405. Methodology in epidemiologic research

P3956
Estimating parameters in the two-compartment model of exhaled nitric oxide
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Introduction: The fractional concentration of exhaled nitric oxide (FeNO) is a biomarker of airway inflammation. FeNO decreases with increasing flow, which has led to the development of mathematical models whose parameters quantify proximal and distal sources. FeNO measured at the conventional 50 ml/s flow rate is primarily from proximal sources, so the parameters may provide additional insight. Parameters are estimated from FeNO data measured at multiple flow rates, but there is no standard estimation method.

Aims and objectives: To evaluate and compare a comprehensive set of existing and novel regression-based estimators of parameters from the two-compartment model of exhaled nitric oxide.

Methods: We used simulated multiple flow datasets to assess the statistical properties of the estimators and multiple flow datasets from 1507 schoolchildren from the Southern California Children’s Health Study (CHS) to investigate regression model fit and the sensitivity of estimates across models.

Results: A novel non-linear least squares model with log transformation fit CHS participant datasets very well (median adjusted R2 = 0.99), satisfied model assumptions (homoskedasticity), and produced estimators with good statistical properties (e.g., negligible bias). In the CHS, alveolar NO concentration (CaNO) estimates were only moderately correlated across estimation methods whereas bronchial flow estimates were highly correlated.

Conclusions: Since CA NO estimation is a key result of multiple flow FeNO analysis, the sensitivity of CA NO estimates highlights the need for standardized methods. No gold standard is available to validate parameter estimators but our work can guide the selection of estimators in future studies.

P3957
Screening for alpha-1 antitrypsin deficiency in Germany – Update 2012
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Background: Alpha-1 antitrypsin deficiency (AATD) is characterized by decreased serum levels of alpha-1 antitrypsin (AAT). The most common clinical manifestations are pulmonary emphysema and liver cirrhosis. Epidemiological estimates postulate around 8000 people in Germany with a severe AATD. Although current guidelines stress the importance of screening for AATD, the majority of patients remains undetected.

Aim: To provide recent screening data from the German central laboratory for AATD in Marburg, Germany.

Methods: From dried blood spot (DBS) samples we performed AAT measurements (for internal use only) and genotyping for S and Z alleles. When either of both tests was suggestive for AATD we went on to perform phenotyping by IEF. When phenotyping resulted in bands suggestive for rare deficiency alleles we conducted complete sequencing of the AAT gene.

Results: In the period from August 2003 to February 2012 more than 50,000 test kits had been requested of which 13,010 kits have been returned. Of these, 75 were not evaluable, and 185 samples had already been submitted before. Our results are based on 12,750 analyzed samples. In descending order of frequency, we have diagnosed the following phenotypes: PIMM (8577, 67.6%), PMZ (2383, 18.6%), FIZZ (846, 6.6%), PMR (637, 4.9%), F SSR (192, 1.51%), FSS (38, 0.29%). 140 samples were submitted to gene sequencing. Here we found 75 rare (R) genotypes (PSZR 59; PMR 10; PSSR 4; PI RR 2).

Conclusion: Almost a third (32.73%) of the submitted samples was found to represent at least a carrier status, and over 8% carried a genotype that is associated with a severe AATD. We conclude that screening is useful to detect AATD and should be expanded in Germany.

P3958
Normality ranges of urine oxidative stress markers (8-OHdG and isoprostane) in Italian people free from respiratory diseases – Preliminary results
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Background: The study of oxidative stress (OxS) is becoming increasingly im-
portant in respiratory disease research. To our knowledge, the reference ranges of urinary 8-hydroxy-deoxyguanosine (8-OHdG) and 8-isoprostane (isoprostane), a DNA and a lipid oxidation product respectively, have not yet been determined in subjects without respiratory diseases.

**Aim:** To assess the reference range of OxS markers in Italian people aged 20-64 free from respiratory diseases (controls).

**Methods:** 8-OHdG and isoprostane were measured in spot-urine samples collected in the frame of Gene-Environment Interactions in Respiratory Diseases (GEIRD) study, a nested multi-case control survey. The biomarkers levels were corrected on urine volume. Controls only were considered for the aim of this work. The possible effects of potential determinants on OxS-biomarkers were studied before determining the normality range in selected subgroups of controls. Multiple linear regression was fitted to data using the logarithm of 8OHdG or isoprostane as dependent variables and sex, age, season, smoking, body mass index as covariates. The appropriate percentiles were calculated.

**Results:** Both SOHdG and isoprostane concentrations were significantly higher in smokers than in non smokers (p=0.025 and 0.047 respectively), while the other covariates did not influence OxS. The 95% SOHdG normality range in non smokers varied from 0.26 to 25.94 ng/ml. The 95% isoprostane reference interval was 0.03-5.42 ng/ml in non smokers.

