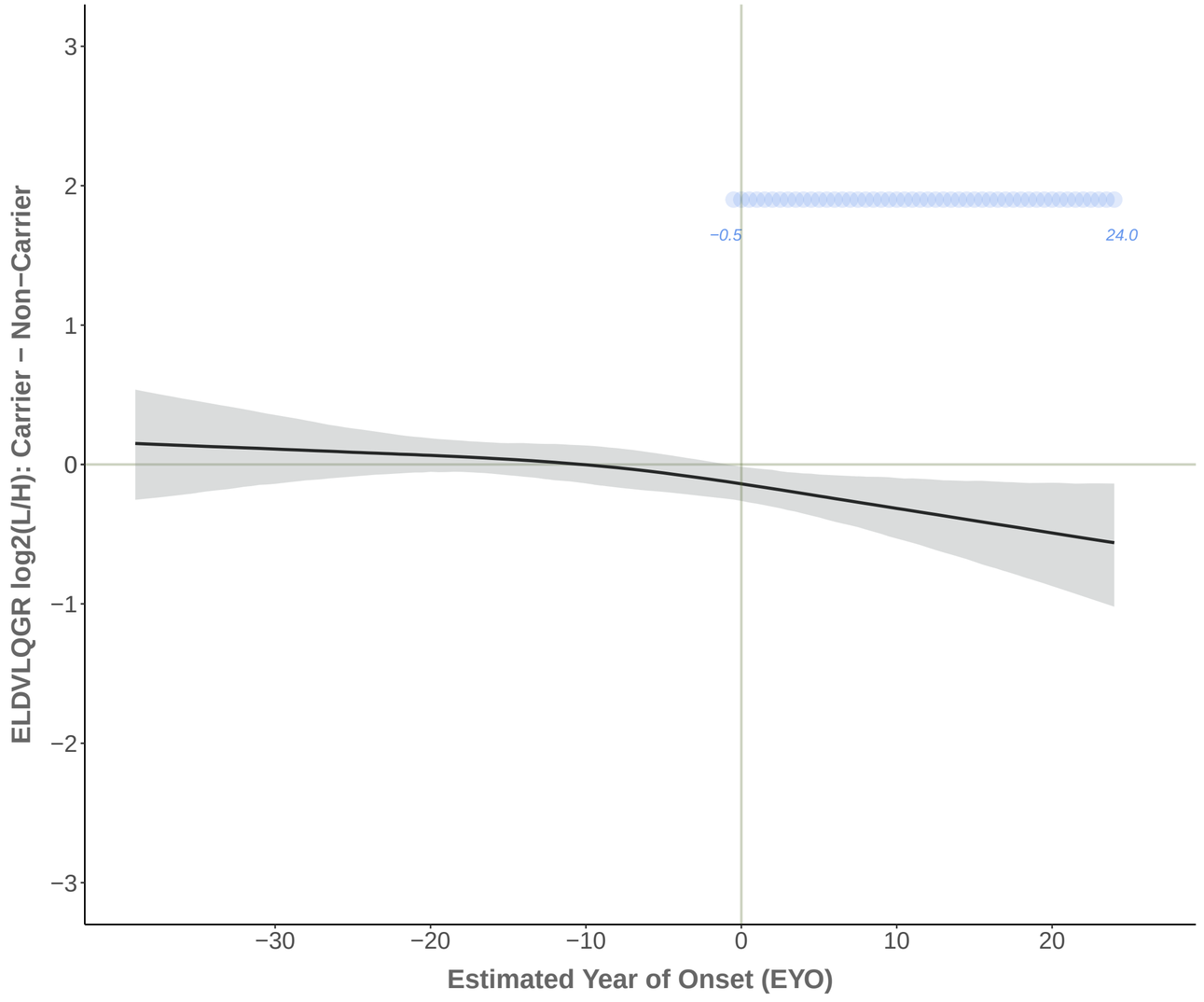
LDHC level difference in mutation carriers and non−carriers with 99% confidence interval.



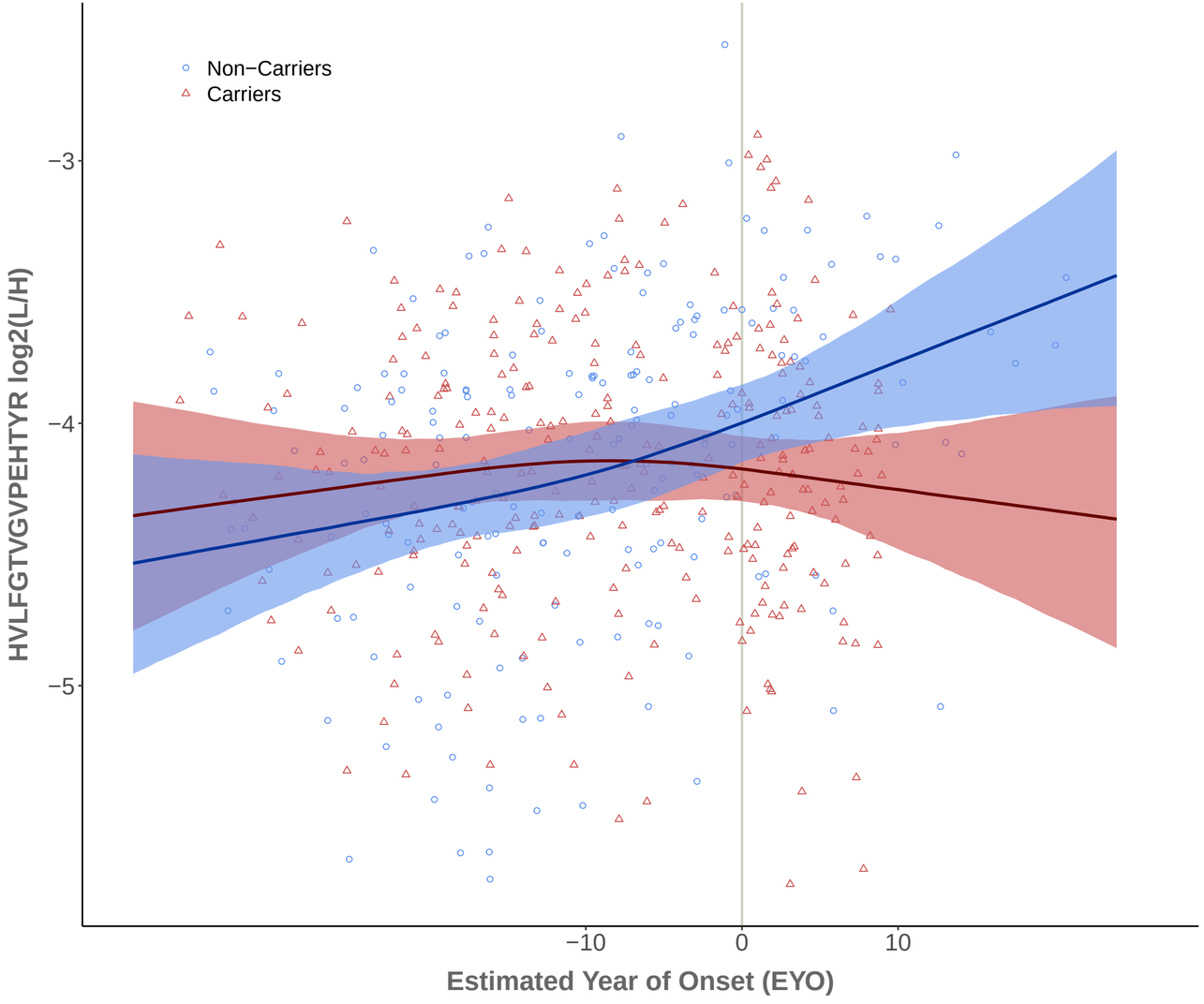
NPTXR level in mutation carriers and non−carriers with 99% confidence interval. 1 outliers removed for visualization purposes.



