Review Article

# Cystatin C at the Crossroads: Unraveling a Multidimensional Biomarker in Alzheimer's Disease and Cognitive Decline

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**Cystatin C (CysC) is increasingly recognized as a critical biomarker at the interface of neurodegeneration, metabolic health, and vascular pathology. This narrative review synthesizes current evidence on the role of CysC in cognitive impairment and Alzheimer's disease, leveraging findings from cross-sectional, longitudinal, genetic, and translational studies. CysC levels are modulated by genetic polymorphisms, pathological processes, and modifiable factors such as dietary habits and systemic metabolic status. Elevated or dysregulated CysC concentrations are consistently associated with increased risk and progression of Alzheimer's disease, mild cognitive impairment, and vascular dementia. Recent research highlights the mechanistic links between CysC and amyloid-beta aggregation, neuroinflammation, autophagy, and proteolytic balance, supporting its relevance as both a diagnostic and therapeutic target. Nevertheless, challenges remain regarding standardization of assays, confounding by renal function, and variability across populations. Most interventional evidence is preclinical, though early-phase translational studies show promise for modulating CysC as a neuroprotective strategy. Integrative, multidimensional approaches combining CysC with genetic, clinical, and neuroimaging data are likely to enhance risk stratification and inform precision medicine in neurodegenerative disorders. Future research must prioritize methodological rigor, population diversity, and longitudinal validation to fully establish CysC as a core biomarker for cognitive decline and Alzheimer's disease.**

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## Introduction

Alzheimer's disease (AD) represents the most prevalent form of dementia in the aging population, posing a formidable challenge to global health systems due to its increasing incidence and the lack of curative treatments [1]. The pathophysiology of AD is multifactorial, involving aberrant proteolysis, amyloid-beta (Aβ) aggregation, neuroinflammation, and progressive neurodegeneration [2][3]. Within this complex landscape, the identification of robust, reliable biomarkers is essential for early diagnosis, disease monitoring, and the development of targeted therapies [4].

Cystatin C (CysC), a potent endogenous inhibitor of cysteine proteases, has emerged as a promising candidate in this context due to its pleiotropic roles in the central nervous system [2]. CysC is implicated in the regulation of protease activity, modulation of amyloidogenic pathways, and mediation of cellular autophagy and proliferation. Experimental and clinical studies have demonstrated that changes in the synthesis and function of CysC can significantly influence the balance between neuronal survival and degeneration, underscoring its dual role as both a neuroprotective factor and a potential marker of disease progression [2][3].

The relevance of CysC extends beyond basic mechanistic insight. Multiple population-based and clinical studies have reported that alterations in circulating CysC levels correlate with cognitive performance and may precede the onset of clinically manifest AD [4][5]. Notably, both cross-sectional and longitudinal investigations suggest that CysC serves not only as a static biomarker but also as a dynamic indicator of cognitive decline risk, particularly in individuals with additional vascular or metabolic comorbidities [6][7][8]. Furthermore, recent advances in genetics have identified polymorphisms in the CST3 gene as modifiers of AD susceptibility, providing a molecular rationale for the observed associations between CysC expression and disease risk [9].

In this narrative review, we synthesize and critically evaluate the evidence regarding the role of cystatin C as a biomarker in cognitive impairment and Alzheimer's disease, prioritizing high-impact reviews, meta-analyses, and clinical studies. Our analysis aims to delineate the mechanistic underpinnings, clinical validity, and translational potential of CysC, while highlighting unresolved questions and emerging perspectives [2][4][6].

## Molecular and Biological Functions of Cystatin C

Cystatin C is a low-molecular-weight, non-glycosylated protein that belongs to the cystatin superfamily of cysteine protease inhibitors, widely expressed in virtually all human tissues, including the central nervous system [2][3]. Under physiological conditions, CysC plays a crucial role in maintaining proteolytic balance by inhibiting the activity of endogenous cysteine proteases, primarily cathepsins, within the endosomal-lysosomal pathway [2]. This regulatory function is essential for neuronal homeostasis, as even subtle disturbances in the protease-inhibitor equilibrium can lead to inappropriate proteolysis, which is implicated in both normal aging and the pathogenesis of diverse neurodegenerative diseases [2] [3].

