Supplemental Table 4. Clean Screened (n=66)

S #		Comment	Duplicates 05	Records screened (Only Original) 06	Records screened (PEDs) 02	Not Lung, In vitro, mouse 10	No exposure assoc OAD 05	radiation and lung cancer 14	No Age r 04	Comment_ Assad	Title	Abstract	URL	Description	Details	ShortDetails	Resource	Type	Identifiers	Db	EntrezUID	Properties
1	1										Receptor for advanced glycation end-products and World Trade Center particulate induced lung function loss: A case-cohort study and murine model of acute particulate exposure.	World Trade Center-particulate matter(WTC-PM) exposure and metabolic-risk are associated with WTC-Lung Injury(WTC-LI). The receptor for advanced glycation end-products (RAGE) is most highly expressed in the lung, mediates metabolic risk, and single-nucleotide polymorphisms at the AGER-locus predict forced expiratory volume(FEV). Our objectives were to test the hypotheses that RAGE is a biomarker of WTC-LI in the FDNY-cohort and that loss of RAGE in a murine model would protect against acute PM-induced lung disease. We know from previous work that early intense exposure at the time of the WTC collapse was most predictive of WTC-LI therefore we utilized a murine model of intense acute PM-exposure to determine if loss of RAGE is protective and to identify signaling/cytokine intermediates. This study builds on a continuing effort to identify serum biomarkers that predict the development of WTC-LI. A case-cohort design was used to analyze a focused cohort of male never-smokers with normal pre-9/11 lung function. Odds of developing WTC-LI increased by 1.2, 1.8 and 1.0 in firefighters with soluble RAGE (sRAGE)≥97pg/mL, CRP≥2.4mg/L, and MMP-9≤397ng/mL, respectively, assessed in a multivariate logistic regression model (ROCAUC of 0.72). Wild type(WT) and RAGE-deficient(Ager-/-) mice were exposed to PM or PBS-control by oropharyngeal aspiration. Lung function, airway hyperreactivity, bronchoalveolar lavage, histology, transcription factors and plasma/BAL cytokines were quantified. WT-PM mice had decreased FEV and compliance, and increased airwayresistance and methacholine reactivity after 24-hours. Decreased IFN-γ and increased LPA were observed in WT-PM mice; similar findings have been reported for firefighters who eventually develop WTC-LI. In the murine model, lack of RAGE was protective from loss of lung function and airwayhyperreactivity and was associated with modulation of MAP kinases. We conclude that in a multivariate adjusted model increased sRAGE is associated with WTC-LI. In our murine model, absence of RAGEmitigated acute deleterious effects of PM and may be a biologically plausible mediator of PM-related lung disease.	/pubmed/28926576	Caraher EJ, Kwon S, Haider SH, Crowley G, Lee A, Ebrahim M, Zhang L, Chen LC, Gordon T, Liu M, Prezant DJ, Schmidt AM, Nolan A.	PLoS One. 2017 Sep 19;12(9):e0184331. doi: 10.1371/journal.pone.0184331. eCollection 2017.	PLoS One. 2017	PubMed	citation	PMID:28926576 | PMCID:PMC5604982	pubmed	28926576	create date:2017/09/20 | first author:Caraher EJ
2	1	not looking at OAD									A Pilot Study Linking Endothelial Injury in Lungs and Kidneys in Chronic Obstructive Pulmonary Disease.	RATIONALE: Patients with chronic obstructive pulmonary disease (COPD) frequently have albuminuria (indicative of renal endothelial cell injury) associated with hypoxemia. OBJECTIVES: To determine whether (1) cigarette smoke (CS)-induced pulmonary and renal endothelial cell injury explains the association between albuminuria and COPD, (2) CS-induced albuminuria is linked to increases in the oxidative stress-advanced glycation end products (AGEs) receptor for AGEs (RAGE) pathway, and (3) enalapril (which has antioxidant properties) limits the progression of pulmonary and renal injury by reducing activation of the AGEs-RAGE pathway in endothelial cells in both organs. METHODS: In 26 patients with COPD, 24 ever-smokers without COPD, 32 nonsmokers who underwent a renal biopsy or nephrectomy, and in CS-exposed mice, we assessed pathologic and ultrastructural renal lesions, and measured urinary albumin/creatinine ratios, tissue oxidative stress levels, and AGEs and RAGE levels in pulmonary and renal endothelial cells. The efficacy of enalapril on pulmonary and renal lesions was assessed in CS-exposed mice. MEASUREMENTS AND MAIN RESULTS:	/pubmed/28085500	Polverino F, Laucho-Contreras ME, Petersen H, Bijol V, Sholl LM, Choi ME, Divo M, Pinto-Plata V, Chetta A, Tesfaigzi Y, Celli BR, Owen CA.	Am J Respir Crit Care Med. 2017 Jun 1;195(11):1464-1476. doi: 10.1164/rccm.201609-1765OC.	Am J Respir Crit Care Med. 2017	PubMed	citation	PMID:28085500 | PMCID:PMC5470750	pubmed	28085500	