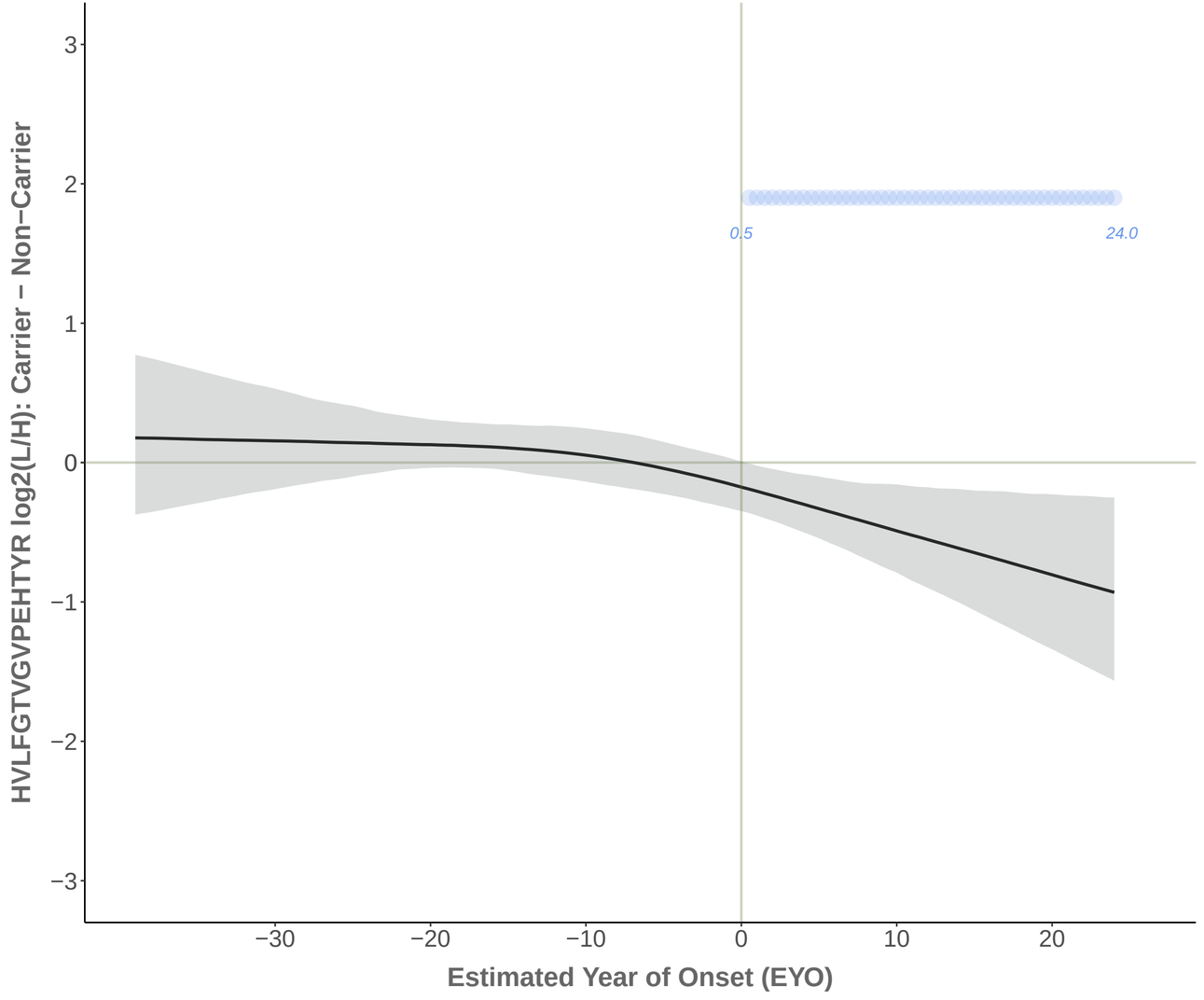
NPTXR level difference in mutation carriers and non−carriers with 99% confidence interval.



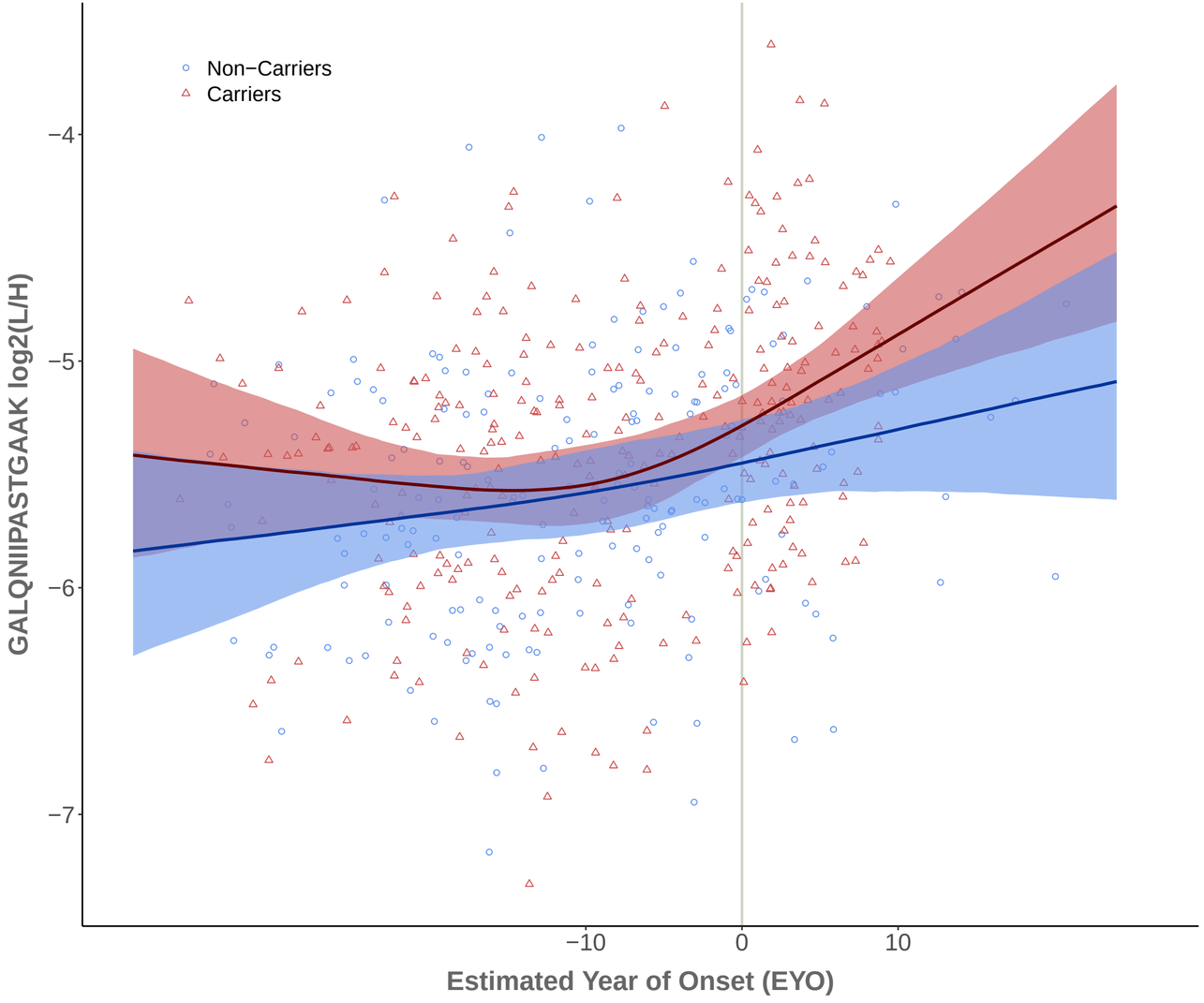
THY1 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



