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Program and Abstracts

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Program

		Abstract No.
08:30 AM	Registration Opens	
09:00	Introduction	
09:10	The Incidence of Guillain Barré Syndrome in Six Italian Regions <i>R. D'Alessandro</i>	1
09:30	Quantile Regression-Based Covariate-Specific Roc Curves <i>X.H.A. Zhou</i>	2
09:50	Incident Parkinson Disease and <i>Line-1</i> DNA Methylation: A Case-Control Study <i>S. Searles Nielsen</i>	3
10:10	Break	
10:30	Impact of Duration and Age at Onset of Hypertension on Cognition in Older Men <i>M. Power</i>	4
10:50	Mild Cognitive Incidence and Long-Term Mortality in an Elderly Population-Based Survey (NEDICES) <i>A. Sánchez-Ferro</i>	5
11:10	Incidence of Primary Brain Tumours Among the Adult Population of Emilia Romagna Region, Italy <i>R. D'Alessandro</i>	6
11:30	Business Meeting	
11:45	Lunch & Keynote Address- Opioids: A Public Health Emergency <i>G. Franklin</i>	
01:20	Prospective Longitudinal Validation Over Time of Clinical Disease Trajectory [CDT] in Amyotrophic Lateral Sclerosis [ALS] Patients by 'ALS Dashboard' Containing Cognitive – Behavior (Depression – Pseudobulbar Affect [PBA]) – Bulbar – Respiratory – Arm – Leg Domains – Rate of Leg and Arm Domain Clinical Stage Changes per Patient Is Statistically Greater than Respiratory or Bulbar Stage Changes <i>B. Rix Brooks</i>	7
01:40	Family History of Multiple Sclerosis in Saskatoon <i>W.J. Hader</i>	8
02:00	Long-Term Survival of Amyotrophic Lateral Sclerosis. A Population-Based Study <i>E. Beghi</i>	9
02:30	Final Closing and Adjournment	

Oral Presentations

O1

The Incidence of Guillain Barré Syndrome in Six Italian Regions

R. D'Alessandro, E. Beghi, M.D. Benedetti, A. Chiò, G. Filippini, G. Logroscino, M. Pugliatti, F. Galeotti, M. Massari, C. Santuccio, R. Raschetti

Bologna, Milano, Verona, Torino, Bari, Sassari and Roma, Italy

Objective: To estimate the incidence of Guillain Barré Syndrome (GBS) among the adult population of six regions in Italy. **Background:** The incidence of Guillain Barré Syndrome may vary from 0.16 to 3.0 per 100,000 person-years. To assess the effect of possible risk factors, carefully determined background rates are necessary. **Method:** The six regions account for 29.5 million inhabitants (25.6 million $\geq$ 18 years). All patients $\geq$ 18 years admitted to 153 neurological units for possible GBS from October 1/2010 to September 30/2011 were registered in a centralized database. Clinical and follow-up data of patients with confirmed GBS were then recorded and automatically classified according to the Brighton Criteria (BC). To assess the completeness of case collection, clinical data of patients discharged with ICD 357.0 during the study period were reviewed. **Results:** 345 patients (210 men, 135 women) were prospectively recorded through neurological units network. Among these 285 fulfilled levels 1 or 2 of the BC and nine level 3. For 51 patients the clinical-laboratory picture did not fulfil the BC. The following forms were observed: 210 AIDP, 38 AMAN, 26 AMSAN, 24 Miller Fisher Syndrome, 47 other GBS variants. The total incidence rate was 1.4/100,000/population. Within the six Regions the age-sex standardised incidence rates ranged from 0.80/100,000 (in Sardinia) to 1.8/100,000 (in Puglia). The incidence was 1.75 among men and 1.08 among women. A clear seasonal variation was observed with a peak in January (0.15/100,000) and the lowest rate in April (0.05/100,000). Fifty-eight patients were further identified by reviewing the discharge codes in four regions. The whole incidence rate including these patients was 1.6/100,000. **Discussion:** The observed incidence rates are within the range observed in Europe. GBS variants may escape BC classification. A clear seasonal variation was found. Regional differences are under analysis.

O2

Quantile Regression-Based Covariate-Specific ROC Curves

X.H.A. Zhou, X. Duan

Seattle, Wash., USA

Objective: We propose a new statistical method for estimating the ROC curves and covariate-specific ROC curves of a diagnostic test with a skewed distribution and a ceiling effect. **Background:**

Many cognitive tests in dementia research have skewed distributions and have a ceiling effect. The current methods for estimating the accuracy of a diagnostic test with a skewed distribution in distinguishing a disease from a non-disease patient are not adequate.

