

## RESEARCH ARTICLE

# CT-based volumetric measures obtained through deep learning: Association with biomarkers of neurodegeneration

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**Abstract**

**INTRODUCTION:** Cranial computed tomography (CT) is an affordable and widely available imaging modality that is used to assess structural abnormalities, but not to quantify neurodegeneration. Previously we developed a deep-learning-based model that produced accurate and robust cranial CT tissue classification.

**MATERIALS AND METHODS:** We analyzed 917 CT and 744 magnetic resonance (MR) scans from the Gothenburg H70 Birth Cohort, and 204 CT and 241 MR scans from participants of the Memory Clinic Cohort, Singapore. We tested associations between six CT-based volumetric measures (CTVMs) and existing clinical diagnoses, fluid and imaging biomarkers, and measures of cognition.

**RESULTS:** CTVMs differentiated cognitively healthy individuals from dementia and prodromal dementia patients with high accuracy levels comparable to MR-based measures. CTVMs were significantly associated with measures of cognition and biochemical markers of neurodegeneration.

**DISCUSSION:** These findings suggest the potential future use of CT-based volumetric measures as an informative first-line examination tool for neurodegenerative disease diagnostics after further validation.

**KEYWORDS**

brain segmentation, cognition, CSF biomarkers, CT, deep learning, dementia, plasma biomarkers

**HIGHLIGHTS**

- Computed tomography (CT)-based volumetric measures can distinguish between patients with neurodegenerative disease and healthy controls, as well as between patients with prodromal dementia and controls.
- CT-based volumetric measures associate well with relevant cognitive, biochemical, and neuroimaging markers of neurodegenerative diseases.
- Model performance, in terms of brain tissue classification, was consistent across two cohorts of diverse nature.
- Intermodality agreement between our automated CT-based and established magnetic resonance (MR)-based image segmentations was stronger than the agreement between visual CT and MR imaging assessment.

**1 | INTRODUCTION**

Neurodegenerative diseases are characterized by a progressive loss of neuronal integrity and function as well as by molecular abnormalities, leading to cognitive decline and dementia.<sup>1,2</sup> The most established biomarkers for neurodegenerative diseases include cerebrospinal fluid (CSF) measures of neuronal injury,<sup>3</sup> brain atrophy measured on structural MR images,<sup>4-8</sup> and positron emission tomography (PET) imaging of brain glucose metabolism, as well as disease-specific measures of amyloid beta (A $\beta$ ) and tau.<sup>9,10</sup> However, these methods are expensive, invasive, or available only in specialized care centers. Brain imaging modalities such as CT and recently established blood-plasma-

derived biomarkers<sup>11,12</sup> can address the issue of cost and availability to some extent. With increased diagnostic utility, CT and plasma biomarkers may become scalable and cost-effective alternatives for neurodegenerative disease diagnostics.

CT is a fast, low-cost, and widely available imaging modality and an alternative for patients who cannot undergo a magnetic resonance (MR) examination.<sup>13</sup> CT-based visual ratings are comparable to those obtained from MR imaging with regard to certain pathomorphological characteristics, and they are correlated significantly with cognitive test results.<sup>13,14</sup> However, MR imaging (MRI) is extensively used for high-resolution atrophy assessment and brain volumetry<sup>15-17</sup> due to its stronger soft-tissue contrast. Atrophy assessment in CT is conducted

through semi-quantitative visual ratings, a subjective, time-consuming approach that requires a trained expert. Recent studies have explored state-of-the-art techniques such as deep learning in automatic cranial CT segmentation.<sup>18,19</sup> We previously used MR-based tissue class segmentations to train deep-learning models to perform tissue classification on cranial CT images.<sup>20</sup> In that study, models based on deep learning called U-Nets<sup>21</sup> were trained to segment gray matter (GM), white matter (WM), CSF, and intracranial volume (ICV) in cranial CT images. Although the segmentation results agreed strongly with those of the reference methods, the question of clinical utility was relegated to future work.

In the present study, we assessed the diagnostic performance of CT-based brain tissue classification by (1) obtaining volumetric measures from CT-based tissue class maps, (2) evaluating the ability of these measures to distinguish patients with neurodegenerative disorders from healthy study participants, and (3) exploring the relationship between these measures and cognition, as well as relevant blood and CSF biomarkers. The results will help to assess the potential of automatic CT image analysis, along with other easily accessible and scalable diagnostic tools such as blood biomarkers, for clinical diagnostic applications.

## 2 | MATERIALS AND METHODS

### 2.1 | Data sets

#### 2.1.1 | Gothenburg H70 Birth Cohort

The Gothenburg H70 Birth Cohort studies are a series of epidemiological investigations carried out periodically since 1971 on large, representative samples of those residents of Gothenburg, Sweden who turn 70 during a particular period.<sup>22</sup> We used data from the 2014–2016 iteration, which included  $n = 1203$  participants in total. CT images were available for  $n = 917$  participants (Figure 1). As expected, a large majority of these (99%;  $n = 904$ ) were cognitively normal.

Of these 917 participants, 79% ( $n = 744$ ) underwent MR scanning within a day of CT scanning. All imaging examinations were conducted at Aleris Röntgen Annedal in Gothenburg (Aleris Group AB, Stockholm, Sweden). A 64-slice Ingenuity CT system (Philips Medical Systems, Best, The Netherlands) was used for CT acquisition, and an Achieva system (3 Tesla; Philips Medical Systems) was used for MRI. Informed consent had been obtained from the participants, and safety procedures were conducted through interviews. An experienced radiologist performed visual ratings of medial temporal atrophy (MTA) on all available CT and MR scans.