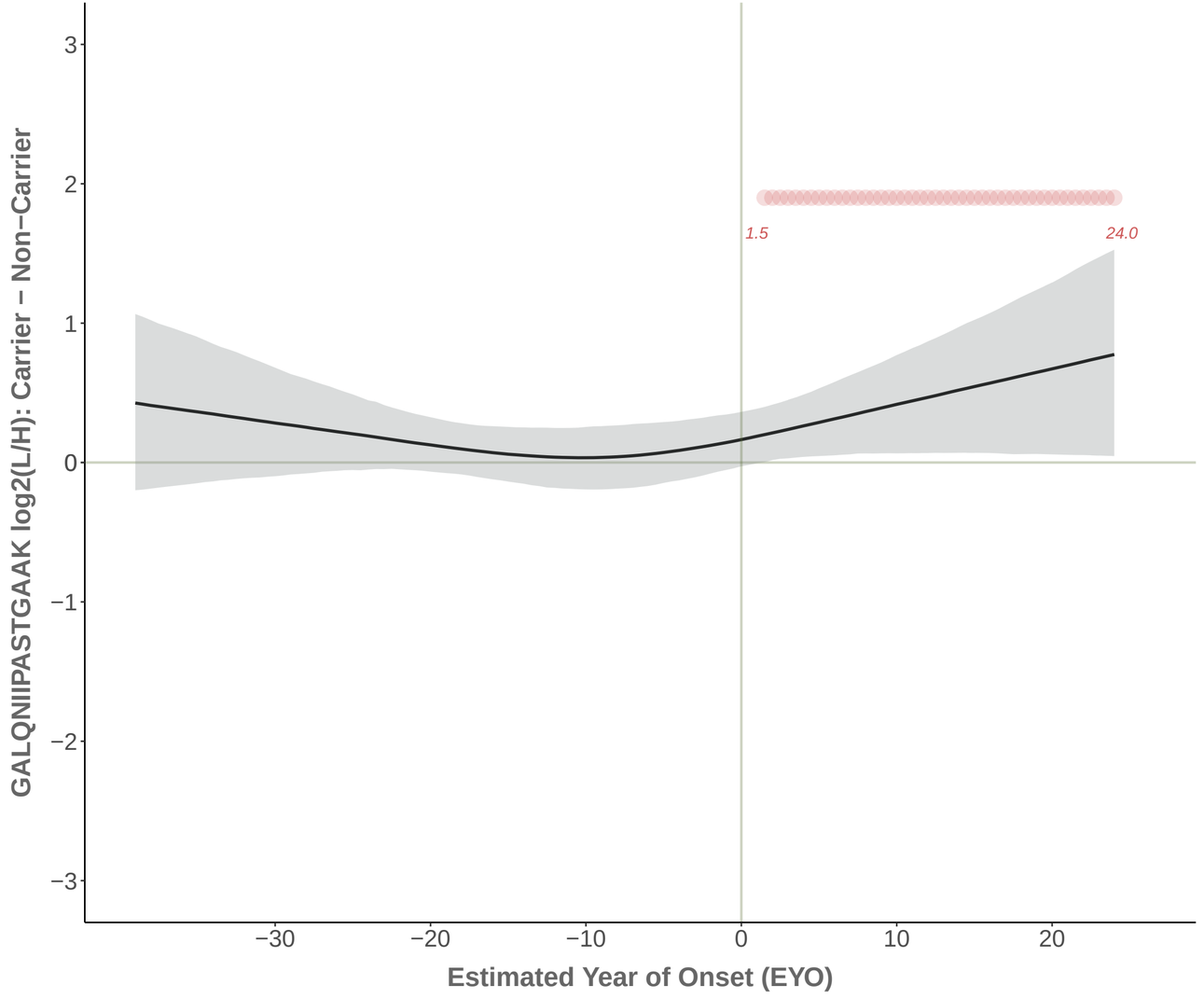
THY1 level difference in mutation carriers and non−carriers with 99% confidence interval.