												Patients with COPD and/or CS-exposed mice had chronic renal injury, increased urinary albumin/creatinine ratios, and increased tissue oxidative stress and AGEs-RAGE levels in pulmonary and renal endothelial cells. Treating mice with enalapril attenuated CS-induced increases in urinary albumin/creatinine ratios, tissue oxidative stress levels, endothelial cell AGEs and RAGE levels, pulmonary and renal cell apoptosis, and the progression of chronic renal and pulmonary lesions. CONCLUSIONS: Patients with COPD and/or CS-exposed mice have pulmonary and renal endothelial cell injury linked to increased endothelial cell AGEs and RAGE levels. Albuminuria could identify patients with COPD in whom angiotensin-converting enzyme inhibitor therapy improves renal and lung function by reducing endothelial injury.									
3	1	assoc of smoking and RAGE in paper									The Ser82 RAGE Variant Affects Lung Function and Serum RAGE in Smokers and sRAGE Production In Vitro.	INTRODUCTION: Genome-Wide Association Studies have identified associations between lung function measures and Chronic Obstructive Pulmonary Disease (COPD) and chromosome region 6p21 containing the gene for the Advanced Glycation End Product Receptor (AGER, encoding RAGE). We aimed to (i) characterise RAGE expression in the lung, (ii) identify AGER transcripts, (iii) ascertain if SNP rs2070600 (Gly82Ser C/T) is associated with lung function and serum sRAGE levels and (iv) identify whether the Gly82Ser variant is functionally important in altering sRAGE levels in an airway epithelial cell model. METHODS: Immunohistochemistry was used to identify RAGE protein expression in 26 human tissues and qPCR was used to quantify AGER mRNA in lung cells. Gene expression array data was used to identify AGER expression during lung development in 38 fetal lung samples. RNA-Seq was used to identify AGER transcripts in lung cells. sRAGE levels were assessed in cells and patient serum by ELISA. BEAS2B-R1 cells were transfected to overexpress RAGE protein with either the Gly82 or Ser82 variant and sRAGE levels identified. RESULTS: Immunohistochemical assessment of 6 adult lung samples identified high RAGE expression in the alveoli of healthy adults and individuals with COPD. AGER/RAGE expression increased across developmental stages in human fetal lung at both the mRNA (38 samples) and protein levels (20 samples). Extensive AGER splicing was identified. The rs2070600T (Ser82) allele is associated with higher FEV1, FEV1/FVC and lower serum sRAGE levels in UK smokers. Using an airway epithelium model overexpressing the Gly82 or Ser82 variants we found that HMGB1 activation of the RAGE-Ser82 receptor results in lower sRAGE production. CONCLUSIONS: This study provides new information regarding the expression profile and potential role of RAGE in the human lung and shows a functional role of the Gly82Ser variant. These findings advance our understanding of the potential mechanisms underlying COPD particularly for carriers of this AGER polymorphism.	/pubmed/27755550	Miller S, Henry AP, Hodge E, Kheirallah AK, Billington CK, Rimington TL, Bhaker SK, Obeidat M, MelÃ©n E, Merid SK, Swan C, Gowland C, Nelson CP, Stewart CE, Bolton CE, Kilty I, Malarstig A, Parker SG, Moffatt MF, Wardlaw AJ, Hall IP, Sayers I.	PLoS One. 2016 Oct 18;11(10):e0164041. doi: 10.1371/journal.pone.0164041. eCollection 2016.	PLoS One. 2016	PubMed	citation	PMID:27755550 | PMCID:PMC5068780	pubmed	27755550