Demographic data, past medical history, and neuropsychological assessments were also obtained from all included individuals. CSF biomarkers of neurodegeneration and Alzheimer's disease (AD) pathophysiology (neurofilament light [NfL], phosphorylated tau [p-tau], A $\beta$ 40, and A $\beta$ 42) were available for 34% ( $n = 316$ ) of participants with CT. Details of CSF sampling and analyses are provided in Rydberg Sterner et al.<sup>22–24</sup> Plasma NfL concentration was measured at the Uni-

### RESEARCH IN CONTEXT

- 1. Systematic Review:** We reviewed the literature using traditional sources (PubMed, Google Scholar). Automated cranial computed tomography (CT) brain tissue classification approaches for brain atrophy assessment and brain volumetry are currently underexplored. The diagnostic performance and association of CT-based volumetric measures with existing biomarkers of neurodegenerative diseases are yet to be evaluated. Previously, we developed a model based on deep learning to perform robust cranial CT segmentation using magnetic resonance (MR)-based labels.
- 2. Interpretation:** Our study highlights the association of CT-based volumetric measures with existing cognitive, biochemical, and other neuroimaging markers. Our findings suggest the potential application of CT-based volumetric measures as a screening tool for patients with dementia and prodromal dementia from cognitively normal individuals.
- 3. Future Directions:** CT-based volumetric measures have potential utility in neurodegenerative disease diagnosis. This potential should be explored further through longitudinal studies.

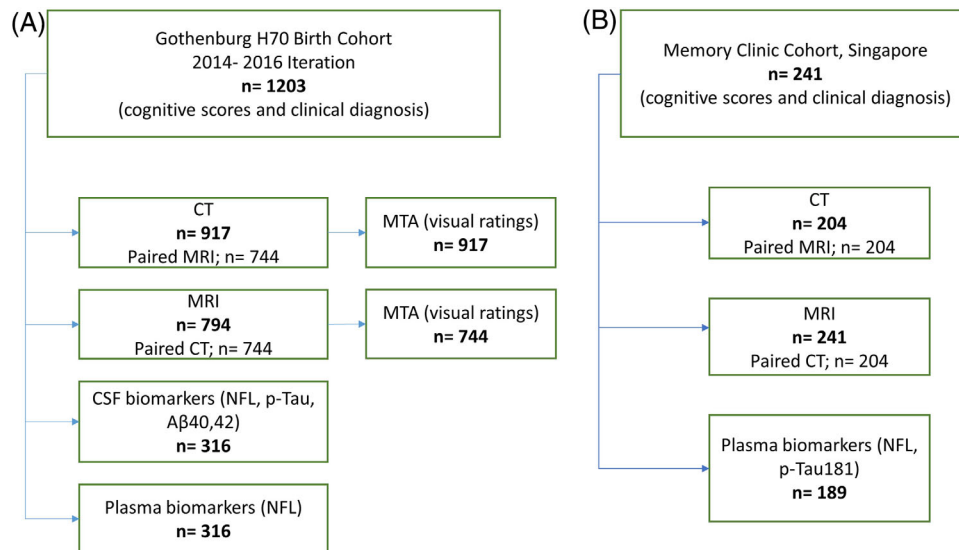
versity of Gothenburg Clinical Neurochemistry Laboratory (Mölnal, Sweden) using the NF-Light Advantage kit on a Simoa HD-1 instrument (Quanterix, Billerica, MA, USA).<sup>25,26</sup>

#### 2.1.2 | Memory clinic Cohort, Singapore

Furthermore, we included patients from the Memory Clinic Cohort of the National University Hospital, Singapore (age  $73.98 \pm 8.2$  years, 51% female), which comprised patients with dementia, patients with prodromal dementia, and cognitively normal individuals (see Table 1 and Figure 1 for details).

We included 204 cranial CT images (dementia,  $n = 93$ ; prodromal dementia,  $n = 89$ ; cognitively normal,  $n = 22$ ) and 241 MR (dementia,  $n = 109$ ; prodromal dementia,  $n = 105$ ; cognitively normal,  $n = 26$ ) images for our study. For all CT images, paired MR images were available. CT scans were performed using a 256 multislice CT scanner (Philips Medical Systems; slice collimation:  $30 \times 0.625$  mm for CT brain, kVp: 120, mAs: mA modulation with reference mAs of 300) at the National University Hospital, Singapore. MR scans were performed on a Magnetom Trio Tim scanner (3 Tesla; Siemens Healthineers AG, Erlangen, Germany), using a 32-channel head coil, at the Clinical Imaging Research Centre, National University of Singapore.

Demographic data, past medical history, and clinical diagnoses were obtained. Dementia diagnoses were based on results from clinical



**FIGURE 1** Flowchart showing the details of (A) the Gothenburg H70 Birth Cohort and (B) Memory Clinic Cohort, Singapore. A $\beta$ , amyloid beta; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; MTA, medial temporal atrophy; NFL, neurofilament light; p-tau, phosphorylated tau (Color print).

assessment and neuropsychological tests. Plasma biomarkers (NFL, p-tau181) were available for  $n = 189/241$  and A $\beta$  status based on PET-based visual assessments was available for  $n = 96/241$  participants with available MR images. Plasma p-tau181 and NFL were measured using the commercially available Simoa pTau-181 Advantage V2 kits and Simoa NF-light Advantage kits, respectively, on the Simoa HD-1 Analyser, per manufacturer's instructions (Quanterix, Billerica, MA, USA).

## 2.2 | Image processing and analysis

### 2.2.1 | Obtaining volumetric measures from CT using models based on deep learning

Previously, we trained U-Net-based models to differentiate tissue classes (GM, WM, CSF, and ICV) on cranial CT.<sup>20</sup> For the present study, we developed U-Net models to derive ventricular CSF (VCSF) maps from cranial CT images. Please refer to [Supplementary Material A1](#) for the summary of the model development. Altogether five classes were derived from all CT scans using these models based on deep learning: GM, WM, CSF, VCSF, and ICV. The models were deployed using TensorFlow 2.0 and Keras 2.3.1 run on Nvidia GeForce RTX 2080 Ti GPU. Tissue class volumes were determined from the segmentation maps obtained using deep learning. Total brain volume (BV) was obtained by summation of GM and WM tissue class volumes. In addition, regression-based adjusted brain tissue volumetric measures were obtained by regressing out the effect of CSF/VCSF from GM/BV<sup>27,28</sup> (Figure 2). Based on the previous literature,<sup>16,29,30</sup> six volumetric measures were obtained from the CT segmentation maps: GM, WM, BV adjusted for CSF, BV adjusted for VCSF, GM adjusted for CSF, and GM adjusted for VCSF.