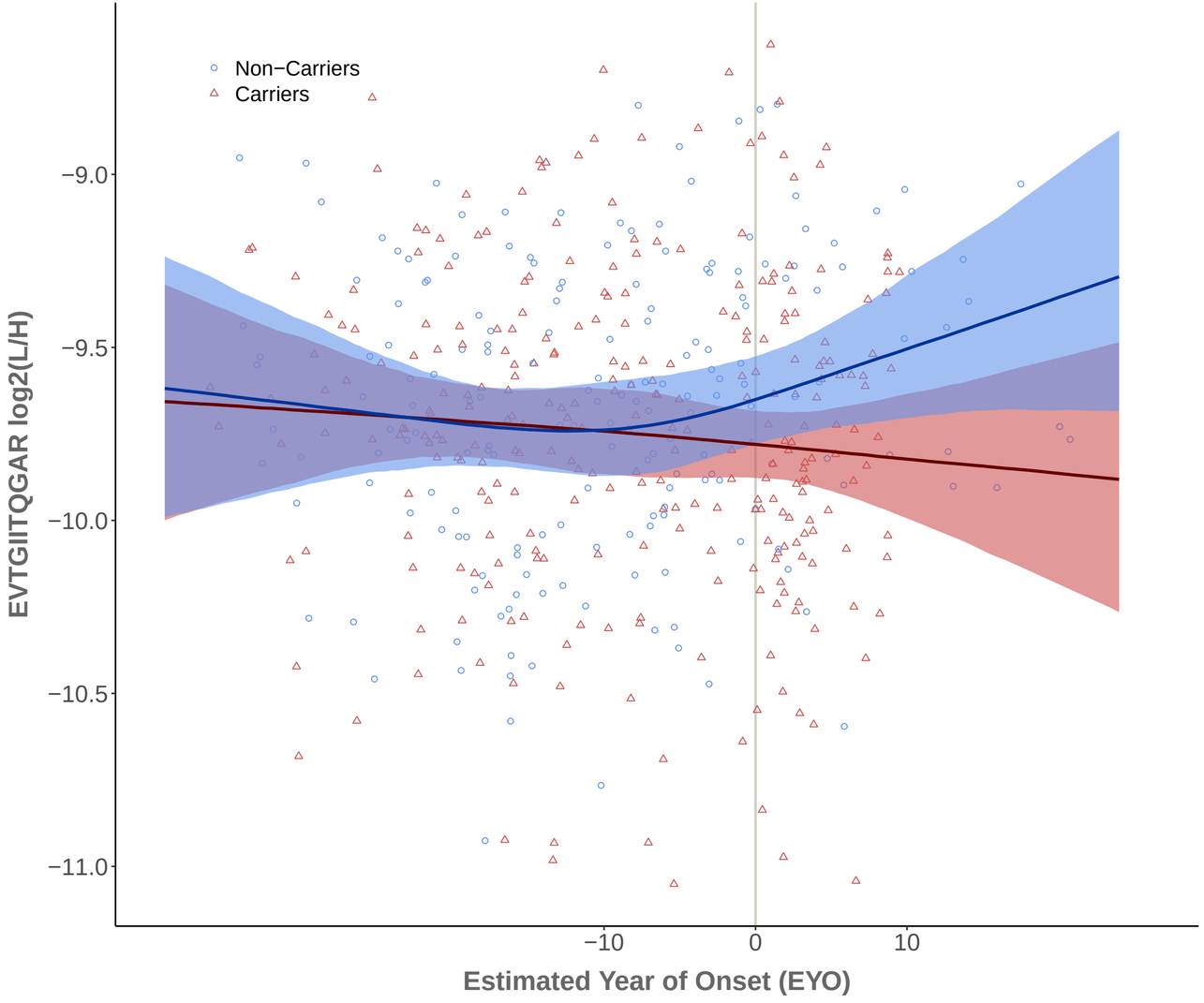
GAPDH level in mutation carriers and non−carriers with 99% confidence interval. 4 outliers removed for visualization purposes.



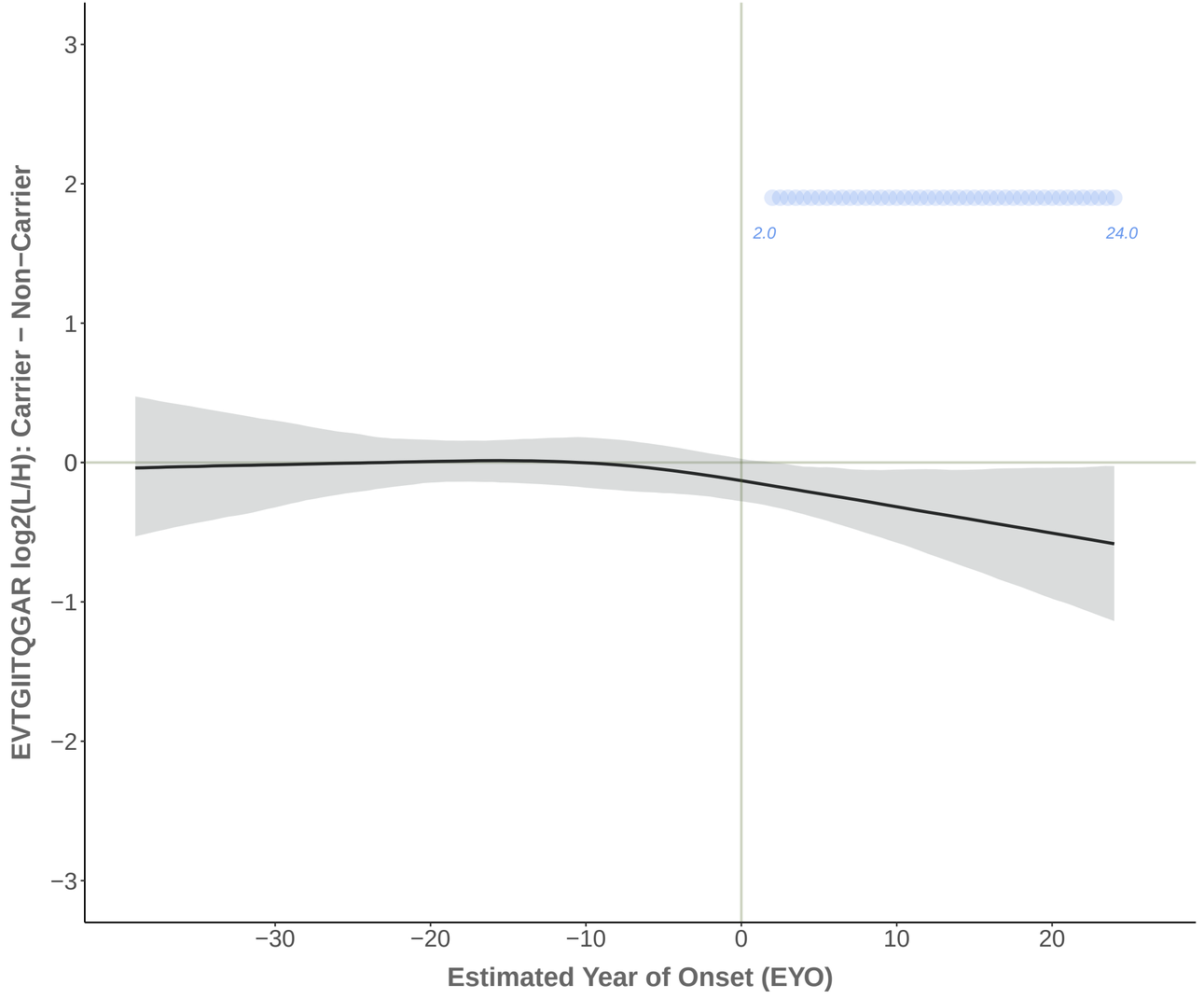
GAPDH level difference in mutation carriers and non−carriers with 99% confidence interval.