4	1										Associations of autophagy with lung diffusion capacity and oxygen saturation in severe COPD: effects of particulate air pollution.	Although traffic exposure has been associated with the development of COPD, the role of particulate matter <10 μm in aerodynamic diameter (PM10) in the pathogenesis of COPD is not yet fully understood. We assessed the 1-year effect of exposure to PM10 on the pathogenesis of COPD in a retrospective cohort study. We recruited 53 subjects with COPD stages III and IV and 15 healthy controls in a hospital in Taiwan. We estimated the 1-year annual mean levels of PM10 at all residential addresses of the cohort participants. Changes in PM10 for the 1-year averages in quintiles were related to diffusion capacity of the lung for carbon monoxide levels (r=-0.914, P=0.029), changes in the pulse oxygen saturation (ΔSaO2; r=-0.973, P=0.005), receptor for advanced glycation end-products (r=-0.881, P=0.048), interleukin-6 (r=0.986, P=0.002), ubiquitin (r=0.940, P=0.017), and beclin 1 (r=0.923, P=0.025) in COPD. Next, we observed that ubiquitin was correlated with ΔSaO2	/pubmed/27468231	Lee KY, Chiang LL, Ho SC, Liu WT, Chen TT, Feng PH, Su CL, Chuang KJ, Chang CC, Chuang HC.	Int J Chron Obstruct Pulmon Dis. 2016 Jul 11;11:1569-78. doi: 10.2147/COPD.S108993. eCollection 2016.	Int J Chron Obstruct Pulmon Dis. 2016	PubMed	citation	PMID:27468231 | PMCID:PMC4946865	pubmed	27468231

												(r=-0.374, P=0.019). Beclin 1 was associated with diffusion capacity of the lung for carbon monoxide (r=-0.362, P=0.028), ΔSaO2 (r=-0.354, P=0.032), and receptor for advanced glycation end-products (r=-0.471, P=0.004). Autophagy may be an important regulator of the PM10-related pathogenesis of COPD, which could cause deterioration in the lung diffusion capacity and oxygen saturation.										
5	1	studies healthy smokers									Advanced glycation endproducts and their receptor in different body compartments in COPD.	BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by chronic airway inflammation and emphysema, and is caused by exposure to noxious particles or gases, e.g. cigarette smoke. Smoking and oxidative stress lead to accelerated formation and accumulation of advanced glycation end products (AGEs), causing local tissue damage either directly or by binding the receptor for AGEs (RAGE). This study assessed the association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. METHODS: Healthy smoking and never-smoking controls (n = 191) and COPD patients (n = 97, GOLD stage I-IV) were included. Autofluorescence (SAF) was measured in the skin, AGEs (pentosidine, CML and CEL) and sRAGE in blood and sputum by ELISA, and in bronchial biopsies by immunohistochemistry. eQTL analysis was performed in bronchial biopsies. RESULTS: COPD patients showed higher SAF values and lower plasma sRAGE levels compared to controls and these values associated with decreased lung function (p <0.001; adjusting for relevant covariates). Lower plasma sRAGE levels significantly and independently predicted higher SAF values (p < 0.001). One SNP (rs2071278) was identified within a region of 50 kB flanking the AGER gene, which was associated with the gene and protein expression levels of AGER and another SNP (rs2071278) which was associated with the accumulation of AGEs in the skin. CONCLUSION: In COPD, AGEs accumulate differentially in body compartments, i.e. they accumulate in the skin, but not in plasma, sputum and bronchial biopsies. The association between lower sRAGE and higher SAF levels supports the hypothesis that the protective mechanism of sRAGE as a decoy-receptor is impaired in COPD.	/pubmed/27117828	Hoonhorst SJ, Lo Tam Loi AT, Pouwels SD, Faiz A, Telenga ED, van den Berge M, Koenderman L, Lammers JW, Boezen HM, van Oosterhout AJ, Lodewijk ME, Timens W, Postma DS, Ten Hacken NH.	Respir Res. 2016 Apr 26;17:46. doi: 10.1186/s12931-016-0363-2.	Respir Res. 2016	PubMed	citation	PMID:27117828 | PMCID:PMC4847335	pubmed	27117828
6	1										Traditional and emerging indicators of cardiovascular risk in chronic obstructive pulmonary disease.	With the increased cardiovascular (CV) morbidity and mortality in subjects with chronic obstructive pulmonary disease (COPD), there is a priority to identify those patients at increased risk of cardiovascular disease. Stable patients with COPD (n = 185) and controls with a smoking history (n = 106) underwent aortic pulse wave velocity (PWV), blood pressure (BP) and skin autofluorescence (AF) at clinical stability. Blood was sent for fasting lipids, soluble receptor for advanced glycation end products (sRAGE) and CV risk prediction scores were calculated. More patients (18%) had a self-reported history of CV disease than controls (8%), p = 0.02, whilst diabetes was similar (14% and 10%), p = 0.44. Mean (SD) skin AF was greater in patients: 3.1 (0.5) AU than controls 2.8 (0.6) AU, p < 0.001. Aortic PWV was greater in patients: 10.2 (2.3) m/s than controls: 9.6 (2.0) m/s, p = 0.02 despite similar BP. The CV risk prediction