### 2.2.2 | Obtaining volumetric measures from MRI

In the Singaporean Memory Clinic Cohort, we segmented 241 MRI data sets into GM, WM, and CSF using the unified segmentation routine in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12>).<sup>31</sup> VCSF and medial temporal lobe (MTL) volumes were measured using the multi-atlas-based segmentation tool MAPER,<sup>32</sup> and ICV was measured using Pincram.<sup>33</sup> These analyses yielded GM, WM, BV adjusted for CSF, BV adjusted for VCSF, GM adjusted for CSF, GM adjusted for VCSF, and MTL from MR data (Figure 2).

## 2.3 | Statistical analyses

We compared the volumetric agreement of CT-based segmentations with MR-based segmentations in the Singaporean Memory Clinic Cohort using intraclass correlation tests. The volumetric similarity of CT- and MR-based segmentations in the Gothenburg H70 Birth Cohort had been tested in our previous work.<sup>20</sup>

We further tested associations between the six CT-based volumetric measures (CTVMs) and CSF biomarkers (NFL, p-tau, A $\beta$ 42/40, and A $\beta$ 42) and plasma NFL in the Gothenburg H70 Birth Cohort, as well as with plasma biomarkers (NFL, p-tau181) in the Singaporean Memory Clinic Cohort. In both cohorts, we also tested the relationships of CTVMs with measures of cognition (Mini-Mental State Examination [MMSE] and Clinical Dementia Rating Sum of Boxes [CDR-SB]). The Shapiro-Wilk test was used to examine the Gaussian distribution of the continuous variables in our data ( $p$  value > 0.05). The cognition measures (MMSE, CDR-SB), raw fluid biomarker concentrations, and CTVMs were not normally distributed. Hence, the associations between these variables were tested using non-parametric tests.

**TABLE 1** Demographics of the individuals from the Gothenburg H70 Birth Cohort and Singaporean Memory Clinic Cohort from whom CT data sets were included.

| CT datasets                 |                                   |                                  |                              |                              |               |
|-----------------------------|-----------------------------------|----------------------------------|------------------------------|------------------------------|---------------|
| Variable                    | H70 Birth Cohort<br>CN<br>n = 917 | Singaporean Memory Clinic Cohort |                              |                              |               |
|                             |                                   | Dementia<br>n = 93               | Prodromal dementia<br>n = 89 | CN<br>n = 22                 |               |
| Age (years)                 | 70.46 ± 2.34                      | 76 ± 7.7                         | 74 ± 8.6                     | 68 ± 6.4                     |               |
| Gender, female (n)          | 484                               | 55                               | 37                           | 8                            |               |
| Education (years)           | 13 ± 4.3                          | 7.3 ± 2.6                        | 7.1 ± 4.5                    | 9.52 ± 4.49                  |               |
| ICV (liters)                | 1.66 ± 0.21                       | 1.82 ± 0.41                      | 1.76 ± 0.47                  | 1.69 ± 0.46                  |               |
| MMSE                        | 28.9 ± 1.85                       | 15.13 ± 4.21                     | 23.52 ± 3.39                 | 27.05 ± 2.08                 |               |
| GM (liters)                 | 0.77 ± 0.03                       | 0.69 ± 0.06                      | 0.75 ± 0.07                  | 0.79 ± 0.07                  |               |
| WM (liters)                 | 0.59 ± 0.03                       | 0.66 ± 0.08                      | 0.69 ± 0.07                  | 0.69 ± 0.06                  |               |
| GM adjusted for CSF         | 0.77 ± 0.07                       | 0.67 ± 0.09                      | 0.76 ± 0.11                  | 0.85 ± 0.12                  |               |
| GM adjusted for VCSF        | 0.78 ± 0.09                       | 0.66 ± 0.09                      | 0.75 ± 0.12                  | 0.83 ± 0.11                  |               |
| BV adjusted for CSF         | 1.36 ± 0.14                       | 1.16 ± 0.15                      | 1.28 ± 0.15                  | 1.38 ± 0.14                  |               |
| BV adjusted for VCSF        | 1.36 ± 1.7                        | 1.15 ± 0.16                      | 1.29 ± 0.14                  | 1.36 ± 0.13                  |               |
| Biochemical markers         |                                   |                                  |                              |                              |               |
| Gothenburg H70 Birth Cohort |                                   | Singaporean Memory Clinic Cohort |                              |                              |               |
| Variable                    | n = 316                           | Variable                         | Dementia<br>n = 70           | Prodromal dementia<br>n = 72 | CN<br>n = 14  |
| Plasma NfL (pg/mL)          | 25.12 ± 25.57                     | Plasma NfL (pg/mL)               | 46.08 ± 47.15                | 28.84 ± 16.29                | 27.43 ± 30.71 |
| CSF NfL (pg/mL)             | 906.3 ± 952.5                     | Plasma p-Tau 181 (pg/mL)         | 3.86 ± 2.23                  | 3.29 ± 1.99                  | 2.62 ± 1.22   |
| CSF p-tau (pg/L)            | 334.04 ± 49.6                     |                                  |                              |                              |               |
| CSF Aβ40 (pg/mL)            | 6208.6 ± 1383.47                  |                                  |                              |                              |               |
| CSF Aβ42 (pg/mL)            | 715.44 ± 225.559                  |                                  |                              |                              |               |

Note: All values are mean ± SD.

Abbreviations: Aβ, amyloid beta; BV, brain volume; CN, cognitively normal; CSF, cerebrospinal fluid; ICV, intracranial volume; MMSE, Mini-Mental State Examination; NfL, neurofilament light; p-tau, phosphorylated tau.