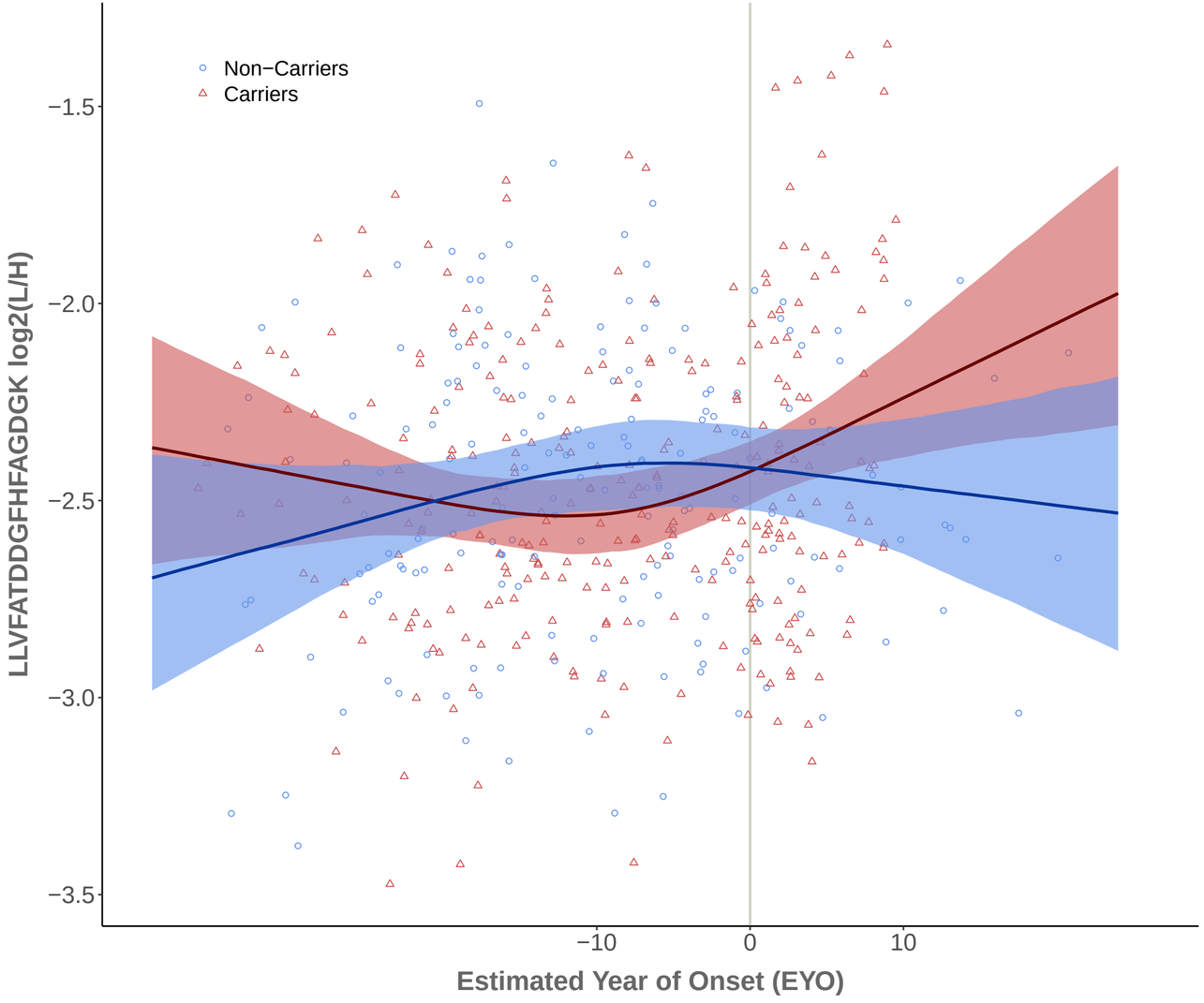
MFGE8 level in mutation carriers and non−carriers with 99% confidence interval. 3 outliers removed for visualization purposes.



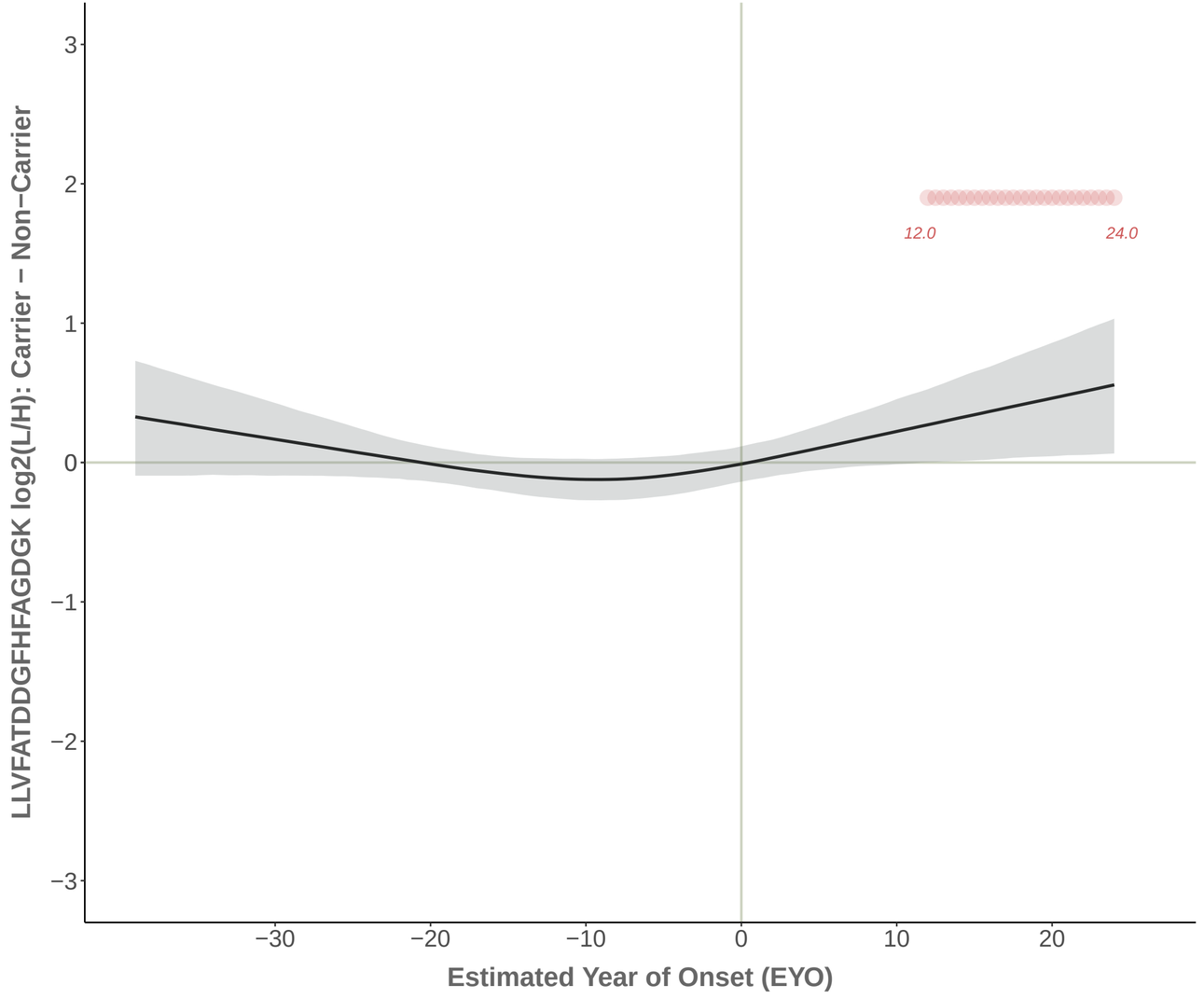
MFGE8 level difference in mutation carriers and non−carriers with 99% confidence interval.



