

Predicting development of Alzheimer's disease in patients with shunted idiopathic normal pressure hydrocephalus

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ABBREVIATIONS

ACC = Accuracy

AD = Alzheimer's disease

AUC = Area Under the Receiver-operator Curve

A β = Amyloid-beta

A β 42 = Amyloid-beta 42

BMI = Body Mass Index

CT = Computed Tomography

CSF = Cerebrospinal Fluid

DSI = Disease State Index

HP τ = Hyperphosphorylated tau

ICP = Intracranial Pressure

iNPH = Idiopathic Normal Pressure Hydrocephalus

KUH = Kuopio University Hospital

MMSE = Mini-Mental State Examination

MTA = atrophy of medial temporal lobe

MRI = Magnetic Resonance Imaging

NPH = Normal Pressure Hydrocephalus

VPS = Ventriculoperitoneal Shunt

ABSTRACT

BACKGROUND: Idiopathic normal pressure hydrocephalus (iNPH) patients often develop Alzheimer's disease (AD) related brain pathology. Disease State Index (DSI) is a method to combine data from various sources for differential diagnosis and progression of neurodegenerative disorders.

OBJECTIVE: To apply DSI to predict clinical AD in shunted iNPH-patients in a defined population.

METHODS: 335 shunted iNPH-patients (median 74 years) were followed until death (n=185) or 6/2015 (n=150). DSI model (including symptom profile, onset age of NPH symptoms, atrophy of medial temporal lobe in CT/MRI, cortical brain biopsy finding,

and *APOE*-genotype) was applied. Performance of DSI model was evaluated with Receiver Operating Characteristic (ROC) Curve analysis.

RESULTS: A total of 70 (21 %) patients developed clinical AD during median follow-up of 5.3 years. DSI-model predicted clinical AD with moderate effectiveness (AUC = 0.75). Significant factors were cortical biopsy (0.69), clinical symptoms (0.66), and medial temporal lobe atrophy (0.66).

CONCLUSION: We found increased occurrence of clinical AD in previously shunted iNPH patients as compared with general population. DSI supported the prediction of AD. Cortical biopsy during shunt insertion seems indicated for earlier diagnosis of comorbid AD.

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a progressive, potentially dementing disorder which is manifested by symptoms including impaired gait, urinary incontinence and cognitive impairment, as well as enlarged brain ventricles [1, 2].

Apart from other neurodegenerative diseases, symptoms of iNPH can be alleviated with cerebrospinal fluid (CSF) diversion, although successful selection of patients for shunt treatment has proven to be difficult [3–5]. Patients diagnosed with iNPH have shown to often have pathological changes related to Alzheimer's disease (AD) [6–12], which has been linked to later development of AD and dementia [13, 14].

Previous studies indicate deterioration of cognition in iNPH patients even after shunt surgery [2, 15, 16], but the prognostic factors of comorbid AD have not been

analyzed.

The Disease State Index (DSI) is a statistical tool designed for multimodal data analysis and clinical decision-making. It is capable for analysis of fragmented data and merging opaque information to well interpretable scores for individual patients and discrimination between patient groups. DSI has been previously successful in differential diagnosis of AD, predicting progression to AD among subjects with mild cognitive impairment (MCI), separating frontotemporal dementia (FTD) from AD, and working with various cohorts [17–20].

In this retrospective cohort study, we compare the occurrence of clinical AD in iNPH with general population and attempt to predict development of AD among shunted iNPH patients, using the DSI. Merging information of individual patients' baseline cortical brain biopsy, radiological markers, symptom profile, and *APOE*-genotype, we intend to develop a model capable of predicting patients in risk of clinical AD.

MATERIALS AND METHODS

Patients and shunt protocol

The Department of Neurosurgery in the Kuopio University Hospital (KUH) serves the defined catchment population in Eastern Finland. Since 1993, the diagnostic workup of KUH Neurosurgery for suspected NPH has included a clinical examination by a neurologist and a neurosurgeon, CT or MRI scan, and a right frontal cortical biopsy [14]. The Kuopio NPH Registry (www.uef.fi/nph) consists of 764 consecutive patients to the end of the year 2012 including baseline and follow-up data from KUH, all

primary health care physicians, and other local hospitals in the KUH catchment area. Demographic data is shown in Table 1. Patients were evaluated for suspected NPH fulfilling the following criteria: 1) 1 to 3 symptoms related to NPH: impaired cognition, gait, or urinary continence; 2) enlarged brain ventricles, i.e. Evans' index > 0.3 in CT or MRI.