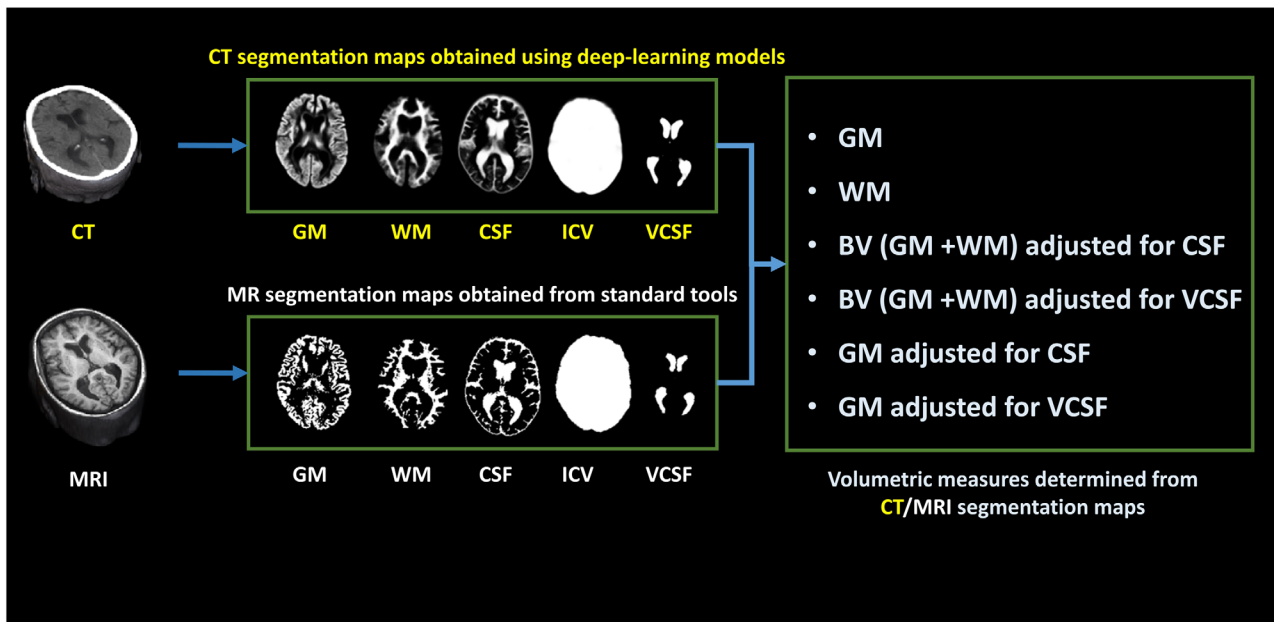
Partial Spearman correlations between CTVMs and other markers of neurodegeneration were employed after adjustment for ICV, age, education, and gender. In the Singaporean Memory Clinic Cohort, we compared CTVMs between diagnoses using Kruskal–Wallis tests. Diagnostic accuracy was assessed by measuring the area under the receiver-operating characteristic (ROC) curve (AUC) along with a 95% bootstrap confidence interval.<sup>34</sup> In addition, we computed the AUC of predicted probabilities from a logistic-regression-based combined model of all six CTVMs. For comparison in the same cohort, we also tested the relationship between MR-based volumetric measures and clinical diagnoses, using the same tests and analytic procedures that were used for evaluating CTVMs. After conducting the Kruskal–Wallis tests and AUC analysis on MR-based volumetric measures, the diagnostic performance of CT- and MR-based volumetric measures was compared. In addition, to understand the relationship between CTVMs and visual atrophy assessments in the Gothenburg H70 Birth Cohort, we tested the conformity of (1) CT-GM with MR-GM and MR-MTA and (2) CT-MTA with MR-MTA and MR-GM using intraclass correlation tests (conformity was calculated from a single measurement and by

using a two-way model). The statistical significance threshold was set at  $p = 0.05$ . All statistical analyses were performed using IBM SPSS Statistics 27 (IBM Corp, Armonk, NY, USA) or R version 4.0.3 (2021).<sup>35</sup>

### 3 | RESULTS

Table 1 lists demographic information, CTVMs, and biochemical biomarker data for all participants from both cohorts. In the Singaporean Memory Clinic Cohort, mean age and education levels were comparable among diagnostic groups. As expected, patients with dementia performed worse on the MMSE than healthy participants ( $15.13 \pm 4.21$  vs  $27.05 \pm 2.08$ ), and mean plasma NfL levels were higher in patients with dementia than in cognitively normal individuals ( $46.08 \pm 47.15$  pg/mL vs  $27.43 \pm 16.29$  pg/mL) or Gothenburg H70 Birth Cohort cognitively normal participants ( $46.08 \pm 47.15$  pg/mL vs  $25.12 \pm 25.57$  pg/mL).

CTVMs were derived from segmentation maps obtained from brain tissue classification of CT images using models based on deep learning.



**FIGURE 2** Imaging-based volumetric measures. The CT-based GM, WM, CSF, ICV and VCSF maps were automatically segmented using deep-learning techniques. The MR images were automatically segmented to GM, WM, and CSF maps using SPM12, ICV map using PinCrani, and VCSF map using MAPER. Six volumetric measures were determined from these segmentation maps. CSF/VCSF adjusted BV/GM volumetric measures were obtained using regression-based adjustment of the respective brain tissue volumes. CSF, cerebrospinal fluid; CT, computed tomography; ICV, intracranial volume; GM, gray matter; MRI, magnetic resonance imaging; WM, white matter; VCSF, ventricular cerebrospinal fluid (Color print).

The models segmented CT images in GM, WM, CSF, VCSF, and ICV in less than 1 minute. In the Singaporean Memory Clinic Cohort, CT volumes correlated strongly with corresponding MR volumes (intraclass correlation coefficient [ICC] of 0.93, 0.86, and 0.81 for GM, WM, and CSF tissue classes, respectively; Figure S1) indicating that CT-based volumes are comparable to MR-based volumes determined from established segmentation algorithms. In the Gothenburg H70 Birth Cohort, the inter-modality kappa coefficient between visual ratings of MTA from CT and MR scans performed by a trained rater was 0.40 for the right hemisphere and 0.43 for the left. It is notable that the conformity between CT- and MR-based GM volumes (ICC = 0.93,  $p < 0.001$ ) was stronger than the conformity between CT- and MR-based MTA scores (ICC = 0.53,  $p < 0.001$  [left hemisphere], ICC = 0.48,  $p < 0.001$  [right hemisphere]) (Table S1).