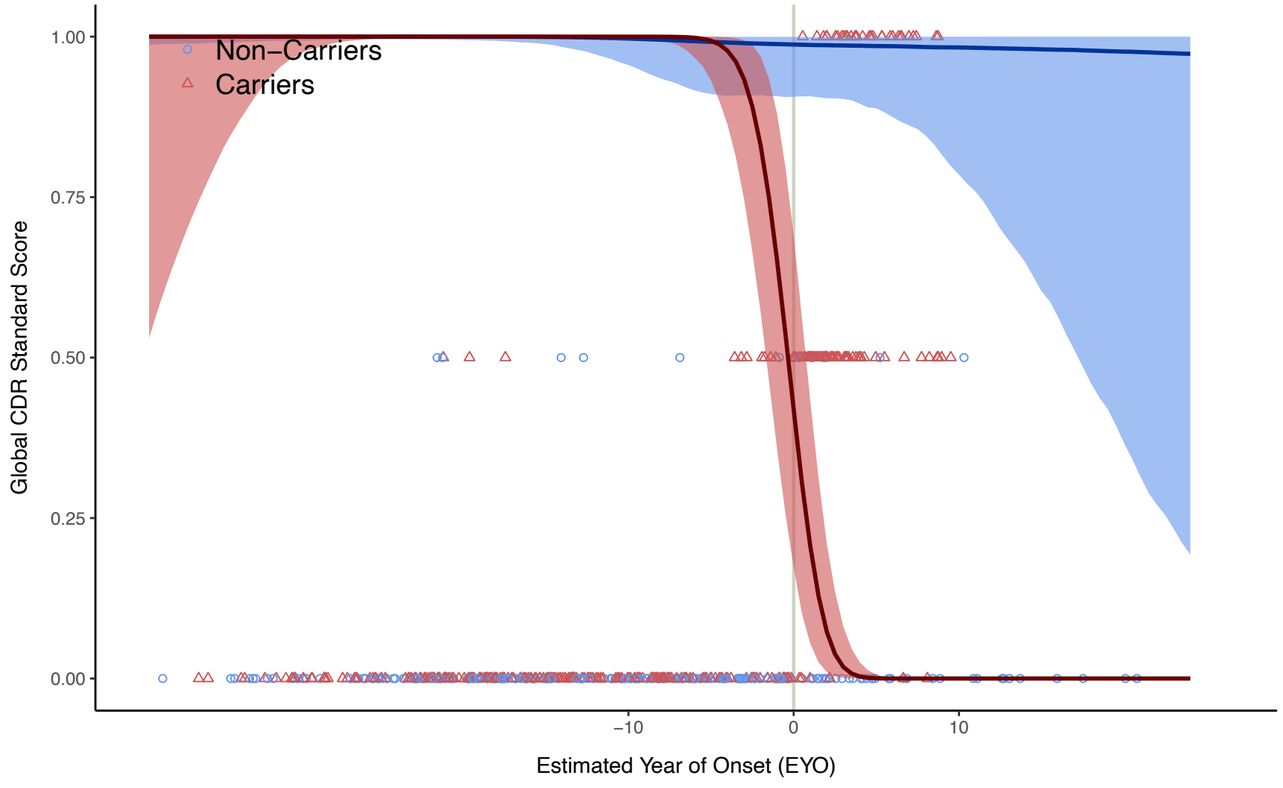
ITGB2 level in mutation carriers and non−carriers with 99% confidence interval. 2 outliers removed for visualization purposes.



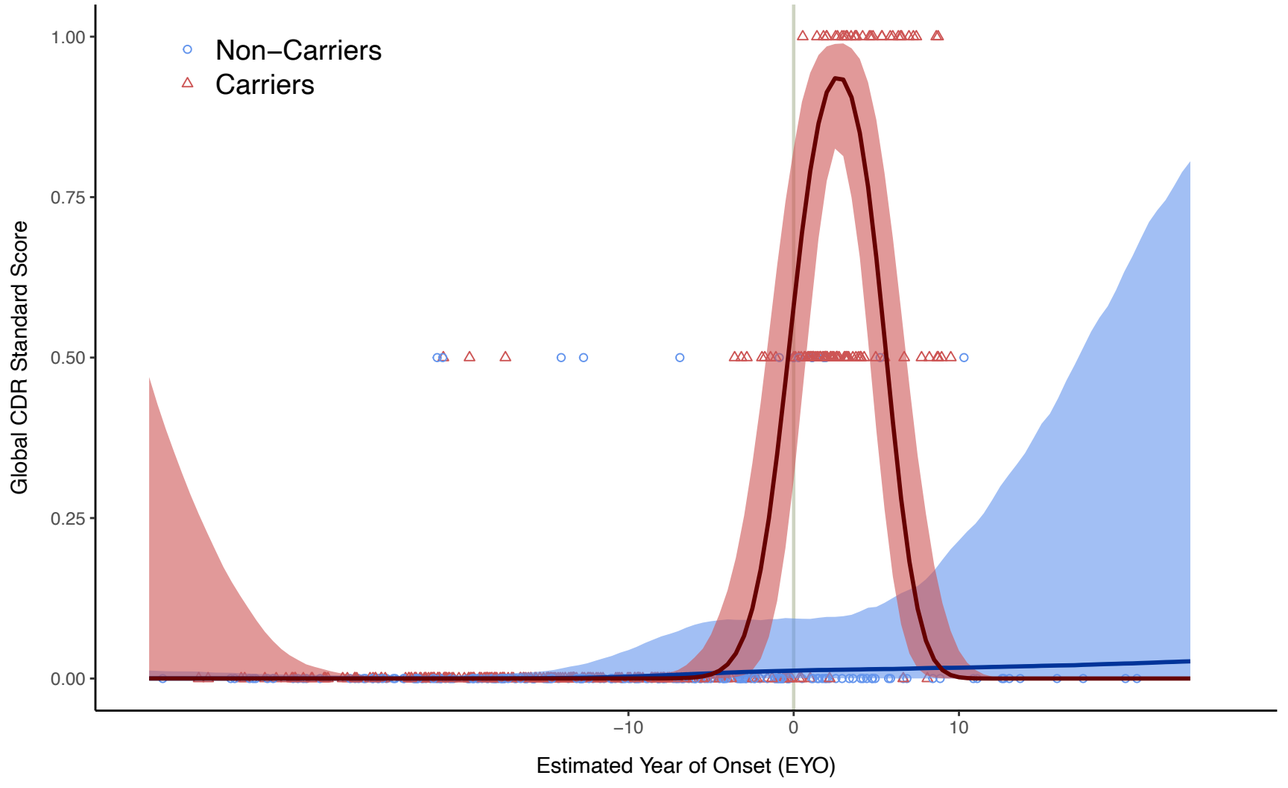
ITGB2 level difference in mutation carriers and non−carriers with 99% confidence interval.