Within the brain, CysC exerts several neuroprotective functions beyond protease inhibition. It has been shown to promote neuronal survival via the induction of autophagy, a process critical for the clearance of damaged organelles and misfolded proteins, thus conferring resilience against neurodegenerative insults [2]. Experimental data also suggest that CysC facilitates cellular proliferation and participates in the modulation of inflammatory responses, indicating a multifaceted contribution to brain homeostasis [2].

Notably, CysC interacts directly with amyloid-beta (Aβ) peptides, binding to soluble forms and inhibiting their aggregation into oligomers and fibrils, which are central to Alzheimer's disease pathology [2][3]. This anti-amyloidogenic property is further corroborated by *in vivo* studies demonstrating that increased expression of CysC reduces amyloid plaque formation, whereas diminished levels may exacerbate amyloid pathology and neuronal vulnerability [3]. Furthermore, CysC is co-localized with Aβ in both vascular and parenchymal amyloid deposits, underscoring its relevance in the neuropathological landscape of Alzheimer's disease [3].

The pleiotropic biological roles of CysC—encompassing inhibition of proteolysis, regulation of autophagy, modulation of inflammation, and direct interaction with neurotoxic protein aggregates—highlight its potential as a therapeutic target and as a biomarker for neurodegenerative disorders [2][3]. These diverse mechanisms support the premise that CysC is not merely a bystander but an active player in the maintenance of neuronal integrity and function.

## Cystatin C in the Pathophysiology of Alzheimer's Disease

The involvement of cystatin C in the pathophysiology of Alzheimer's disease is multifaceted and substantiated by a range of experimental, clinical, and genetic evidence. Altered expression and secretion of CysC in the brain have been observed in various neurodegenerative disorders, including AD, highlighting its relevance in disease mechanisms [2][3]. A critical feature of AD pathology is the deposition of oligomeric and fibrillar forms of Aβ in the neuropil and cerebral vessels, which is tightly linked to neurodegeneration and cognitive decline [3].

One of the most compelling mechanistic insights is the direct interaction between CysC and Aβ. In vitro studies have established that CysC binds to soluble Aβ, thereby inhibiting its oligomerization and subsequent fibril formation, both hallmarks of AD neuropathology [2][3]. In transgenic mouse models overexpressing amyloid precursor protein, increased CysC levels were associated with reduced Aβ plaque burden, while a deficiency of CysC accelerated amyloid deposition and neuronal loss [2]. Moreover, the co-localization of CysC with Aβ in both senile plaques and vascular amyloid deposits has been consistently observed in the brains of AD patients and non-demented aged individuals, suggesting a conserved protective mechanism [3]. Table 1 summarizes key mechanistic and experimental studies elucidating these neuroprotective and anti-amyloidogenic roles of CysC in AD models.

| Authors (Year) | Experimental Model | Mechanistic Findings | Main Observations |
|---|---|---|---|
| Mathews & Levy (2016)[2] | *In vitro*, *in vivo* (animal models); transgenic and knockout mice | Inhibits cathepsin B; induces autophagy; protects neurons via endosomal-lysosomal pathway; inhibits Aβ aggregation; CysC manipulation alters plaque formation and neurodegeneration | Multiple neuroprotective pathways; potential prevention of neurodegeneration; CysC modulation impacts AD pathology |
| Kaur & Levy (2012)[3] | In vitro, transgenic mice, cell lines; human brain tissue | Binds Aβ, inhibits oligomerization/fibril formation; co-localizes with Aβ in plaques; deficiency increases vulnerability; protects neurons from Aβ toxicity | Anti-amyloidogenic effects; supports neuroprotection; CysC deficiency worsens pathology |
| Liu et al. (2023)[10] | CysC knockout mice; retinal ischemia/reperfusion; primary endothelial cells | Loss of CysC increases capillary degeneration, permeability, inflammation; recombinant CysC restores barrier and reduces inflammatory mediators | CysC regulates vascular permeability and inflammation post-ischemic stress |

**Table 1.** Summary of Mechanistic and Experimental Evidence on Cystatin C in Neurodegeneration and Alzheimer's Disease

Beyond its anti-amyloidogenic effects, CysC may modulate the neuroinflammatory milieu characteristic of AD. CysC is known to regulate the activity of endosomal-lysosomal cysteine proteases such as cathepsin B, whose dysregulation can exacerbate neuroinflammation and neuronal injury [2]. There is also evidence that CysC can induce autophagy, further contributing to the clearance of protein aggregates and damaged cellular components, thus attenuating neuronal stress and degeneration [2].