**Conclusion:** Provisional 95% normality range for urinary 8OHdG and isoprostane were determined in subjects free from respiratory diseases.

**P3959**

Levels of cat, grass and mite specific IgE and symptoms on specific exposure

**Methods:** 8-OHdG and isoprostane were measured in spot-urine samples collected in the frame of Gene-Environment Interactions in Respiratory Diseases (GEIRD) study, a nested multi-case control survey. The biomarkers levels were corrected on urine volume. Controls only were considered for the aim of this work. The possible effects of potential determinants on OxS-biomarkers were studied before determining the normality range in selected subgroups of controls. Multiple linear regression was fitted to data using the logarithm of 8OHdG or isoprostane as dependent variables and sex, age, season, smoking, body mass index as covariates. The appropriate percentiles were calculated.

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**P3961**

Efficacy of COPD detection by using a community-based annual screening program for lung cancer

**Methods:** 8-OHdG and isoprostane were measured in spot-urine samples collected in the frame of Gene-Environment Interactions in Respiratory Diseases (GEIRD) study, a nested multi-case control survey. The biomarkers levels were corrected on urine volume. Controls only were considered for the aim of this work. The possible effects of potential determinants on OxS-biomarkers were studied before determining the normality range in selected subgroups of controls. Multiple linear regression was fitted to data using the logarithm of 8OHdG or isoprostane as dependent variables and sex, age, season, smoking, body mass index as covariates. The appropriate percentiles were calculated.

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**P3962**

Computed tomography of the parasinal sinuses in chronic obstructive pulmonary disease

**Methods:** 8-OHdG and isoprostane were measured in spot-urine samples collected in the frame of Gene-Environment Interactions in Respiratory Diseases (GEIRD) study, a nested multi-case control survey. The biomarkers levels were corrected on urine volume. Controls only were considered for the aim of this work. The possible effects of potential determinants on OxS-biomarkers were studied before determining the normality range in selected subgroups of controls. Multiple linear regression was fitted to data using the logarithm of 8OHdG or isoprostane as dependent variables and sex, age, season, smoking, body mass index as covariates. The appropriate percentiles were calculated.

**Results:** Both SOHdG and isoprostane concentrations were significantly higher in smokers than in non smokers (p=0.025 and 0.047 respectively), while the other covariates did not influence OxS. The 95% SOHdG normality range in non smokers varied from 0.26 to 25.94 ng/ml. The 95% isoprostane reference interval was 0.03-5.42 ng/ml in non smokers.

**Conclusion:** Provisional 95% normality range for urinary 8OHdG and isoprostane were determined in subjects free from respiratory diseases.
Our results provide evidence for the benefit of the intervention in patients with mild-to-moderate COPD. The bronchodilator effect was maintained over 24 hours, and the improvement in lung function was associated with a reduction in respiratory symptoms and an improvement in quality of life. The findings suggest that the bronchodilator cocktail may be an effective and safe treatment option for patients with mild-to-moderate COPD, and further studies are needed to evaluate its long-term efficacy and safety.
P3968
Newly developed simple QoL questionnaire in early detection of COPD in a population of smokers at risk for COPD development

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Aim: Assessing the role of a simple newly developed Qol questionnaire (MARKOQ) in early detection of COPD in a population at risk for COPD.

Methods: MARKOQ is a self-administered questionnaire with 18 questions. Subjects were smokers with ≥20 pack-years, both gender, 40-65 yrs of age, with no diagnosis of COPD. They were referred to a pulmonologist (history, physical, lung function) for diagnosis of COPD and the staging. MARKOQ was administered twice: at primary care clinic and 2-4 weeks later at a pulmology clinic.

Results: Sample included 219 consecutive subjects (48.5% male), mean (SD) age 52.6 (6.9) yrs with 30.8 (17.4) pack-years. 25.3% were diagnosed as COPD (stage I: 21.8%, stage II: 3.6%, stage III: 10.7%, stage IV: 9.2%). Chronic respiratory symptoms showed very good internal consistency of MARKOQ (Cronbach's alpha=0.89) and test-retest reliability (r=0.84). The correlation with CAT scores was r=0.54. MARKOQ significantly discriminated (F=4.0, p<0.001) patients with GOLD stage II or higher (mean=19.9, SD=8.7) from those in stage I (mean=12.9, SD=10.1) and "healthy smokers" (mean=12.9, SD=8.4) (CAT scores were not discriminative). Correlations of MARKOQ scores were only significant for FEV1%. (r=0.22, p<0.003).

Conclusions: The MARKOQ developed for an early detection of COPD may be able to detect early changes in QoL complementary to lung function impairment. The exact validity of the MARKOQ will be known after the release of the questionnaire.