### 3.1 | CT-based volumetric measures across diagnostic groups

In the Singaporean Memory Clinic Cohort, we found that CTVMs could distinguish dementia patients from cognitively normal subjects (CT-GM adjusted for CSF: AUC = 0.87, 95% confidence interval [CI]: 0.79, 0.96; Figure 3A) yielding AUC values that were equal to or slightly lower than MR-based measurements (MR-BV adjusted for CSF, AUC: 0.91, 95% CI: 0.85, 0.96). CT-based GM volume also yielded AUC values comparable to MR-based MTL volume when distinguishing patients with dementia from cognitively normal individuals (CT-GM:

AUC = 0.86, MR-MTL: AUC = 0.86; Figure S2). Predicted probabilities from logistic-regression-based combined models of various CT volumetric measures yielded higher AUC values in comparison individual CTVMs (for combined model with all CTVMs, AUC: 0.95, 95% CI: 0.91, 0.99, Figure 3) and comparable AUCs from logistic-regression-based combined models of various MR volumetric measures (AUC: 0.95).

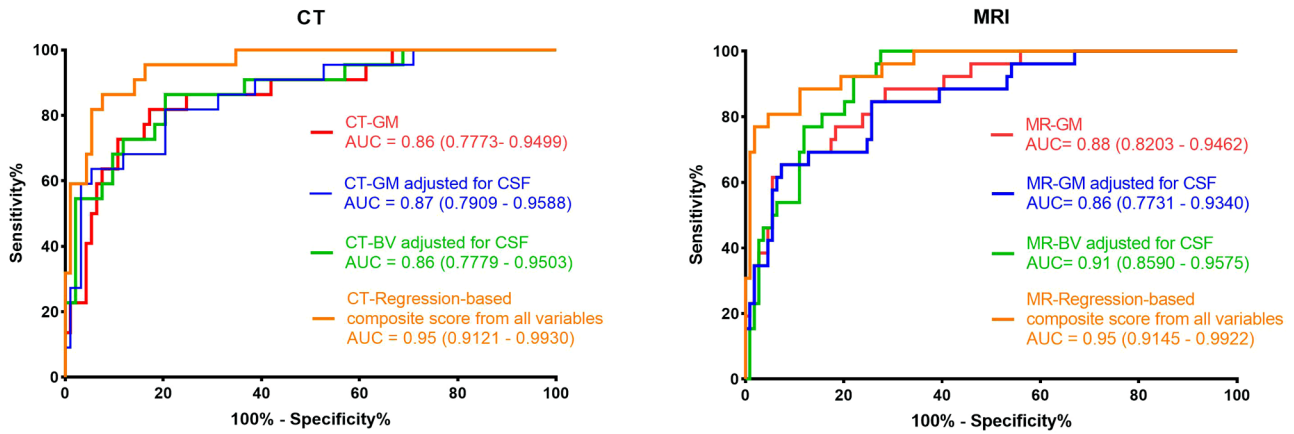
Of interest, CTVMs and regression-based predicted probabilities of CTVMs could distinguish patients with prodromal dementia (CT-GM: AUC = 0.7, 95% CI: 0.57, 0.81) from cognitively normal individuals reasonably well (Figure 3B, Figure 4), with performance comparable to MR-based volumetric measures (MR-BV adjusted for CSF, AUC: 0.71, 95% CI: 0.60, 0.81). Figure 3 and Figure S2 show the ROC curves of various measures for distinguishing between diagnostic groups.

Overall, CTVMs differentiated robustly and significantly between the various diagnostic groups, with mean CTVMs being lowest in patients with dementia, followed by prodromal dementia and highest in the cognitively normal group (Figure 4). The distribution of CTVMs across various diagnostic groups was comparable to that of MR-based volumetric measures (Figure 4).

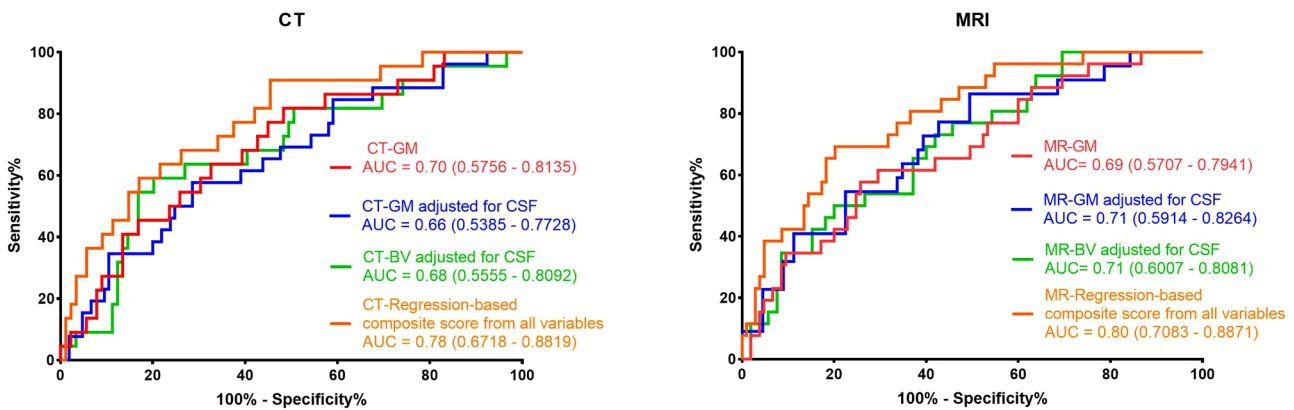
### 3.2 | CT-based volumetric measures and cognition

In the Singaporean Memory Clinic Cohort, CTVMs were significantly associated with measures of cognitive impairment as indicated on CDR-SB and MMSE scores (Table S2). Higher CDR-SB and lower MMSE correlated with smaller GM volumes ( $\rho = -0.44$ ,  $p < 0.001$  and  $\rho = 0.42$ ,

## (A) Dementia vs CN



## (B) Prodromal dementia vs CN



**FIGURE 3** ROC curves for (A) dementia versus CN and (B) prodromal dementia versus CN using CT- and MR-based volumetric measures in the Memory Clinic Cohort, Singapore ( $n = 204$ ). All volumes were adjusted for intracranial volume. The ROC curves of variables with AUC above 0.6 are shown. AUC, area under the curve; BV, brain volume; CSF, cerebrospinal fluid; CN, cognitively normal; GM, gray matter; ROC, receiver-operating characteristic (Color print).