scores did not differentiate between patients and controls nor were the individual components of the scores different. The sRAGE levels were not statistically different. We present different indicators of CV risk alongside each other in well-defined subjects with and without COPD. Two non-invasive biomarkers associated with future CV burden: skin AF and aortic PWV are both significantly greater in patients with COPD compared to the controls. The traditional CV prediction scores used in the general population were not statistically different. We provide new data to suggest that alternative approaches for optimal CV risk detection should be employed in COPD management.	/pubmed/26965223	John M, McKeever TM, Haddad MA, Hall IP, Sayers I, Cockcroft JR, Bolton CE.	Chron Respir Dis. 2016 Aug;13(3):247-55. doi: 10.1177/1479972316636995. Epub 2016 Mar 10.	Chron Respir Dis. 2016	PubMed	citation	PMID:26965223 | PMCID:PMC5720186	pubmed	26965223

7	1	blood biomarkers in CT assessed emphysema (includes sRAGE), not assesses the exposure assoc OAD									The association of plasma biomarkers with computed tomography-assessed emphysema phenotypes.	RATIONALE: Chronic obstructive pulmonary disease (COPD) is a phenotypically heterogeneous disease. In COPD, the presence of emphysema is associated with increased mortality and risk of lung cancer. High resolution computed tomography (HRCT) scans are useful in quantifying emphysema but are associated with radiation exposure and high incidence of false positive findings (i.e., nodules). Using a comprehensive biomarker panel, we sought to determine if there was a peripheral blood biomarker signature of emphysema. METHODS: 114 plasma biomarkers were measured using a custom assay in 588 individuals enrolled in the COPDGene study. Quantitative emphysema measurements included percent low lung attenuation (%LAA) ≤ -950 HU, ≤ - 910 HU and mean lung attenuation at the 15th percentile on lung attenuation curve (LP15A). Multiple regression analysis was performed to determine plasma biomarkers associated with emphysema independent of covariates age, gender, smoking status, body mass index and FEV1. The findings were subsequently validated using baseline blood samples from a separate cohort of 388 subjects enrolled in the Treatment of Emphysema with a Selective Retinoid Agonist (TESRA) study. RESULTS: Regression analysis identified multiple biomarkers associated with CT-assessed emphysema in COPDGene, including advanced glycosylation end-products receptor (AGER or RAGE, $p < 0.001$), intercellular adhesion molecule 1 (ICAM, $p < 0.001$), and chemokine ligand 20 (CCL20, $p < 0.001$). Validation in the TESRA cohort revealed significant associations with RAGE, ICAM1, and CCL20 with radiologic emphysema ($p < 0.001$ after meta-analysis). Other biomarkers that were associated with emphysema include CDH1, CDH 13 and SERPINA7, but were not available for validation in the TESRA study. Receiver operating characteristics analysis demonstrated a benefit of adding a biomarker panel to clinical covariates for detecting emphysema, especially in those without severe airflow limitation (AUC 0.85). CONCLUSIONS: Our findings, suggest that a panel of blood biomarkers including sRAGE, ICAM1 and CCL20 may serve as a useful surrogate measure of emphysema, and when combined with clinical covariates, may be useful clinically in predicting the presence of emphysema compared to just using covariates alone, especially in those with less severe COPD. Ultimately biomarkers may shed light on disease pathogenesis, providing targets for new treatments.	/pubmed/25306249	Carolan BJ, Hughes G, Morrow J, Hersh CP, O'Neal WK, Rennard S, Pillai SG, Belloni P, Cockayne DA, Comellas AP, Han M, Zemans RL, Kechris K, Bowler RP.	Respir Res. 2014 Oct 12;15:127. doi: 10.1186/s12931-014-0127-9.	Respir Res. 2014	PubMed	citation	PMID:25306249 | PMCID:PMC4198701	pubmed	25306249