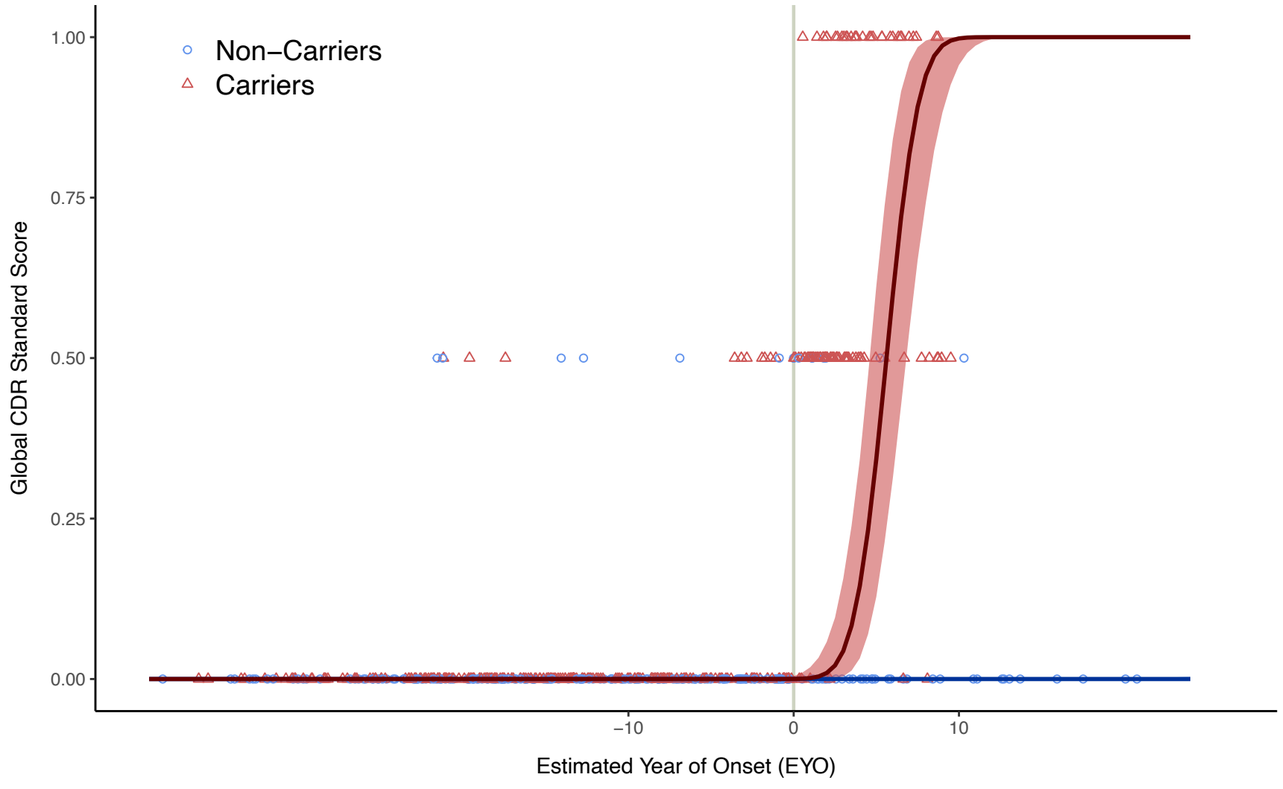
Probability of having Global CDR standard score of 0 in mutation carriers and non−carriers with 99% confidence interval. 14 outliers removed for visualization purposes.



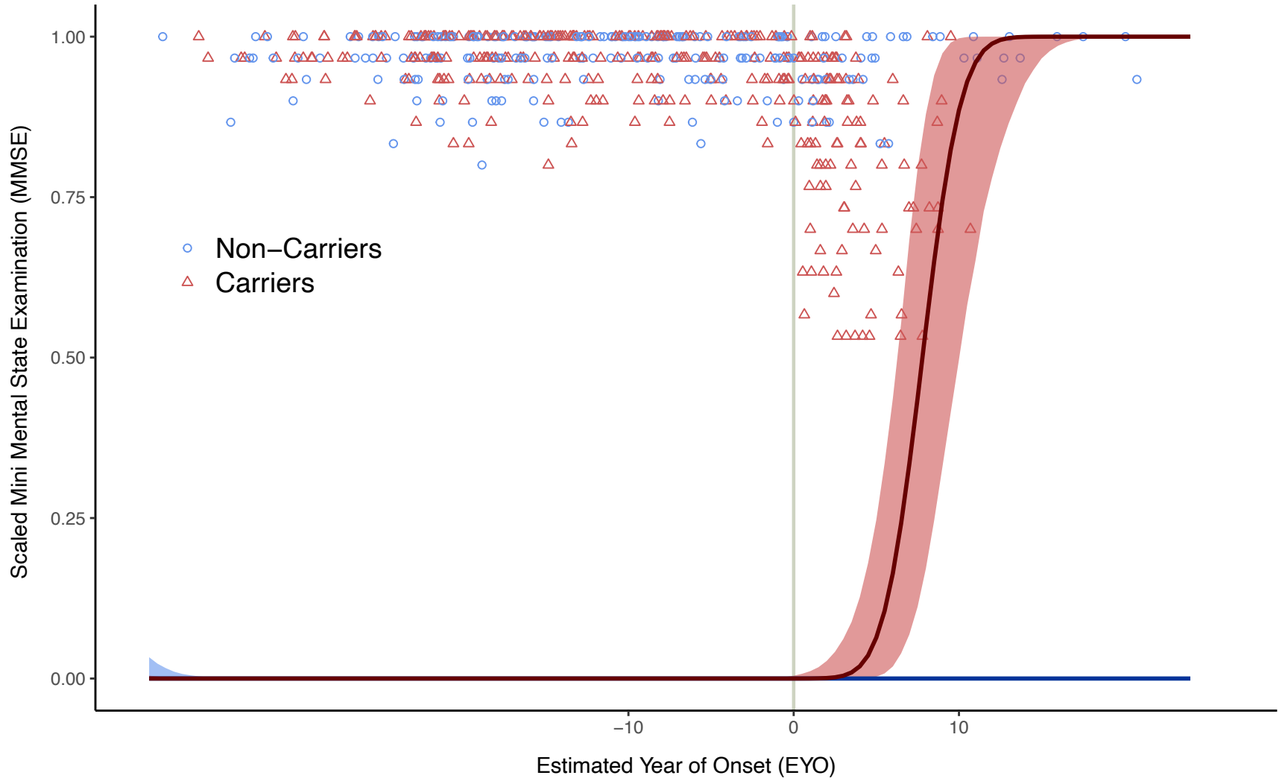
Probability of having Global CDR standard score of 0.5 in mutation carriers and non−carriers with 99% confidence interval. 14 outliers removed for visualization purposes.