Genetic studies provide additional support for a pathophysiological role of CysC in AD. A coding polymorphism in the CST3 gene, which encodes CysC, has been associated with an increased risk for

late-onset AD, particularly in synergy with the APOE4 allele [9]. This genetic interaction points to a complex interplay between CysC-mediated proteostasis and established AD risk pathways.

Taken together, these data converge on the concept that CysC serves as both a modulator of amyloid pathology and a broader regulator of proteolytic and inflammatory processes in the aging brain [2][3]. Disruption of CysC homeostasis, whether through genetic variation, altered expression, or secondary to disease, may therefore constitute a critical step in the cascade leading to neurodegeneration and clinical dementia.

## Genetic Variability and Risk: CST3 Polymorphisms

Genetic variation in the CST3 gene, encoding cystatin C, has been implicated as a modifier of risk for Alzheimer's disease (AD), with several studies demonstrating both independent and synergistic effects with other major genetic risk factors. One of the earliest and most compelling findings relates to a coding polymorphism in CST3, which has been shown to confer increased susceptibility to late-onset AD [9]. Notably, the CST3-A allele appears to act as an accumulation risk factor for early-onset AD and demonstrates a synergistic relationship with the APOE4 allele in individuals aged between 60 and 74 years, indicating that the presence of both genetic variants may potentiate the overall risk of disease onset [9].

These findings are supported by subsequent molecular studies that link CST3 polymorphisms to altered expression and secretion of cystatin C in the brain, potentially disrupting the tightly regulated balance between proteases and their inhibitors that is essential for neuronal homeostasis [2][3]. The implication is that genetic alterations in CST3 may compromise the neuroprotective functions of cystatin C, rendering individuals more vulnerable to the pathogenic effects of amyloid aggregation, neuroinflammation, and subsequent neurodegeneration [3].

Further evidence for the pathophysiological relevance of CST3 variants is provided by research demonstrating that these polymorphisms are associated with changes in the risk and progression of AD not only in general populations but also in those with familial or early-onset forms of the disease [9]. Additionally, the observed synergy with APOE4 underscores the multifactorial and polygenic nature of AD risk, where interactions between multiple genetic loci converge to modulate disease susceptibility and trajectory.

Taken together, the current evidence positions CST3 polymorphisms as significant genetic modifiers in AD, both independently and in concert with established risk alleles such as APOE4. These findings underscore the importance of integrating genetic screening for CST3 variants into risk stratification frameworks, particularly for individuals with a family history of AD or early cognitive decline [2][9].

## Cystatin C as a Clinical Biomarker

The clinical utility of CysC as a biomarker for cognitive impairment and AD has been extensively investigated across diverse study populations and research designs. Numerous cross-sectional and longitudinal studies have demonstrated that serum and plasma levels of CysC are significantly higher in patients with AD compared to age- and sex-matched healthy controls [1][11][12]. Importantly, elevated CysC levels are also observed in patients with mild cognitive impairment (MCI) and vascular dementia, suggesting a broader role in the spectrum of neurodegenerative diseases [4][12]. A synthesis of key studies investigating CysC as a biomarker in Alzheimer's disease and cognitive impairment is presented in Table 2.