8	1										Soluble receptor for advanced glycation end-products and progression of airway disease.	BACKGROUND: The receptor for advanced glycation end-products (RAGE) is highly expressed in the lung, where it is believed to have a homeostatic role. Reduced plasma levels of soluble RAGE (sRAGE) have been reported in patients with chronic obstructive pulmonary disease (COPD). The aim of the present study was to evaluate the association of plasma sRAGE levels with a longitudinal decline of lung function. We have also measured plasma levels of high mobility group box 1 (HMGB1), a RAGE ligand which has been associated with chronic inflammatory diseases including COPD. METHODS: Baseline plasma concentrations of sRAGE and HMGB1 were measured in non-smokers (n = 32), smokers without COPD (n = 212), and smokers with COPD (n = 51), and the associations of the plasma sRAGE and HMGB1 levels with longitudinal declines of lung function during a 4-year follow-up period were analysed. RESULTS: The plasma levels of sRAGE were significantly lower in smokers without COPD and in smokers with COPD, as compared to those of non-smokers. Plasma sRAGE levels positively correlated with FVC and FEV1 and inversely correlated with BMI and pack-years. Lower sRAGE	/pubmed/24758342	Iwamoto H, Gao J, Pulkkinen V, Toljamo T, Nieminen P, Mazur W.	BMC Pulm Med. 2014 Apr 24;14:68. doi: 10.1186/1471-2466-14-68.	BMC Pulm Med. 2014	PubMed	citation	PMID:24758342 | PMCID:PMC4021457	pubmed	24758342

											levels were associated with greater declines of FEV1/FVC over 4 years in all participants. Moreover, multivariate regression analysis indicated that the baseline plasma sRAGE concentration was an independent predictor of FEV1/FVC decline in all groups. A subgroup analysis showed that decreased sRAGE levels are significantly associated with a more rapid decline of FEV1/FVC in smokers with COPD. There was no significant correlation between plasma HMGB1 levels and longitudinal decline of lung function. CONCLUSIONS: Lower plasma concentrations of sRAGE were associated with greater progression of airflow limitations over time, especially in smokers with COPD, suggesting that RAGE might have a protective role in the lung.									
9	1										Overexpression of RAGE contributes to cigarette smoke-induced nitric oxide generation in COPD.	BACKGROUND: Receptor for advanced glycation end products (RAGE), a multiple-ligands receptor, is implicated in chronic obstructive pulmonary disease (COPD). This study was designed to investigate the potential role of RAGE in nitric oxide (NO) generation, an endogenous marker of nitrosative stress in COPD. METHODS: Lung tissues from COPD patients were used to describe the relationship between RAGE expression and NO level. RAGE expression was assessed by immunohistochemistry, western blot, and ELISA. Human bronchial epithelial cells (16HBE) were cultured with cigarette smoke extract (CSE). Neutralizing antibody against RAGE was used to detect the role of RAGE in CSE-induced NO generation by 16HBE cells. RESULTS: Compared with nonsmoker controls, overexpression of RAGE was significantly detected in COPD smokers ($p < 0.01$), but not healthy smokers and nonsmokers with COPD, which was dominantly expressed at bronchiolar epithelia. Correlation analysis showed that RAGE in COPD smokers was positively related to NO level, smoking status, and lung function decline. In cultured 16HBE cells treated with CSE, soluble RAGE was reduced; however, full-length RAGE was enhanced significantly as the same trend as NO generation. Moreover, increased NO level and NO synthase activity, decreased total glutathione (a major cellular antioxidant), enhanced nuclear translocation of p65 (a key molecule of nuclear factor (NF)-κB) and release of NF-κB-dependent proinflammatory cytokines were all reversed by pretreatment of anti-RAGE antibody. CONCLUSIONS: These findings suggest that overexpression of RAGE contributes to CS-induced NO generation in COPD with involvement in NF-κB activation.	/pubmed/24535058	Chen L, Wang T, Guo L, Shen Y, Yang T, Wan C, Liao Z, Xu D, Wen F.	Lung. 2014 Apr;192(2):267-75. doi: 10.1007/s00408-014-9561-1. Epub 2014 Feb 18.	Lung. 2014	PubMed	citation	PMID:24535058	pubmed	24535058