Methods: We propose to use the idea of quantile regression to estimate a ROC regression model. We use the composite quantile regression to simultaneously estimate regression parameters as well as baseline inverse survival function in a regression model for the ROC curve. Based on fitted residuals, we then use empirical survival functions to estimate the ROC regression curve. **Results:** We first establish that the proposed estimators for covariate-specific ROC curves are consistent and asymptotic normally distributed. Our extensive simulation studies show that the new methods greatly outperform the existing methods for estimating the ROC curves of a diagnostic test with a skewed distribution. We illustrate the application of the proposed methods in a clinical study on the diagnostic accuracy of the MMSE in predicting the progression of normal subjects to dementia using the Uniform Data Set (UDS), collected by National Alzheimer's Coordinating Center (NACC) from 29 Alzheimer's Disease Centers (ADCs) throughout the United States. The test under evaluation is the Mini Mental State Examination (MMSE), which is a brief 30-point questionnaire test used to screen for cognitive impairment with lower score indicating more severe impairment. **Conclusions:** Our theoretical and empirical studies show that our newly proposed quantile-based statistical methods for estimating covariate-specific ROC curves greatly outperform the existing methods.

O3

Incident Parkinson Disease and *LINE-1* DNA Methylation: A Case-Control Study

S. Searles Nielsen, H. Checkoway, R. Butler, H. Nelson, F. Farin, W.T. Longstreth, Jr., G. Franklin, P. Swanson, K. Kelsey

Seattle, Wash. and Providence, R.I., USA

Objective: To assess whether Parkinson disease (PD) is associated with methylation of long interspersed nucleotide element-1 (*LINE-1*) retrotransposons. **Background:** Parkinson disease (PD) is a neurodegenerative disorder associated with a reduced number of dopaminergic neurons in the substantia nigra. *LINE-1* retrotransposons may mobilize during neurodevelopment, and are hypothesized to lead to apoptosis of neural precursor cells. *LINE-1* methylation may influence mobility of these retrotransposons, yet the relation between PD and *LINE-1* methylation remains unexplored. **Methods:** In a case-control study of incident PD in non-Hispanic Caucasians from western Washington State, we assessed *LINE-1* methylation from leukocytes obtained shortly after diagnosis in 1992–2008 (292 cases and 401 unrelated neurologically normal controls). We used multivariate regression adjusting for sex and age to examine the relation between PD and *LINE-1* methylation, tobacco smoking and other factors. **Results:** Overall, PD was not associated with *LINE-1* methylation. However, the relationship between *LINE-1* methylation and selected environmental factors differed between cases and controls. Notably, ever regularly smoking tobacco was associated with decreased *LINE-1* methylation in controls (linear regression $\beta = -0.24$, 95% CI $-0.43, -0.04$)

but not cases ($\beta=0.06$, 95% CI -0.17 , 0.28 , interaction p-value 0.06). **Conclusions:** Individuals predisposed to develop PD may possibly have innate differences in their ability to respond to environmental exposures, including tobacco smoke. Studies with prospectively obtained DNA will be required to confirm that these initial results are not due to chance or a secondary effect of PD or its treatment on *LINE-1* methylation. Studies of PD and methylation of smoking-related genes may also prove useful.

O4

Impact of Duration and Age at Onset of Hypertension on Cognition in Older Men

M. Power, E. Tchetgen, J. Schwartz, M. Weisskopf

Boston, Mass., USA

Objective: Our objective was to illustrate the impact of hypertension on cognition in older adults as a function of duration and age at onset of hypertension after inverse-probability weighting to mitigate the influence of dependent censoring. **Background:** The apparent age-dependent association between hypertension and cognition suggests that hypertension may differently impact cognition depending on age at onset and duration. **Methods:** Our study sample includes 1284 participants from the Normative Aging Study, which began in 1963, who were under 45 and free of hypertension at baseline. Participants underwent medical examination, including assessment of hypertension, roughly every 4 years. 758 completed cognitive testing between 1993 and 2005. Using linear marginal structural models with inverse probability weighting for censoring and confounding, we estimated the independent associations of age at onset and duration of hypertension on mean age-standardized cognitive test z-score at the first cognitive assessment. **Results:** Converting to hypertension at any point during follow-up was associated with a 0.14 point lower mean cognitive test z-score (95% confidence interval (CI): -0.26 , -0.02). Within the range of our data, the contribution of duration was twice as strong (Beta: -0.02 per year of duration, 95%CI: -0.04 , -0.003) as the contribution of age at onset (Beta: -0.01 per year of age, 95%CI: -0.03 , 0.01). After inverse probability weighting for dependent censoring, increasing duration of hypertension is a strong predictor of lower cognition. **Conclusions:** While we cannot conclusively rule out a possible independent effect of age at onset, especially at ages beyond the range of our data, we found little support for one.