Patients shunted for iNPH were included in the analysis, but those with iNPH and comorbid clinical AD at baseline were excluded from the prognostication analysis (Figure 1). Selection for shunt surgery was done with 24-h intraventricular pressure (IVP) monitoring until the end of 2010 with indications for shunt: 1) a basal ICP above 10 mmHg; or 2) the presence of any A waves or more than 30% B waves during the 24-hour ICP monitoring [3, 14, 21]. Since 2011, a three-step protocol was used for shunt surgery selection: first a lumbar CSF removal of 20 ml (tap test) was performed for all patients, and 20 % improvement in gait speed was considered positive response; patients with negative tap test underwent a lumbar infusion test, where conductance of 10 or less was considered pathological [22]; and those with negative result both in tap test and infusion test were shunted based on 24-h IVP monitoring as described above. Ventriculoperitoneal shunts (VPS) with a medium-pressure differential pressure valve until 2010 and adjustable PS Medical Strata valve since 2010 were used for shunting. The initial response to the shunt – defined as improvement in the patient's gait, memory, or urinary incontinence – was observed by the clinician 2 to 3 months after the shunt placement at the outpatient clinic.

The clinical follow-up was continued in local hospitals and by primary care physicians. Adequate follow-up data to evaluate clinical dementia was missing for 24

patients (Figure 1). Study population was followed for a median period of 5.3 years (range 0.2 – 21), during which 185 patients died. Data from KUH archives, local hospitals, and primary care physicians was collected and causes of death were obtained from the national registries to detect development of clinical AD. AD was diagnosed according to revised NINCDS-ADRDA criteria [23], and examinations by geriatricians and neurologists were taken in to account. Study neurologists specialized in memory disorders (AMK, ON) have evaluated the follow-up information of the study patients and verified dementia diagnoses as described before [2]. If shunt malfunction or cognitive impairment was suspected, the patients were referred for neurological and neurosurgical re-evaluation. During the follow-up, a total of 91 shunt revisions were made.

Clinical and cognitive data

Clinical symptoms included in the analysis were gait impairment, cognitive impairment, urinary incontinence, and other symptoms, such as vertigo, tremor and headache. The symptoms were further divided into three subgroups according to the time of occurrence of the symptom: 1) the first symptom; 2) the main symptom; and 3) present symptom, i.e. the symptom was present during clinical assessment. In addition, the onset age of NPH symptoms and presence of full NPH symptom triad were included. Comorbidities such as any cardiovascular disease, diabetes, or any previous neurological condition were included in the analysis. To evaluate influence of cognitive deterioration on outcome, the Mini-Mental State Examination (MMSE, range 0-30, 30 indicating good cognitive performance) was included in the analysis [24].

Radiological data

Within the registry, patients had CT or MRI, or both imaging data available. For this analysis, data obtained by MRI was preferred over CT. Images were evaluated by radiologist visually for atrophy of left and right medial temporal lobe (Scheltens grade), white matter changes in periventricular and deep white matter, and disproportionality between sylvian and suprasylvian subarachnoid spaces [25, 26]. In addition, Evans' index was calculated.

Histological evaluation of brain biopsy

The paraffin-embedded biopsy samples were sectioned (7 μ m) and stained with hematoxylin-eosin, and immunostained with monoclonal antibodies directed to amyloid beta (A β) (6F/3D, M0872; Dako; dilution 1:100; pretreatment 80% formic acid 1 hour) and hyperphosphorylated tau (HP τ) (AT8, 3Br-3; Innogenetics; dilution 1:30) as described previously [27]. In all samples immunoreactivity for A β and HP τ was graded as present or absent by a neuropathologist [28]. In total, cortical brain biopsy data was available for 331 patients, with 5 cases of inconclusive histological data.

APOE-genotyping

A PCR method was used in the analysis of *APOE* (n = 197), as described previously [13]. For the analysis, ϵ 4 was classified as carrier or non-carrier.