10	1	somking assoc COPD compared with healthy controls									Association of polymorphisms of the receptor for advanced glycation end products gene with COPD in the Chinese population.	The receptor for advanced glycation end products (RAGE) is a cell surface molecule of the immunoglobulin superfamily that binds diverse endogenous ligands involved in the development of chronic diseases and inflammatory damage. A growing body of evidence has suggested that RAGE is involved in the development and progression of chronic obstructive pulmonary disease (COPD). The present study investigated the existence of an association among three polymorphisms (-374T/A, -429T/C, and G82S) of the RAGE gene with the risk of COPD in the Chinese population. The RAGE genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism in 216 patients with COPD and 239 age-matched healthy individuals. Our study demonstrated that the frequencies of the GS genotype and the S allele in the G82S mutation were significantly higher in COPD patients than in controls (odds ratios [OR]=1.70, 95% confidence interval [CI]: 1.15-2.50, p=0.0098 and OR=1.42, 95% CI: 1.06-1.91, p=0.023, respectively). Further stratification analysis by smoking status revealed that the presence of the GS genotype conferred a higher risk of developing COPD in current smokers (p=0.044). In contrast, mutations at -374T/A and -	/pubmed/24520905	Li Y, Yang C, Ma G, Gu X, Chen M, Chen Y, Zhao B, Cui L, Li K.	DNA Cell Biol. 2014 Apr;33(4):251-8. doi: 10.1089/dna.2013.2303. Epub 2014 Feb 12.	DNA Cell Biol. 2014	PubMed	citation	PMID:24520905 | PMCID:PMC3967375	pubmed	24520905

											429T/C did not demonstrate any association with COPD, even after taking into account the patients' smoking history. Our study provides preliminary evidence that the G82S polymorphism in the RAGE gene is associated with an increased risk of COPD and that the GS genotype of the G82S variant is a risk factor for COPD in the Chinese population.										
11	1	somking assoc COPD compared with healthy controls (eclipse)									The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study.	BACKGROUND: Emphysema is a key contributor to airflow limitation in chronic obstructive pulmonary disease (COPD) and can be quantified using CT scanning. We investigated the change in CT lung density in a longitudinal, international cohort of patients with COPD. We also explored the potential relation between emphysema and patient characteristics, and investigated if certain circulating biomarkers were associated with decline in CT lung density. METHODS: We used a random coefficient model to assess predictors of both CT lung density and its longitudinal change over 3 years in 1928 patients with COPD enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study. Lung density was measured for every voxel in the CT scan and after correcting for lung volume was expressed as the density at lowest 15th percentile point of the distribution. This study is registered with ClinicalTrials.gov, number NCT00292552. FINDINGS: Lung density at baseline was influenced by age, sex, body-mass index, current smoking status and smoking history, and severity of airflow limitation. The observed decline in lung density was variable (mean decline -1·13 g/L [SE 0·06] per year). The annual decline in lung density was more rapid in women (additional -0·41 [SE 0·14] g/L per year, p=0·003) than men and in current smokers (additional -0·29 [SE 0·14] g/L per year, p=0·047) than in former smokers. Circulating levels of the biomarkers surfactant protein D (SP-D) and soluble receptor for advanced glycation endproduct (sRAGE) were significantly associated with both baseline lung density and its decline over time. INTERPRETATION: This study shows that decline in lung density in COPD can be measured, that it is variable, and related to smoking and gender. We identified potential biochemical predictors of the presence and progression of emphysema.	/pubmed/24429093	Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Crim C, Duvoix A, Fauerbach PN, Lomas DA, Macnee W, Mayer RJ, Miller BE, MÃ¼ller NL, Rennard SI, Silverman EK, Tal-Singer R, Wouters EF, Vestbo J; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators..	Lancet Respir Med. 2013 Apr;1(2):129-36. doi: 10.1016/S2213-2600(13)70006-7. Epub 2013 Feb 1.	Lancet Respir Med. 2013	PubMed	citation	PMID:24429093	pubmed	24429093