O5

Mild Cognitive Incidence and Long-Term Mortality in an Elderly Population-Based Survey (NEDICES)

A. Sánchez-Ferro, R. Trincado, I. Contador, A.J. Mitchell, V. Puertas-Martín, A. Villarejo, J. Benito-León, F. Bermejo-Pareja

Madrid and Salamanca, Spain, Leicester, United Kingdom

Introduction: Mild Cognitive Impairment (MCI) has more than 15 definitions in Medline literature. We aimed to define MCI by means of a Spanish adaptation of MMSE (MMSE-37) and normal IADL with (Spanish adaptation of FAQ of Pfeffer) and compare its mortality risk. **Methods:** We evaluated the Neurological Disorders in Central Spain cohort (NEDICES) participants in two different cross-sectional surveys (1994–1995 and 1997–1998). We excluded all demented subjects as well as those with MCI diagnoses (prevalent cases) at baseline (1994–1995). We made two MCI definitions based on a) psychometric classification as it was performed in the baseline survey (by cognitive categories 1.5 SD below the mean of the cohort) and b) clinical criteria. We addressed the mortality of these groups with a Cox-proportional hazard model. **Results:** The final sample included 1,697 participants of whom 470 subjects could be classified as MCI without considering the subjective complain (incidence rate 82.2 cases per 1,000 person-years) or 186 with it (32.8 cases per 1,000 person-years). When a more stringent psychometric criteria were applied only 61 patients (12.4 cases per 1,000 person-years) remained as MCI (50.8% pure amnesic, 26.2% amnesic multidomain and 23% Non amnesic). Mortality risk was increased in some MCI groups. **Conclusions:** Depending on the classification used different incident figures could be estimated and long term prognosis of the groups changed. Mortality risk is increased in some groups of MCI persons, but not all, and it depends on the classification system used. Identifying which subjects are at increased risk of mortality could help to refine the definition of MCI in epidemiological studies.

O6

Incidence of Primary Brain Tumours Among the Adult Population of Emilia Romagna Region, Italy

R. D'Alessandro, F. Albani, S. Ferro, E. Baldin, S. Testoni, S. de Pasqua, A. Brandes, A. Baruzzi

Bologna, Italy

Objective: To set up a prospective Registry and to estimate the incidence and prognosis of primary brain tumours (PBT) of the neuroepithelial group among the adult population of the Emilia-Romagna Region (3,983,346 inhabitants). **Background:** There are no prospective studies on the incidence of PBT among large populations in Italy. **Methods:** Specialists in neurology, neuroradiology, neurosurgery, oncology, radiotherapy, biomolecular and anatomical pathology, and genetics throughout the Region were invited use the project website (www.perno.it) to notify all new adult cases of suspect PBT observed from 1st January 2009 and living in the

Emilia Romagna region. Clinical findings allowing the final diagnosis were then collected from original clinical records. ICD discharge codes from hospitals of Region and neighbouring areas from 1st January 2009 to 31st March 2010 were also reviewed. PBT diagnosis was based on histological confirmation or typical radiological findings with no evidence of cancer elsewhere. **Results:** Four hundred and sixteen cases (239 men, 177 women) of PBT were recorded from 1st January to 31st December 2009. Of these 109 were identified from ICD discharge codes. Histological confirmation was obtained in 236 cases (56%). Of these, 151 (63%) were diagnosed as glioblastoma (GBM) and 85 as other neuroepithelial tumours (37%). One hundred and eighty patients had a clinical and radiological diagnosis only. Of these, 124 (66%) showed features of high grade gliomas. Patients identified from ICD codes were older (73 vs 63 years) and more often women (50% vs 40%). The PBT 2009 incidence rate/100,000 persons/year was 10.4 (95% CI: 9.4–11.5), higher in men (12.4 95%CI: 10.9–14.1) than in women (8.6 95%CI: 7.4–10). **Conclusions:** Our PBT incidence rates are among the highest reported. GBM is the most common tumour type. Elderly patients and women may be under-reported in prospective studies.