| Author(s) | Study Design | Population / Sample | Main Findings | Key Observations |
|---|---|---|---|---|
| Mathews & Levy (2016) [2] | Review | Experimental and clinical evidence | CysC exerts neuroprotective roles; inhibits Aβ aggregation, regulates proteolysis, induces autophagy | CysC as a therapeutic candidate and biomarker |
| Kaur & Levy (2012) [3] | Review | Experimental, *in vitro* and *in vivo* studies | CysC binds Aβ, inhibits oligomerization/fibril formation; reduced CysC increases vulnerability | Protective effects in AD pathogenesis |
| Sundelöf et al. (2008)[5] | Prospective cohort | Elderly men (n=1,153 at age 70, n=761 at age 77) | Low CysC levels predict higher AD risk; decrease in CysC over time increases risk | CysC as an early marker, independent of comorbidities |
| Nair et al. (2020)[4] | Meta-analysis | 12 studies: 2,433 MCI patients, 1,034 controls | High CysC associated with increased risk of mild cognitive impairment, especially in Asian populations | Supports role as an early biomarker |
| Wang et al. (2017)[12] | Cross-sectional | 88 dementia (43 AD, 45 VaD), 45 controls | CysC higher in AD/VaD than controls; correlates with severity; ROC AUC 0.816 (AD) | CysC + HDL improves diagnostic accuracy |
| Chen et al. (2021)[11] | Cross-sectional | 463 AD, 1,389 healthy controls | AD patients have higher serum CysC; higher levels associated with worse cognitive performance | Supports clinical relevance |
| Bogdan et al. (2023)[1] | Case-Control Study | AD patients have higher median CysC; dietary habits explain 51% of CysC variance | Lifestyle-modifiable biomarker | |
| Ma et al. (2023)[6] | Longitudinal cohort | 11,503 from HRS/CHARLS (US, China) | Elevated CysC and decreased eGFRcys predict faster cognitive decline, independent of creatinine | CysC as a risk factor/prodromal biomarker |
| Beyer et al. (2001)[9] | Genetic association | 159 AD patients, 155 controls | CST3-A allele increases risk for early-onset AD; synergy with | Genetic risk interaction |

| Author(s) | Study Design | Population / Sample | Main Findings | Key Observations |
|---|---|---|---|---|
| | | | APOE4 in 60- to 74-year-olds | |

**Table 2.** Summary of Key Studies on Cystatin C in Alzheimer's Disease

Meta-analytic evidence supports a robust association between increased CysC concentrations and the risk of MCI, with subgroup analyses indicating that this relationship may be particularly pronounced in certain populations, such as individuals of Asian descent [4]. Diagnostic accuracy analyses, including receiver operating characteristic (ROC) curves, have shown that CysC alone or in combination with other markers such as high-density lipoprotein (HDL), can reliably differentiate AD and vascular dementia from healthy subjects, with area under the curve (AUC) values indicating strong discriminatory power [12].

Interestingly, longitudinal cohort studies reveal that alterations in CysC levels may precede the clinical manifestation of AD, positioning CysC as a potential prodromal biomarker [5]. Low serum CysC in elderly men has been associated with a higher risk of developing AD over time, independently of other established risk factors and comorbidities [5]. Conversely, other studies have identified a U-shaped association between CysC and cognitive outcomes after ischemic stroke or transient ischemic attack, where both low and excessively high CysC levels confer an increased risk of post-stroke cognitive impairment [8].

Analytical considerations further highlight the utility and limitations of CysC as a biomarker. Multiple linear regression and logistic models consistently demonstrate independent associations between serum CysC and cognitive performance indices, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores, after adjusting for confounding variables including age, sex, education, and renal function [6][7][11]. Furthermore, a decreased estimated glomerular filtration rate based on CysC (eGFRcys) is linked to accelerated cognitive decline, even after accounting for creatinine-based eGFR [6].

The evidence indicates that CysC represents a promising biomarker for the diagnosis, risk stratification, and prognosis of cognitive impairment and dementia, with potential utility in both clinical and research settings. However, the nonlinear nature of its association with cognitive outcomes and the influence of

confounding variables, such as renal function and comorbidities, underscore the necessity for integrative approaches and further standardization in its clinical application [5][6][8].

## Cystatin C in Cognitive Decline Beyond Alzheimer's Disease

While the association between CysC and AD is well established, an expanding body of evidence underscores its relevance in other forms of cognitive decline, notably MCI, vascular dementia, and post-stroke cognitive dysfunction [4][8][12]. In particular, increased serum and plasma CysC levels have been observed in patients with MCI compared to healthy controls, indicating that CysC may serve as a prodromal biomarker, identifying individuals at an elevated risk of progressing to overt dementia [4].

Meta-analytical data reinforce the role of CysC in early cognitive dysfunction, with a strong association between higher CysC concentrations and MCI risk, especially among Asian populations [4]. Moreover, CysC is found to be significantly elevated in vascular dementia, further implicating its involvement in the pathophysiology of cerebrovascular-related cognitive impairment [12]. Importantly, studies employing ROC analyses suggest that CysC, either alone or combined with HDL, improves the diagnostic accuracy for distinguishing vascular dementia from Alzheimer's disease and from healthy aging [12].