P3969
External multicentric validation of a COPD detection questionnaire

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Introduction: Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. The development of a simple questionnaire can help to improve the diagnosis.

Objective: External validation of the questionnaire to detect COPD in Argentina.

Material and Methods: We performed a questionnaire in subjects with over 40 years old and history of smoking ≥ 10 or more pack/year. Demographic data and pre and post bronchodilator spirometry were performed. Subjects with previous diagnosis of COPD or asthma were excluded.

Results: 468 subjects were evaluated.100 (21.1%) had spirometric diagnosis of COPD. In univariate analysis patients with COPD had higher median age (58 years vs 54 years, p < 0.001), pack years (PY) smoked (40 vs 30, p < 0.001), lower BMI (26 vs 28, p = 0.02), higher incidence of males (68.8% vs 43.9%, p < 0.001), cough for 3 months (55.2% vs 33.8%, p < 0.001), chronic cough (47.9% vs 28.8%, p < 0.001), phlegm for 3 months (56% vs 37.2, p = 0.02), chronic phlegm (40.6% vs 26.1%, p = 0.005), dyspnea (62.5% vs 51.9%, p = 0.06), wheezing (55.2% vs 47%, p = 0.15), wheezing without infection (38.5% vs 33.9%, p = 0.39), stote at home (10.4% vs 7.5%, p = 0.35) and risk profession (19.8% vs 18.5%, p = 0.78). The presence of at least 3 of these variables had a sensitivity of 95% and a specificity of 25.29%, positive predictive value (PPV) of 22.62% and negative predictive value (NPV) of 95.65%. The presence of at least 6 variables had a sensitivity of 90% and a specificity of 70.97%, a PPV of 50% and a NPV of 95.65%

Conclusion: This simple questionnaire for demographic and clinical data can be useful for detection of COPD.

P3970
Childhood asthma control test: Validation of the Arabic Turkish dialect version in 51 patients

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Childhood Asthma Control Test and c-ACT was translated in different languages. We propose to validate the Arabic Turkish dialect version by checking if it’s understood by patients and their parents and the conformity with the control criteria of international recommendations. Cross-sectional study was conducted in 51 asthmatic children, aged from 4 to 11 years, followed for at least 6 months. c-ACT was administered before consultation. The level of asthma control was compared to that estimated by the expert based on GINA criteria with an evaluation period of 4 weeks. Understanding of this Arabic version has been confirmed with the patients and their parents. This version showed a satisfactory internal consistency with Cronbach’s alpha equal to 0.853. The area under the ROC curve equal to 0.993 is highly significant (p < 0.001). The c-ACT showed a significant discriminative ability of patients with different level of control of their asthma (p < 0.001). The study of the performance of c-ACT 19 point threshold, to identify children uncontrolled, found a sensitivity of 73.7% and negative predictive value of 86.5%. Considering the 20 point threshold, sensitivity and negative predictive value reached respectively 94.7% and 96.9%. There is a significant correlation (p < 0.0001) between the level of control patients detected by the c-ACT and that estimated by the specialist with a kappa coefficient equal to 0.778. Most children have understood the Arabic version of the c-ACT. This study demonstrated a good correlation between the result of c-ACT in dialectal Arabic and clinical evaluation. The usefulness of this version will be evaluated after its release.

P3971
Shortness of breath associated with chronic conditions among those with and without asthma or COPD


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Background: Some chronic conditions may result from similar underlying mechanisms or may exacerbate lung disease suggesting the investigation of inter-relationships. We sought to determine if SOB was more common among adults with chronic conditions and to examine this association among those with and without asthma or COPD.

Methods: In 2010 we conducted a cross-sectional mail survey of rural households as part of the Saskatchewan Rural Health Study. One adult per home provided information about each adult living in the home. There were 8201 adults from 4624 households (42% participation) included. We examined the associations between reported diagnosed chronic conditions (diabetes, cardiovascular disease, and sleep apnea) and SOB after adjusting for potential confounders and stratifying by history of doctor-diagnosed asthma or COPD. High SOB was defined by a score of 3+ on the MRC breathlessness scale.

Results: The respondents’ mean age was 56 years (SD=16 years) with 51% of the population being female. Approximately 14% had a MRC score ≥3. After adjustment, there was increased risk of high MRC score associated with the presence of diabetes (odds ratio (OR)=1.68, 95% confidence interval (CI)=1.32-2.14), cardiovascular disease (OR=2.18, 95%CI=1.80-2.65), and sleep apnea (OR=2.19, 95%CI=1.46-3.00). The associations with SOB were weaker among those with asthma or COPD with the exception of that for sleep apnea, which was stronger.

Conclusions: Some conditions were associated with high SOB among those with and without a history of lung disease. These relationships may result from common pathways, possibly inflammatory, and may preclude more serious chronic lung disease.