O7

Prospective Longitudinal Validation Over Time of Clinical Disease Trajectory [CDT] in Amyotrophic Lateral Sclerosis [ALS] Patients by 'ALS Dashboard' Containing Cognitive – Behavior (Depression – Pseudobulbar Affect [PBA]) – Bulbar – Respiratory – Arm – Leg Domains – Rate of Leg and Arm Domain Clinical Stage Changes Per Patient Is Statistically Greater Than Respiratory or Bulbar Stage Changes

B. Rix Brooks

Charlotte, N.C., USA

Background: CDT is currently evaluated per-patient by ALS Functional Rating Scale-Revised (ALSFERS-R) without attention to cognitive and behavioral (depression/pseudobulbar affect-PBA) domains that are not included in current proposed staging algorithms. **Objective:** Assess CDT with 'ALS Dashboard' longitudinally to define differences in rate of clinical stage changes in different domains. **Setting:** Multidisciplinary ALS Clinic. **Methods:** ALS patients [199/263], categorized as El Escorial Criteria Clinically Definite (EECD) [90] or Awaji-Shima Criteria Clinically Definite (ASCD) [109] were staged longitudinally according to ALS Dashboard criteria. **Results:** At diagnostic visit in EECD/ASCD ALS > stage-3 cognitive [8.9% / 13.8%] and respiratory dysfunction [7.8% / 4.6%] was similar, but > stage-3 PBA [11.1% / 2.8%; $p=0.0400$], depression [25.6% / 10.0%; $p=0.007$], bulbar-dysfunction [45.6% / 13.8%; $p=0.0001$], arm-dysfunction [35.6% / 8.3%; $p=0.0001$], leg-dysfunction [55.6% / 33.9%; $p=0.0040$] were significantly increased in EECD-ALS. ALS Dashboard identifies earlier development of Affect-Bulbar-Arm-Leg, but not Cognitive-Respiratory > stage-3 disease in EECD- than ASCD-ALS patients with subsequent faster progression in EECD-ALS patients. Development of increased Leg clinical stages [0.22 + 0.09

(SD) stages per patient per 3 months] was identical with increased Arm clinical stages [0.18 + 0.10] but statistically increased [$p=0.0495$] compared with increased Bulbar clinical stages [0.10 + 0.09] and increased Respiratory clinical stages [0.03 + 0.03] post diagnostic visit. **Conclusion:** ALS Dashboard is a novel tool for analyzing accumulation of disease severity within a single patient and across different patients. ALS severity in some, but not all domains, segregates differently with a higher proportion of > stage-3 Leg-Arm-Bulbar disease in EECD than ASCD ALS. The prospective rate of development of advanced leg and arm stages was statistically greater than the development of bulbar and respiratory stages. ALS Dashboard provides description of ALS milestone changes that permits more precision in comparing domains involved than rates of disability measured by ALSFRS-R.

O8

Family History of Multiple Sclerosis in Saskatoon

W.J. Hader

Saskatoon, Sask., Canada

Objectives: To identify the frequency of MS persons who have affected family members, to compare the clinical characteristics and estimate the probability of survival after onset between the familial and sporadic cases of Multiple Sclerosis. **Background:** A population-based prevalent cohort of 150 clinical definite cases ascertained on 1 January 1977 in Saskatoon Saskatchewan, was followed for 35 years. The familial rate was reported as 17.3% on prevalence date. **Methods:** The cohort was reviewed each decade and records maintained. The search for relatives continued until January 2012. Family relationships, disability outcomes according to Kurtzke Disability Status Scale, and survival times were estimated. SPSS V19 and Kaplan-Meier were used for analysis. **Results:** Of the 150 patients, 49 non-related cases (32.7%) reported 86 relatives with MS, 13/48 men and 36/102 women. There were 41/86 (47.7%) close relatives and 45/86 (53.3%) distant relatives (1st, 2nd, 3rd cousins). 18 families had 2 or more relatives with MS. The average age of onset of sporadic men was 33.9 ± 10 years and 27.6 ± 8.4 years for familial cases and 29.3 ± 8.3 years and 26.8 ± 8.5 years for women. ($P=.017$) After 35 years 29 (19.3%) cases, 9 men and 20 women have survived. 13/29 (44.8%) were familial cases. There were 16 cases DSS ≤ 6, of which 3/6 men and 6/10 women were familial and 13 cases DSS > 6, including 0/3 men and 4/10 women familial cases. The median survival after onset for sporadic and familial men was 33 (CI 26.1–39.9) and 35 (CI 17.4–52.6) years, and 36 (CI 32.7–39.3) and 51 (CI 45.4–56.2) years for women. ($P<.001$) The mean duration of life for sporadic and familial men was 64.6 and 62.9 years, and 63.2 and 70.9 years for women. **Conclusion:** This longitudinal natural history study reveals a high aggregation of familial cases and supports a genetic influence in the etiology of Multiple Sclerosis.