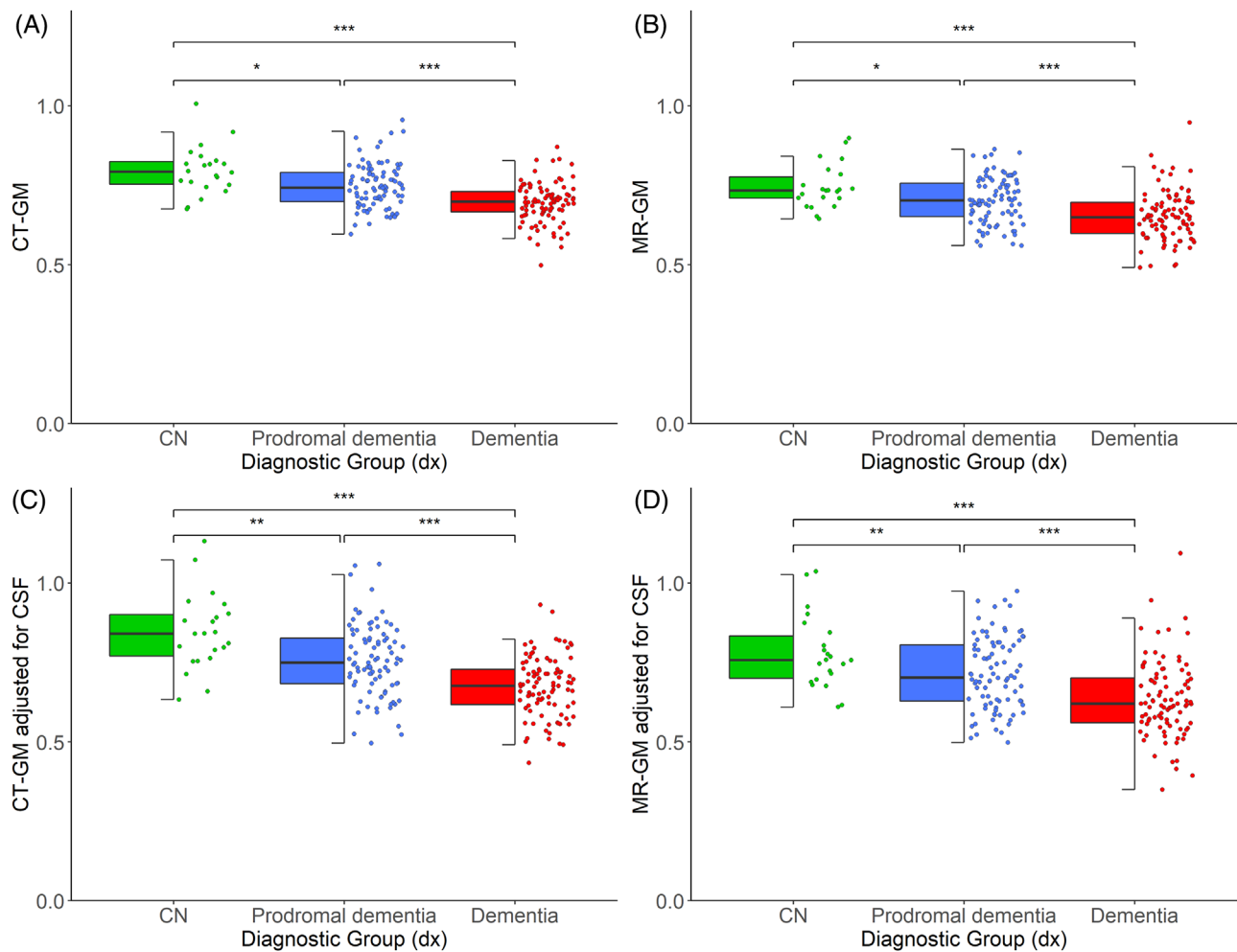
$p < 0.001$ , respectively; Figure 5). In the cognitively normal individuals from the Gothenburg H70 Birth Cohort, CTVMs were significantly, yet more weakly, correlated with CDR-SB and MMSE scores (Table S3).

### 3.3 | CT-based volumetric measures and their association with biochemical disease markers in plasma and CSF

In the Singaporean Memory Clinic Cohort, CTVMs were significantly associated with plasma-based NfL and p-tau181 (Table S2, Figure 5). The strongest correlations were seen with plasma NfL ( $\rho = -0.33$ ,  $p < 0.001$ , using CT-BV adjusted for VCSF). In the cognitively normal individuals from the Gothenburg H70 Birth Cohort, CTVMs were moderately correlated with plasma levels of NfL ( $\rho = -0.09$ ,  $p = 0.004$ , using GM), and CSF levels of NfL, A $\beta$ 42, t-tau, p-tau, and notably, A $\beta$ 42/40 ( $\rho = 0.18$ ,  $p = 0.002$ , using CT-BV adjusted for VCSF).

## 4 | DISCUSSION

Cranial CT images contain valuable information for characterizing neurodegenerative disease that can be extracted quantitatively with automatic image analysis. The present study is the first to demonstrate comprehensively that quantitative imaging markers automatically obtained from CT images corroborate the results of standard diagnostic methods used in clinical research and practice. The measurements were enabled by training a dedicated deep neural network with suitable data sets (CT images plus tissue class maps obtained through classical MR image analysis). Once trained, the model works effectively on pure CT data, enabling quantitative assessment of structural brain integrity in persons who have not undergone MR scanning. Although runtime behavior was not assessed systematically, the results suggest that processing time does not pose an obstacle to clinical use. We demonstrated this effectiveness on CT images of 1121 participants in two distinct cohorts, one sampled from an elderly population ( $n = 917$ )



**FIGURE 4** Distribution of CT- and MR-based volumetric measures across diagnostic groups in the Memory Clinic Cohort, Singapore ( $n = 204$ ). \*\*\* $p < 0.001$ , \*\* $p < 0.01$ , \* $p < 0.05$ ; uncorrected  $p$ -values derived from Kruskal–Wallis test. All volumes were adjusted for intracranial volume. BV, brain volume; CN, cognitively normal; CSF, cerebrospinal fluid; GM, gray matter (Color print).

and one from individuals consulting a memory clinic ( $n = 204$ ). Enabling CT-based assessment of neurodegeneration has important clinical potential, as CT scanners are more widely available than MR equipment, and CT is often suitable even for patients with contraindications for MR scanning.