P3972
Detection of quality of life with COPD assessment test in chronic obstructive pulmonary disease and effect of dyspnea on disease-specific quality of life in these patients

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Background: The measurements for level of dyspnea such as Medical Research Council (MRC) dyspnea grade or modified Borg dyspnea scale were used common in the trials. COPD assessment test (CAT) is a recently introduced to use to disease-specific quality of life and follow-up of the patients with COPD.

Objective: We aimed that assessed effect of the dyspnea on disease-specific quality of life detected by CAT score in the patients with COPD.

Methods: In this study, 90 stable patients with COPD as defined by the GOLD criteria were included. The level of dyspnea was assessed with two different scales, MRC dyspnea scale and modified Borg dyspnea scale, and disease-specific quality of life assessed with the CAT score.

Results: Patients’ mean ± SD age was 68.5±10.9 (range 41 – 97 years). A significant relationship was established among CAT score, MRC dyspnea scale, modified Borg dyspnea scale, the GOLD stage of the patients with COPD. There

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was a positive correlation between dyspnea scales and the GOLD stage of the patients \( (p<0.001) \), and also positive correlation between CAT score and dyspnea scales \( (p<0.001) \). The CAT score and dyspnea scales had a significant correlation with hospitalization and emergency room applications \( (p<0.05) \).

**Conclusion:** It is suggested that dyspnea is an important symptom that impact the quality of life in the patients with COPD. The CAT is simple, fast and an easy intelligible measurement for the disease-specific quality of life and it is correlated with levels of dyspnea of the patients with COPD.

**P3973**

**Validation of quality of life questionnaire St George's for patients with respiratory diseases in Colombia, Latin America**

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**Background:** The SGRQ a self-administered questionnaire specific for pulmonary diseases, validated in different cultures and countries. The objective of this study was to adapt one specific scale of quality of life in patients with acute and chronic pulmonary diseases in Colombia, Latin America.

**Materials and methods:** The Spanish version of the SGRQ was applied to 277 patients with COPD and asthma; the different components and overall scores of SGRQ were described; the forced expiratory volume in one second (FEV1), % predicted FEV1, 6-minute walk test (6MWT) and SF36 were used in the assessment battery.

**Results:** The SGRQ showed Cronbach’s alpha coefficient internal consistence was 0.94 for the overall total scale, 0.89 for symptoms, 0.93 for activity and 0.89 for impact. Correlations of coefficient inter-reliability were 0.82 and intra-reliability 0.65 for the overall scores. The contents validity of the three factor structure was established: in construct validity met a slight difference between acute and chronic patients in activity with statistically and clinically significant \( (p<0.05) \). On evaluation of the concurrent validity of the SGRQ and the score of physical function \( (0.67) \), vitality \( (0.51) \) and social function \( (0.46) \) of SF36 good correlations were found. The responsiveness showed statistical differences \( (p<0.05) \) with the scores being lesser in the second measurement (better quality of life).

**Conclusions:** SGRQ version for acute and chronic patients in Colombia is psychometrically equivalent to the original version, reliable, valid and could be used in our country and Spanish speaking countries with similar ethnic, cultural and social conditions.

**P3974**

**How accurate are assessments of exacerbations through patient self-reports?**

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**Background:** Patient self-report is the most common method to ascertain COPD exacerbations but its accuracy is unknown. Low accuracy of measurements leads to underestimation of treatment effects.

**Aims and objectives:** To evaluate the accuracy of different methods to ascertain COPD exacerbations in longitudinal studies and to estimate the effect of misclassification in randomised trials.

**Methods:** We used event-based definition of exacerbations that required newly prescribed systemic corticosteroids and/or antibiotics. Methods to ascertain exacerbations in 411 primary care COPD patients from ICE COLD ERIC cohort over 3 years included (1) 6-months follow-ups and (2) review of patient charts by an experienced physician. These 2 methods were compared against reference standard of adjudication committee (AC) where 3-4 experienced physicians independently adjudicated exacerbations followed by AC meeting where consensus on final classifications was reached. We calculated sensitivity and specificity and re-estimated the effects of long-acting bronchodilators vs. placebo on exacerbations by correcting for misclassification.

**Results:** 59.6% of 411 patients had at least 1 exacerbation during the 3 years according to the AC. Patient self-reports had a sensitivity and specificity of 84% and 75%, adjudication by single physicians between 88-96% and 87-99%. The pooled relative risk reduction from meta-analysis changed from 11% (95% CI 1-29%) to 35% (4-56%) when corrected for misclassification.

**Conclusions:** Conventional methods to assess exacerbations without central adjudication are likely to underestimate treatment effects substantially. Use of central or expert adjudication could reduce sample size requirements by up to 5-fold.