Long-Term Survival of Amyotrophic Lateral Sclerosis: A Population-Based Study*E. Pupillo, P. Messina, A. Millul, E. Beghi*

Milano, Italy

Objective: To calculate the survival rate of amyotrophic lateral sclerosis (ALS) in a population-based cohort of newly diagnosed patients. **Background:** Few reports have been published on the long-term survival of ALS in large representative samples of the general population. **Methods:** All consecutive patients from a population-based registry during the years 1998 through 2002 in nine provinces of Lombardy, Northern Italy (population 4,947,554) were followed until death or to March 29 2012, whichever came first. Age, sex, date of onset of symptoms, site of onset (bulbar/generalized vs. spinal), date of diagnosis, and El-Escorial diagnostic category were collected. Survival was assessed using Kaplan-Meier curves. Comparisons were made with the log-rank test. The Cox's proportional hazards function was used to identify independent prognostic predictors. **Results:** Included were 517 patients (224 women and 293 men aged 18 to 92 years). Spinal-onset ALS was present in 335 cases (64.8%). The mean (SD) disease duration at diagnosis was 10.6 (9.4) months. Definite ALS was diagnosed in 231 cases (44.7%), probable ALS in 138 (26.7%), probable laboratory supported ALS in 18 (3.5%), possible ALS in 79 (15.3%), and suspected ALS in 51 (9.9%). Fifteen cases were later excluded because they were duplicate (7), the date of the diagnosis was unknown (6), or the diagnosis was outside the study period (2). The cumulative time-dependent survival at 1, 5, and 10 years was 77.3, 25.2, and 13.7%. Independent predictors were age (<45yr vs. >75yr, HR=3.42, 95% CI: 2.21–5.29), El-Escorial category (suspected vs. definite ALS, HR=1.49; 1.05–2.12), onset (spinal vs. bulbar/generalized, HR=1.30; 1.06–1.60) and gender (men vs. women HR=1.24; 1.01–1.51). Compared to older women with bulbar-onset ALS, younger men with spinal-onset ALS have an HR of 8.97 (3.64–22.10). **Conclusions:** The outcome of ALS varies with ALS phenotype. Longer survival is predicted by younger age, spinal onset and male gender.

- Albani, F. 199
- Baldin, E. 199
- Baruzzi, A. 199
- Beghi, E. 198, 201
- Benedetti, M.D. 198
- Benito-León, J. 199
- Bermejo-Pareja, F. 199
- Brandes, A. 199
- Butler, R. 198
- Checkoway, H. 198
- Chiò, A. 198
- Contador, I. 199
- D'Alessandro, R. 198, 199
- de Pasqua, S. 199
- Duan, X. 198
- Farin, F. 198
- Ferro, S. 199
- Filippini, G. 198
- Franklin, G. 198
- Galeotti, F. 198
- Hader, W.J. 200
- Kelsey, K. 198
- Logroscino, G. 198
- Longstreth, W.T., Jr. 198
- Massari, M. 198
- Messina, P. 201
- Millul, A. 201
- Mitchell, A.J. 199
- Nelson, H. 198
- Power, M. 199
- Puertas-Martín, V. 199
- Pugliatti, M. 198
- Pupillo, E. 201
- Raschetti, R. 198
- Rix Brooks, B. 200
- Sánchez-Ferro, A. 199
- Santuccio, C. 198
- Schwartz, J. 199
- Searles Nielsen, S. 198
- Swanson, P. 198
- Tchetgen, E. 199
- Testoni, S. 199
- Trincado, R. 199
- Villarejo, A. 199
- Weisskopf, M. 199
- Zhou, X.H.A. 198