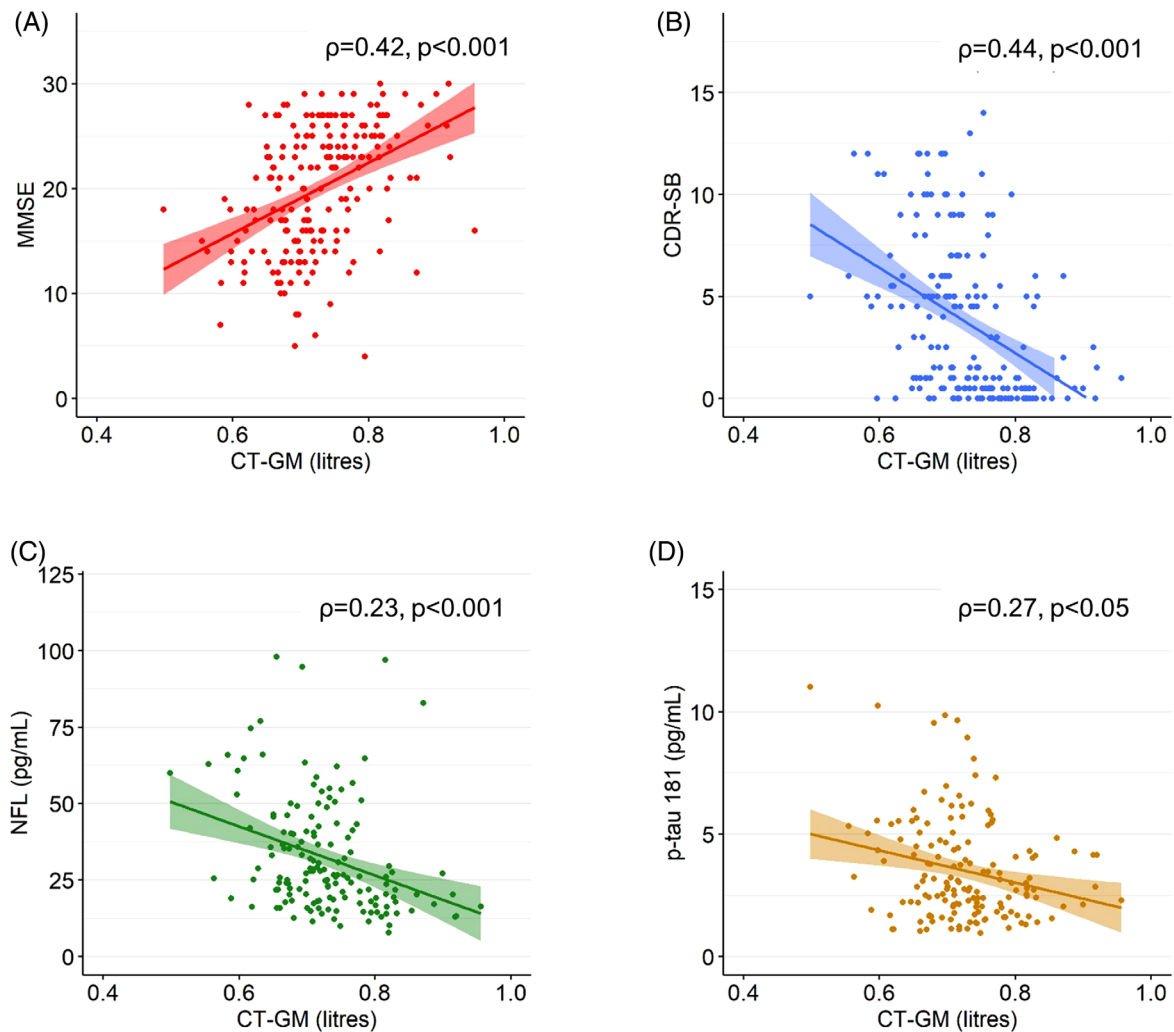
We investigated the association of CT-based volumetric measures with established markers of neurodegenerative diseases. Our main findings are that CT imaging biomarkers obtained through volumetric analysis based on deep learning (1) differentiate between patients and healthy controls, with similar performance as when using MR-based measures; and (2) strongly correlate with relevant cognitive, biochemical, and neuroimaging markers of neurodegenerative diseases associated with dementia. Together, these findings indicate that CT-based volumetric measures are promising imaging markers for the primary assessment of neurodegenerative diseases.

The first key finding of this study is that CTVMs differentiated between various diagnostic groups with high accuracy. The distribution pattern of CTVMs across various diagnostic groups is consistent with findings from previous studies.<sup>16,36,37</sup> In the patients with pro-

drodromal dementia, we measured volumes that were larger than those of the dementia groups, but smaller than those of the cognitively normal group. An interesting finding is that CTVMs differentiated between prodromal dementia and cognitively normal groups (AUC: 0.70, Figure 3b, Figure 4), indicating a potential application in the screening of dementia and neurodegeneration. Among the six volumetric measures derived from the five direct CT volumetric measures, GM, GM adjusted for CSF, and BV adjusted for CSF showed the strongest performance in differentiating between diagnostic groups. Predicted probabilities from logistic-regression-based combined models of various CTVMs yielded the highest AUCs values in comparison individual CTVMs in distinguishing both dementia and prodromal dementia from cognitively normal individuals.