Recent large-scale prospective studies have also elucidated the relationship between CysC and cognitive outcomes following acute cerebrovascular events. In the context of mild ischemic stroke and transient ischemic attack, CysC displays a U-shaped association with long-term cognitive impairment, wherein both low and excessively high levels confer an increased risk of post-stroke cognitive decline [8]. These findings emphasize the nuanced, context-dependent roles of CysC in neurovascular pathology and highlight its potential as a biomarker not only for neurodegeneration but also for vascular cognitive syndromes.

Furthermore, longitudinal data from community-based cohorts show that a decreased eGFRcys is associated with accelerated cognitive decline, independent of creatinine-based renal function measures [6]. This suggests that CysC integrates both neurodegenerative and systemic vascular/metabolic risk factors, reinforcing its clinical value in risk prediction algorithms that span diverse etiologies of cognitive impairment.

In this context, the evidence substantiates the utility of CysC as a cross-diagnostic biomarker, facilitating the identification and stratification of patients at risk for various forms of cognitive decline beyond classical Alzheimer's pathology [4][6][8][12].

## Modifiable Factors and Translational Implications

Recent research indicates that serum CysC levels are not only determined by genetic and pathological factors but are also modulated by lifestyle and metabolic variables, thereby opening potential avenues for preventive and translational strategies in cognitive impairment and AD [1][7]. In a cross-sectional analysis of Alzheimer's patients, dietary habits explained a significant proportion of the variance in CysC concentrations, suggesting that nutritional interventions might influence CysC-mediated pathways and, by extension, the risk or progression of neurodegenerative disorders [1]. These findings underscore the need to elucidate how specific dietary patterns or nutrients modulate proteolytic balance, inflammation, and amyloid dynamics through the regulation of CysC.

Beyond nutrition, CysC levels are closely linked to systemic metabolic and vascular health, particularly renal function—a well-recognized determinant of both cognitive and cardiovascular risk [6][7]. Elevated CysC is frequently observed in the context of chronic kidney disease, metabolic syndrome, and advanced age, each of which independently increases the likelihood of cognitive decline. Thus, effective management of comorbidities such as hypertension, diabetes, and chronic renal impairment may exert indirect neuroprotective effects through the normalization of CysC concentrations [6].

Translationally, CysC emerges as a promising biomarker for clinical trials and patient stratification. Its sensitivity to both disease-related and modifiable environmental factors positions it as a dynamic indicator of brain health, capable of reflecting both risk exposure and therapeutic response [1]. Moreover, the mechanistic links between CysC, autophagy, inflammation, and amyloid-beta aggregation provide compelling targets for future pharmacological interventions designed to harness or potentiate its neuroprotective properties [2].

Finally, CysC is not only a marker of disease burden but also a potential mediator of lifestyle and therapeutic interventions, bridging basic science and clinical translation in the evolving landscape of dementia prevention and personalized medicine [1][2][6].

## Limitations of Current Evidence and Methodological Challenges

Despite the growing body of research on cystatin C (CysC) as a biomarker for cognitive impairment and Alzheimer's disease, several limitations persist that challenge its immediate translation into clinical practice. First, heterogeneity in study designs—ranging from cross-sectional to longitudinal and meta-

analytical frameworks—results in variable definitions of diagnostic thresholds, follow-up durations, and patient populations [4][6]. These discrepancies complicate direct comparisons and the generalizability of findings across diverse clinical settings.

Analytical and pre-analytical factors further constrain the reliability of CysC measurements. Differences in assay methodologies, sample handling, and timing of collection can significantly influence measured CysC levels, introducing variability that may obscure true biological associations [7]. Moreover, many studies adjust for renal function given its strong influence on CysC concentrations, but residual confounding by kidney disease, age, and comorbid metabolic conditions remains a substantial concern [6] [7].

Another limitation is the current scarcity of interventional studies directly targeting CysC modulation in human neurodegenerative disease. Most evidence remains observational or preclinical, leaving gaps in knowledge regarding causality, dose-response relationships, and the therapeutic safety profile of CysC-modulating interventions [2]. Furthermore, while some studies suggest non-linear, even U-shaped, associations between CysC and cognitive outcomes, the mechanistic basis and clinical implications of these patterns are not yet fully elucidated [8].