CSF AD-biomarkers

The lumbar CSF levels of A β ₁₋₄₂, total-tau, and phosphorylated-tau₁₈₁ were measured by commercial ELISA kits (Innotest β -amyloid₁₋₄₂, Innotest Tau-Ag, Innotest

Phosphotau_(181P), Innogenetics, Ghent, Belgium) according to the manufacturer's protocol, as described previously [29]. Individual CSF values of p-tau, total-tau and A β ₁₋₄₂ were included in the analysis [30]. In total, CSF data was available for 95 patients.

Reference populations

Cardiovascular Risk factors, Aging and Dementia (CAIDE) is a population-based study in the Kuopio and Joensuu town areas in Eastern Finland. The study design has been previously described in detail [31]. The target population included 3559 individuals (56.5 % women, 43.5 % men) aged 40-64 years (mean 51.2, SD 5.9) at the first examination in either 1972, 1977, 1982 or 1987. Two re-examinations were conducted in 1998 and 2005-2008, including a comprehensive protocol for dementia assessment [31]. Dementia diagnoses until the end of 2008 were also obtained from national registers (Hospital Discharge Register, Drug Reimbursement Register and Causes of Death Register) [32]. Incidence of dementia in the entire target population during 1972-2008 was 15.3% (544 cases out of 3559 individuals). In the 1511 individuals who survived and participated in at least one CAIDE re-examination, incidence of dementia was 16.6% (250 cases).

In addition, primary causes of death and total count of deceased population were obtained from Statistic Finland registry [33]. Primary causes of death were obtained from the year 2015, as the end of follow-up in study population was in June 2015. Dementia as a primary cause of death consisted of ICD-10 diagnoses of F01, F03, G30, and R54. Dementia was a primary cause of death in 7624 (15.7 %) cases of 48 438 total deceased in Finland in the year 2015, regardless of age.

Disease State Index

The DSI is a statistical method that allows us to compare patient's data to cases with a known diagnosis [18]. The values, ranging from zero to one, indicate similarity to the positive group, which is in this case the development of subsequent AD. All available data from patients, whether continuous, binary or categorical, can be included in the DSI analysis, and the method does not require a complete dataset but can tolerate missing values, making it ideal for clinical work or a retrospective registry study.

The DSI method is based on comparison of patients' measurements between two groups. The measurements from patients with a known diagnosis from these two groups form two distributions to which the patient under analysis is compared. The patient's similarity to the positive group is calculated using a fitness function for each taken measurement. The fitness function is defined as:

$$fitness = \frac{false\ negative\ rate}{false\ negative\ rate + false\ positive\ rate}$$

It is calculated for each measurement value using the value as the point of classification threshold. If there are no false negatives, fitness is 0, while at the point when there are no false positives, fitness becomes 1. This is the DSI value for the individual measurements. Additionally, the relevance for each measurement is calculated. Relevance depicts the ability to discriminate between two groups with values ranging from 0, meaning no difference between groups to 1, meaning a complete separation of the groups. The relevance is computed as

$$relevance = sensitivity + specificity - 1,$$

where the sensitivity and specificity are obtained by classifying the training data using the measure. DSI is first calculated for each measurement (e.g. Amyloid β positivity), then for each measurement group (e.g. Cortical brain biopsy) and then all groups together as total DSI.

A total DSI value is computed by averaging the DSI values of each measure by applying weighting with the relevance values:

$$DSI = \frac{\sum \text{relevance} \cdot \text{fitness}}{\sum \text{relevance}}.$$

This method has been described in detail previously [18].

Statistical analysis

Groups used for this analysis were patients with clinical AD and without clinical AD at the end of the follow-up (Figure 1). For statistical analysis of demographic and clinical data, IBM SPSS Statistics 24.0 software was used. For statistical testing between study groups, Chi-square test was used for nominal variables and Mann-Whitney U-test for ordinal or continuous. Chi-square test using *post-hoc* Bonferroni correction for pairwise comparisons was used between cohorts. Values of $p < 0.05$ were considered significant.

To remove marginal information and noise, measurements for the DSI analysis were selected with significance threshold of $p < 0.05$ in Mann-Whitney U-test.