The second key finding of our study is that CTVMs are associated with cognition and biochemical markers of neurodegenerative disorders. In both cohorts, lower CT-based volumes were associated with lower MMSE scores and with higher levels of CDR-SB. Other studies have shown that higher levels of plasma and CSF NfL correlate with lower MMSE scores, decreased brain volume, and reduced cortical





**FIGURE 5** CT- and MR-based volumes with other neurodegenerative disease biomarkers. Correlation of CT- and MR-based GM volumes with (A) MMSE, (B) CDR-SB, (C) plasma NfL, and (D) plasma p-tau181 in the Memory Clinic Cohort, Singapore ( $n = 204$ ). The correlation values ( $\rho$ ) were obtained from partial rank correlation analysis between CT-based volumetric measures and other biomarkers controlled for intracranial volume, age, gender and education. CDR-SB, Clinical Dementia Rating Sum of Boxes; GM, gray matter; MMSE, Mini-Mental State Examination; MR, magnetic resonance; NfL, neurofilament light; p-tau, phosphorylated tau (Color print).

thickness.<sup>38,39</sup> We found significant indirect correlations between levels of plasma NfL and CTVMs. In the Gothenburg H70 Birth Cohort, higher levels of CSF NfL were correlated with lower levels of CTVMs. Studies by Karikari et al.,<sup>40</sup> Moscoso et al.,<sup>41</sup> and Wang et al.<sup>42</sup> similarly showed inverse correlations between plasma p-tau181 and smaller brain volumes. In the Singaporean Memory Clinic Cohort, higher levels of plasma p-tau181 were correlated with lower CTVMs. Together, our findings suggest that CTVMs correlate well with clinical and biochemical measures. Among the six CT-based volumetric measures GM, GM adjusted for CSF, BV adjusted for VCSF, and GM correlated VCSF correlated with most biochemical markers of neurodegeneration in the Singaporean Memory Clinic Cohort (Table S2), as did GM adjusted for VCSF, GM adjusted for CSF, BV adjusted for VCSF, and BV adjusted for CSF in the Gothenburg H70 Birth Cohort (Table S3).

We further found that CT-based volumetric measures correlate strongly with MR-based measures and display comparable diagnos-

tic performance, notably also compared with MR-MTL (Figure S2), the most established quantitative measure of medial temporal lobe atrophy.<sup>43–45</sup> Atrophy of the MTL is an important diagnostic biomarker of many neurodegenerative disorders, most specifically in AD.<sup>44,46,47</sup> Furthermore, we found that the intermodality agreement between our automated CT- and established MRI-segmentations was distinctly stronger than the agreement between visual CT and MRI assessment. In the Gothenburg H70 Birth Cohort, the intermodality kappa coefficient between visual ratings of MTA from CT and MR scans performed by a trained rater was 0.40 for the right hemisphere and 0.43 for the left hemisphere, and the ICC between CT-MTA and MR-MTA was 0.48 and 0.53 for the right hemisphere and left hemisphere, respectively. The volumetric ICC between CT-GM and MR-GM obtained from our automated and established MR-based methods was 0.93 for the same data sets. Currently, brain structure integrity in CT is evaluated predominantly using visual assessments, whereas MRI is preferred for

differential diagnosis and atrophy assessment. Our findings emphasize that with further validation, automatic CT image analysis could be used potentially for the evaluation of brain structure integrity in the first-line examination of cognitive decline, with faster and more reproducible results than visual ratings, while showing performance comparable to that of MRI. Our deep-learning models perform tissue classification on head CT images in less than 1 minute.

A major aspect of our study is that we investigated the association of CT-based volumetric measures with established and novel markers of neurodegenerative diseases (blood- and CSF-based as well as measures of cognition) in two large, well-characterized cohorts for which paired CT and MRI data were available. The first cohort consisted predominantly of cognitively normal participants, and the other consisted of various diagnosis groups of dementia. This allowed us to train our deep-learning models on the predominantly healthy cohort and validate the models on both cohorts. By having access to both CT and MR scans of the same subjects, we were able to validate the structural similarity of CT-based segmentation maps and compare the classification performance of CTVMs in both cohorts. Of interest, the deep-learning models developed in our previous study<sup>17</sup> worked well on the Singaporean Memory Clinic Cohort without reference to MRI data and without further training. One of the widely discussed limitations of deep-learning models is the relative lack of reproducibility.<sup>48</sup> In our study, the trained model was remarkably successful when applied to previously unseen data sets acquired on other scanners.

Limitations of our study include that we had amyloid status (96 of 241) available only for a fraction of the Memory Clinic Cohort. Hence, the clinical diagnoses of patients reported in this study are likely a reflection of cognitive status and associated underlying pathology rather than diagnoses based on biomarker evidence of a specific etiology. In addition, our deep-learning models were trained on MR-based labels only; therefore, our study cannot answer whether alternative means of generating training labels on CT images (manual or other) would have been beneficial. Furthermore, we explored the diagnostic performance of CT-based volumetric measures on cross-sectional data. The diagnostic performance of CTVMs on longitudinal data is yet to be explored. In the future we plan to conduct prospective studies to study the impact of longitudinal effects of neurodegeneration on CTVMs. Along with the diagnostic performance, we evaluated the association between CTVMs and other imaging, cognitive, and biochemical markers of neurodegenerative diseases in this study. Recently few studies have explored multimodal data integration for the prediction, early detection, and assessment of neurodegenerative diseases—especially AD.<sup>49–51</sup> In the future we plan to explore the role of CTVMs in multimodal data analysis for the early detection of neurodegeneration, especially the role of CTVMs in combination with plasma and cognition-based markers.

In summary, CT imaging biomarkers obtained through volumetric analysis based on deep learning are associated with relevant imaging, cognitive, and biochemical markers of neurodegenerative diseases. These volumetric measures differentiate between patients with dementia diagnoses (even at early disease stages) and cognitively healthy individuals, offering diagnostic performance comparable

to established MR-based markers of neurodegenerative diseases. We propose our automated method to produce CT-based volumetric measures that can support clinical dementia diagnostics, even in early disease stages. Together with novel blood biomarkers, CT-based quantitative measures could be useful tools for the first-line examination of individuals presenting with cognitive decline.

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## CONFLICT OF INTEREST STATEMENT

H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen,

Novo Nordisk, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Celectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.B. served as a consultant at advisory boards and data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is also the co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. S.K. has served at scientific advisory boards and/or as a consultant for Geras Solutions and Biogen (outside submitted work). M.S. has served on advisory boards for and receives funding from Roche Diagnostics and Novo Nordisk (outside scope of submitted work). The other authors have no conflicts of interest pertinent to this manuscript. Author disclosures are available in the [Supporting Information](#).

## CONSENT STATEMENT

Necessary patient/participant consent for Gothenburg H70 Birth Cohort and Memory Clinic Cohort Study, Singapore, has been obtained and the appropriate institutional forms have been archived.

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## SUPPORTING INFORMATION

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