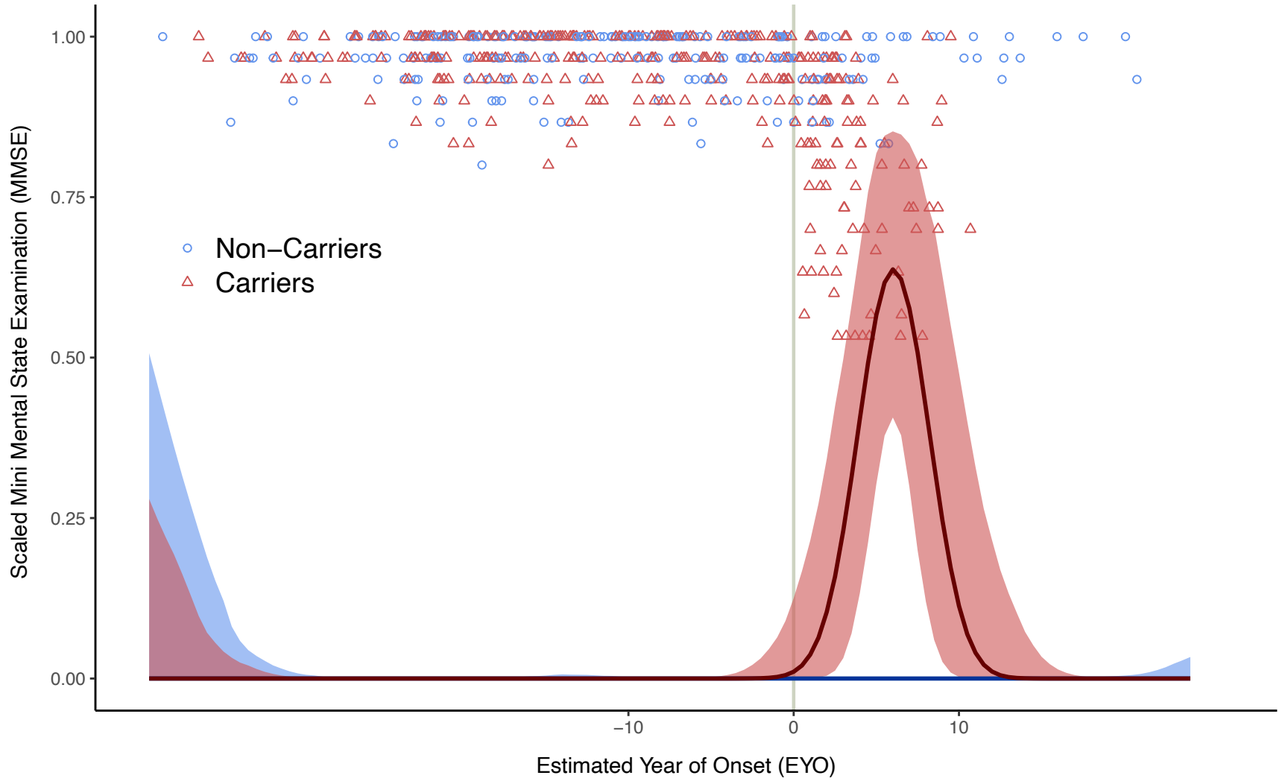
Probability of having Global CDR standard score greater than or equal to 1 in mutation carriers and non−carriers with 99% confidence interval. 14 outliers removed for visualization purposes.



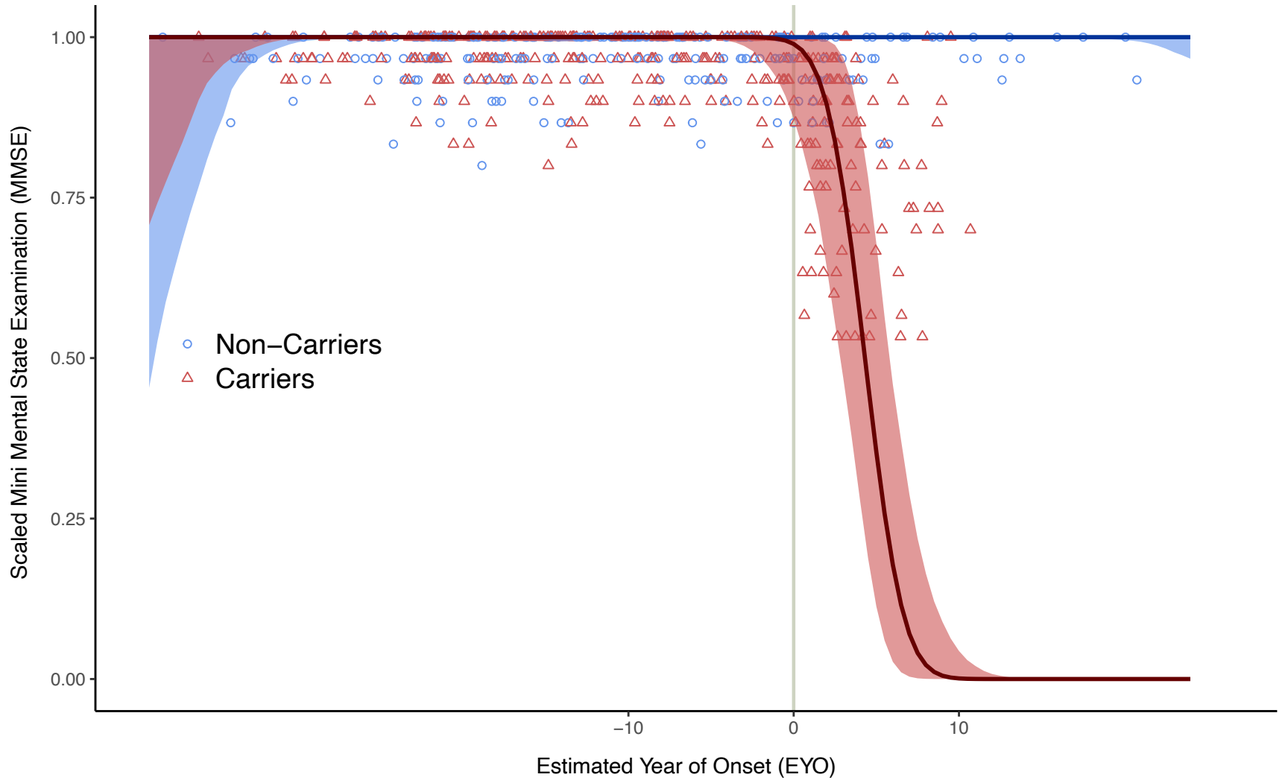
Probability of having MMSE < 19 in mutation carriers and non−carriers with 99% confidence interval. 17 outliers removed for visualization purposes.



Probability of having MMSE between 19 and 24 (inclusive) in mutation carriers and non−carriers with 99% confidence interval. 17 outliers removed for visualization purposes.



Probability of having MMSE >24 in mutation carriers and non−carriers with 99% confidence interval. 17 outliers removed for visualization purposes.



Biomarker Levels by Estimated Year of Disease Onset in ADAD. Periods of significant difference between carriers and non-carriers are highlighted in the difference plot on the right (red indicates significantly increased levels in carriers, blue indicates significantly decreased levels in carriers). Shaded areas represent the 99% credible interval. L/H, ratio of endogenous peptide signal (light) to the isotopically labeled standard peptide signal (heavy).