As there was no previously trained reference population available, the DSI classification results were calculated with 100×10 -fold cross validation. Participants

were divided into 10 random subgroups and each group was tested against a training set containing the 9 other subgroups. This procedure was completed 100 times, for a total of 1000 test runs. Means, standard deviations and 95% confidence intervals for each round of cross validation were then calculated and averaged for the 100 test rounds. DSI value of 0.5 was used as the classification threshold between the compared groups. Performance of the DSI was measured with AUC (area under receiver-operator curve), classification accuracy, sensitivity and specificity. Classification accuracy is the percentage of patients with correct prediction of AD diagnosis at follow-up.

To test the effect of each measurement group on the total DSI score, we did a drop-out analysis, where one-by-one each group (age, symptoms, radiology, biopsy and APOE) was left out of the total model. The results were compared to the full DSI model with all groups included.

Stratification for DSI model was done, with classification accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) calculated for each individual cut-off.

Random Forest analysis with Matlab function TreeBagger was done to ensure and validate the performance of DSI.

Ethical Issues

The study was approved by the KUH Research Ethical Committee, the Finnish National Supervisory Authority for Welfare and Health, and the Finnish Ministry of

Social Affairs and Health. Brain biopsy was part of clinical routine. Informed consents were obtained for *APOE*-genotyping and CSF AD-biomarker samples.

Data availability

The informed consent restricts free availability of the individual data. However, the data used in this study are available in de-identified form from the corresponding author upon reasonable request and research collaboration agreement.

RESULTS

In total 70 out of 335 shunted iNPH patients (21 %) developed clinical AD during median follow-up of 5.3 years (range 0.2 – 21). Occurrence of AD was significantly increased in study population when compared to dementia in general population cohorts (Table 3) (Figure 4). Mean age of clinical AD diagnosis was 78.6 years (range 71 – 89). Used model yielded AUC of 0.75 and accuracy of 0.69 for total DSI index (Table 2). Significant analyzed factors for the DSI model were age (AUC = 0.64), clinical symptoms (AUC = 0.66), radiology (AUC = 0.66), cortical brain biopsy (AUC = 0.69), and *APOE*-genotyping (AUC = 0.62). Individual measurements are presented in Supplementary Table 1. Excluding cortical brain biopsy from DSI model lowered its effectiveness to AUC of 0.70 and accuracy of 0.66 (Supplementary Table 2). Stratification analysis of the model used is presented in Figure 3 and in Supplementary Table 3. Distribution of DSI values between groups is shown in Figure 2 calculated using the whole population as the training group.

Significance threshold removed baseline MMSE, gait impairment as first or present symptom, urinary incontinence, other symptoms, comorbidities, Evans' index, periventricular and deep white matter changes, disproportionality between sylvian and suprasylvian subarachnoid spaces, and CSF AD-biomarkers from the comparison. All specific measurements included in this study can be found in the supplementary material (Supplementary Table 1). The Random Forest analysis obtained the prediction effectiveness of $AUC = 0.76$, which is in line with the results from the DSI.

DISCUSSION

To our knowledge, this is the first study where the occurrence of clinical AD was compared between probable iNPH and general population. Also, this is the largest follow-up study with iNPH patients regarding clinical AD. We have used the DSI method to predict later development of clinical AD among 335 shunted iNPH patients of Kuopio NPH Registry cohort. With this cohort, we had an extensive median follow-up time of 5.3 years (range 0.2 – 21) and low drop-out rate of 6.7 % to observe patients' clinical condition and development of subsequent AD.

The DSI model predicts later development of clinical AD with moderate effectiveness ($AUC = 0.75$). The combined model of clinical symptoms, cortical brain biopsy, atrophy of medial temporal lobe, and *APOE* -genotype, was better at differentiation of groups, than any of the individual factors used in the model. We consider that this demonstrates well the advantage of using the DSI model for current dataset.

Stratification analysis further revealed, that as negative predictive value (NPV) for the

whole population was 79 %, NPV for patients with DSI < 0.3 was 94 %. In addition, positive predictive value (PPV) was 21 % for the whole population, but PPV = 49 % when DSI > 0.7, giving risk-ratio 2.3 for AD development for these patients. Although overall effectiveness of DSI model was moderate, it can identify groups of patients who are at very low risk or in clearly increased risk of subsequent AD.