Population diversity is another critical issue. Many large cohorts are limited to specific ethnic groups or geographical regions, raising questions about the external validity of findings and the need for multi-ethnic, multinational research initiatives [4][6]. Finally, while CysC shows promise as part of multidimensional biomarker panels, standardization in its integration with other biochemical and neuroimaging markers is needed for practical clinical deployment.

Collectively, these challenges underscore the need for methodological rigor, larger and more diverse prospective cohorts, and robust validation in interventional contexts before CysC can be fully established as a core biomarker in the neurodegenerative disease landscape.

## Future Directions and Perspectives

Ongoing research continues to expand the understanding of CysC as a biomarker in cognitive impairment and Alzheimer's disease, but several promising avenues remain to be fully explored. Integrative approaches that combine CysC measurements with multiomic platforms—including genomics, proteomics, and metabolomics—hold the potential to unravel novel mechanistic insights and enhance the specificity and sensitivity of risk prediction models [2][6].

Prospective, large-scale, and multi-ethnic cohort studies are critically needed to address current limitations in population diversity and to validate the generalizability of CysC-based biomarker algorithms across different demographic and clinical contexts [4][6]. The deployment of CysC in multidimensional risk stratification tools, integrating clinical, biochemical, and neuroimaging data, may further support the development of precision medicine in neurodegenerative disorders [1][6].

Therapeutically, targeting CysC pathways—either directly or through upstream modulators—represents an attractive strategy, although most data remain preclinical. Early-phase studies in animal models have shown that enhancing CysC activity may confer neuroprotection by reducing amyloid pathology and supporting autophagy, but translation to human clinical trials is still incipient [2]. Future research should prioritize the safety, efficacy, and long-term impact of such interventions in diverse patient populations.

Additionally, there is a growing interest in the role of modifiable factors, including dietary and lifestyle interventions, in the regulation of CysC and associated neurodegenerative risk [1]. The integration of behavioral, pharmacological, and molecular approaches may ultimately yield more comprehensive and individualized prevention and treatment strategies.

The future of CysC research lies in the adoption of integrative, multidimensional, and translational methodologies that bridge bench and bedside, ultimately enhancing our capacity to diagnose, monitor, and potentially modify the course of cognitive decline and Alzheimer's disease.

## Conclusion

Cystatin C has emerged as a multifaceted biomarker at the intersection of neurodegeneration, vascular health, and metabolic regulation. Evidence from diverse populations supports its association with cognitive impairment, Alzheimer's disease, and related disorders, highlighting both its diagnostic potential and mechanistic relevance. CysC levels reflect the influence of genetic, pathological, and modifiable lifestyle factors and may serve not only as a marker of disease burden but also as an indicator of intervention efficacy.

Despite substantial advances, key challenges remain: variability in analytical methods, confounding from renal and metabolic comorbidities, population-specific effects, and limited interventional data constrain the immediate clinical translation of CysC. However, integrative approaches—combining CysC with multiomic, clinical, and neuroimaging data—promise to refine risk stratification and enable precision medicine in dementia care.

Future research should focus on methodological standardization, large-scale validation across diverse cohorts, and the development of targeted interventions modulating CysC pathways. As understanding deepens, CysC is poised to become an integral component of biomarker panels guiding the early detection, monitoring, and potential modification of cognitive decline and Alzheimer's disease.

## Abbreviations

- **Aβ:** Amyloid-beta
- **AD:** Alzheimer's Disease
- **AUC:** Area Under the Curve
- **APOE4:** Apolipoprotein E epsilon 4 allele
- **CSF:** Cerebrospinal Fluid
- **CST3:** Gene encoding Cystatin C
- **CysC:** Cystatin C
- **DSST:** Digit Symbol Substitution Test
- **eGFRcys:** Estimated Glomerular Filtration Rate based on Cystatin C
- **HDL:** High-Density Lipoprotein
- **MCI:** Mild Cognitive Impairment
- **MMSE:** Mini-Mental State Examination
- **MoCA:** Montreal Cognitive Assessment
- **ROC:** Receiver Operating Characteristic
- **VaD:** Vascular Dementia

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## Declarations

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