Pathological findings in cortical brain biopsy were the most effective predictive factor of clinical AD in our analysis (AUC = 0.69). A β immunoreactivity was more predictive (AUC = 0.65) than HP τ (AUC = 0.57), with higher occurrence in later clinical AD group. Presence of A β and HP τ pathology has been linked to later development of AD [6] as well as hampered shunt surgery outcome [8, 9, 34]. HP τ immunoreactivity was more frequent in AD group, and when combined with A β contributed to increased effectiveness of separation in cortical brain biopsy measurement group. Interestingly, 31% of the iNPH cases without subsequent AD had a positive biopsy for A β with an additional 5% being positive for both A β and HP τ . These patients will likely develop subsequent AD with longer follow-up. Furthermore, 32% of cases who developed subsequent, clinical AD were negative for A β and HP τ on their biopsy. This highlights the progressive nature of AD, and also suggest that although clinical presentation could be alike to AD there can be mixed pathology behind the developed cognitive impairment, e.g. vascular dementia [8]. We conclude that obtaining brain biopsy during shunt insertion for iNPH patients is substantial aid for later prediction of clinical AD.

The group of combined clinical symptoms was the second most effective analyzed risk (AUC = 0.66). Combining single factors to a group was effective, as the most

powerful was cognitive impairment as main symptom (AUC = 0.64). Onset age of NPH symptoms performed equally (AUC = 0.64), but its impact on final model was limited, as the effectiveness of the DSI remained nearly the same in drop-out analysis. Patients developing subsequent clinical AD were characterized by older onset age of NPH symptoms, less frequent gait impairment as the most disturbing symptom, and more often cognitive impairment as the first symptom, main symptom, and present symptom at baseline. Cognitive impairment as part of NPH symptoms has been linked to later development of dementia, mostly caused by AD [14]. Our study suggests that clinical symptoms are beneficial for clinical AD prediction.

From individual factors, atrophy of medial temporal lobe (MTA) was the most discriminating (AUC = 0.66). Patients with later clinical AD had more severe baseline MTA measured with Scheltens scale when compared to the patients, who did not develop clinical AD. MTA's effectiveness to predict further progression of AD dementia at prodromal stage has been well documented [35, 36]. It would be feasible to assume that MTA could be used for iNPH shunt surgery outcome prediction, as development of AD hampers the prolonged response to treatment [27]. However, this has not been the case [3, 26], which may be result of the limited follow-up time of 3 months at outpatient clinic. Although MTA was not measured for the whole cohort (n = 119), we consider that the baseline visual assessment of MTA can be used in conjunction with other factors to predict later development of clinical AD. However, it should be noted that the atrophy of MTA might be overestimated in iNPH especially prior to shunt surgery [21].

APOE ϵ 4 allele is the most important independent genetic risk factor for late onset AD [37]. Previously it has been shown to correlate with cortical brain biopsy A β plaques, and to predict later AD with relatively high specificity (77 %) [13]. In current study, occurrence of *APOE* ϵ 4 allele was higher among patients who developed clinical AD. Its effectiveness was relatively weak (AUC = 0.59), but as previously reported, specificity of *APOE* ϵ 4 allele was highest among analyzed risk factors (81 %). We found *APOE*-genotyping useful for the DSI model.

Interestingly, MMSE and lumbar CSF biomarkers were not significant in our analysis. Baseline values of MMSE were at the same level among comparison groups. As MMSE has been shown to be insensitive to AD progression, it would be interesting to study Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) results and its subtests, especially episodic memory, before and after shunt treatment [38]. We may hypothesize that later development of AD would be predicted by only modest or no cognitive improvement in CERAD-NB postoperatively. Lumbar CSF levels of p-tau 181, total tau, and amyloid beta₁₋₄₂ were also not significant in the analysis, and there was only a slight trend of lower amyloid beta₁₋₄₂ among clinical AD group. Lumbar CSF biomarkers have been under rigorous research for iNPH shunt treatment response, but with mixed results [39, 40]. Although lumbar CSF biomarkers of neurodegeneration are strongly associated with AD [41], it does not seem to apply in our cohort of patients shunted for iNPH possibly due to obfuscating effect of impaired CSF clearance [42], or because of limited number of patients with CSF data available. As patients with suspected NPH have not developed dementia, comorbid AD in this subgroup is in very early stage, possibly rendering lumbar CSF analysis inoperative. We think this highlights the

usefulness of cortical biopsy among these patients. As it is evident that occurrence of clinical AD is increased in patients with iNPH, further study is needed to clarify whether AD pathology is a real risk factor for iNPH or iNPH a risk factor for AD. A pathophysiological link has been proposed [43] and changes in amyloid β processing is detected [44] but CSF shunt does not improve symptoms of AD (without concomitant iNPH) [45]. For future prospects, ratio of A β 42/40 should be evaluated with iNPH cohort [46] and prognosticators for other concomitant dementias should be examined [47].

There was a tendency of higher shunt revision rate among patients without later clinical AD, although statistically insignificant. There were no differences between patients with later clinical AD and those without in baseline Evans' index, iNPH classification, shunt insertion protocol, initial shunt response, or occurrence of white matter changes. This advocates that both groups are initially iNPH cases shunted with credible indications, strengthening importance of our study. Diagnoses of clinical AD have also been gathered from several clinics and primary care centers, mitigating the single-center bias. In addition, rich selection of validated measurements, long follow-up time, and large study population strengthens the findings of our study. Follow-up time could have been longer for more definitive analysis, but majority of study population (91 %) had a follow-up time longer than two years. Our results rather under than overestimate the difference in the occurrence of AD between general population and probable iNPH since dementia in general population include also other conditions than AD, and the other comorbid dementias in iNPH cohort were not considered. Also, comorbid AD diagnosed prior to CSF shunt was an exclusion criterion.

DSI was found feasible tool for multimodal data-analysis. With the dataset used, prediction accuracy was evidently enhanced when single risk factors were merged together. Current results call for repeated studies for shunted iNPH patients, as prediction accuracy of later clinical AD could be further enhanced by repeated DSI analyses during follow-up, not only at baseline. Possible clinical application of the DSI could be twofold: first application after referral in conjunction with clinical examination and preliminary NPH differential diagnostics, and second after shunting for follow-up prognosis for NPH patients.

CONCLUSIONS

This is the first study where the occurrence of clinical AD was compared between probable iNPH and general population. Up to one fifth of shunted iNPH patients develop subsequent clinical AD, which can be predicted with moderate effectiveness using DSI model consisting of symptom profile, atrophy of medial temporal lobe, cortical brain biopsy, and *APOE*-genotype. Obtaining cortical brain biopsy during shunt insertion is a substantial aid for prediction of clinical AD. DSI's ability to enhance predictive accuracy using multimodal data was found effective with current cohort.

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Brain biopsy and invasive IVP-measurement were part of clinical routine. The Finnish National Supervisory Authority for Welfare and Health has approved to use that information for the research purposes in cases the informed consent was not available. Informed consents were obtained from all patients for *APOE*-genotyping and AD-biomarker assessments.

FIGURE LEGENDS

Figure 1. Flowchart of the 764 patients with suspected idiopathic normal pressure hydrocephalus (iNPH) between 1993 and 2012 from the Kuopio NPH Registry. The study population consisted of 335 patients shunted for idiopathic NPH with adequate follow-up data. Patients were divided into two groups according to development of clinical Alzheimer's disease (AD) during follow-up.

Figure 2. Disease State Index (DSI) data distribution for patients who developed clinical Alzheimer's disease (AD) during follow-up and patients without AD on follow-up. The more separate the two distributions are, the better differentiation that can be obtained between the groups with DSI values. The vertical axis represents the probability density and the horizontal axis is a DSI scale from 0.0 to 1.0. DSI closer to zero denotes data similarity for the first state (patients without AD) in the comparison, whereas a DSI value closer to one indicates data similarity to the second state (patients with AD) in the comparison. The distribution is calculated using the complete population as the training group.

Figure 3. Stratification analysis for DSI model used. PPV = positive predictive value, NPV = negative predictive value. Suggested optimal cut-off value of 0.45, where NPV reaches 0.90, is shown as a vertical black line.

Figure 4. Relative occurrence of dementia in study population, CAIDE-cohort, and Statistics Finland registry 2015 for primary cause of death. Cardiovascular Risk factors, Aging and Dementia (CAIDE) is a population-based study in the Kuopio and Joensuu town areas in Eastern Finland [25]. Primary causes of death were obtained from Statistics Finland for year 2015, where dementia consists of ICD-10 diagnoses F01, F03, G30, R54 [27]. Chi-square test was used to test for significance between groups.

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