12	1										The receptor for advanced glycation end products and its ligands: a new inflammatory pathway in lung disease?	The binding of the receptor for advanced glycation end products (RAGE) with its ligands begins a sustained period of cellular activation and inflammatory signal amplification in different tissues and diseases. This binding could represent an as yet uninvestigated pathway of inflammatory reaction in the lung, where the presence of the receptor has been largely documented and advanced glycation end products (AGEs) are produced by nonenzymatic glycation and oxidation of proteins and lipids, driven by smoke and pollutants exposure or inflammatory stress. We immunohistochemically assessed the expression of RAGE and of its major proinflammatory ligands, N-epsilon-carboxy-methyl-lysine, S100B and S-100A12 in normal lung and in non-neoplastic lung disorders including smoke-related airway disease, granulomatous inflammation, postobstructive damage and usual interstitial pneumonia. In normal lung low expression of the receptor was observed in bronchiolar epithelia, type II pneumocytes, macrophages and some endothelia. S100A12 and S100B were expressed, respectively, in granulocytes and in dendritic cells. Carboxy-methyl-lysine was present in bronchiolar epithelia and macrophages. In all pathological conditions associated with inflammation and lung damage overexpression of both the receptor and of AGEs was observed in bronchiolar epithelia, type II alveolar pneumocytes, alveolar macrophages and endothelia. RAGE overexpression was more evident in epithelia associated with inflammatory cell aggregates. Fibroblasts in usual interstitial pneumonia expressed both the receptor and AGEs. The number of	/pubmed/16941014	Morbini P, Villa C, Campo I, Zorzetto M, Inghilleri S, Luisetti M.	Mod Pathol. 2006 Nov;19(11):1437-45. Epub 2006 Aug 25.	Mod Pathol. 2006	PubMed	citation	PMID:16941014	pubmed	16941014

											S100A12 and S100B immunoreactive inflammatory cells was variable. S100A12 was also expressed in mononuclear inflammatory cells and in activated epithelia. The activation of the inflammatory pathway controlled by the RAGE is not specific of a single lung disease, however, it may be relevant as a nonspecific pathway of sustained inflammation in lung tissue, and on this basis therapeutic approaches based on receptor blockage can be envisaged.										
13	0	NOT_LUNG				1					DNA methylation of extracellular matrix remodeling genes in children exposed to arsenic.	Several novel mechanistic findings regarding to arsenic's pathogenesis has been reported and some of them suggest that the etiology of some arsenic induced diseases are due in part to heritable changes to the genome via epigenetic processes such as DNA methylation, histone maintenance, and mRNA expression. Recently, we reported that arsenic exposure during in utero and early life was associated with impairment in the lung function and abnormal receptor for advanced glycation endproducts (RAGE), matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) sputum levels. Based on our results and the reported arsenic impacts on DNA methylation, we designed this study in our cohort of children exposed in utero and early childhood to arsenic with the aim to associate DNA methylation of MMP9, TIMP1 and RAGE genes with its protein sputum levels and with urinary and toenail arsenic levels. The results disclosed hypermethylation in MMP9 promotor region in the most exposed children; and an increase in the RAGE sputum levels among children with the mid methylation level; there were also positive associations between MMP9 DNA methylation with arsenic toenail concentrations; RAGE DNA methylation with iAs, and %DMA; and finally between TIMP1 DNA methylation with the first arsenic methylation. A negative correlation between MMP9 sputum levels with its DNA methylation was registered. In conclusion, arsenic levels were positive associated with the DNA methylation of extracellular matrix remodeling genes;, which in turn could modifies the biological process in which they are involved causing or predisposing to lung diseases.	/pubmed/28579250	Gonzalez-Cortes T, Recio-Vega R, Lantz RC, Chau BT.	Toxicol Appl Pharmacol. 2017 Aug 15;329:140-147. doi: 10.1016/j.taap.2017.06.001. Epub 2017 Jun 1.	Toxicol Appl Pharmacol. 2017	PubMed	citation	PMID:28579250	pubmed	28579250
14	0	review		1							Plausible Roles for RAGE in Conditions Exacerbated by Direct and Indirect (Secondhand) Smoke Exposure.	Approximately 1 billion people smoke worldwide, and the burden placed on society by primary and secondhand smokers is expected to increase. Smoking is the leading risk factor for myriad health complications stemming from diverse pathogenic programs. First- and second-hand cigarette smokecontains thousands of constituents, including several carcinogens and cytotoxic chemicals that orchestrate chronic inflammatory responses and destructive remodeling events. In the current review, we outline details related to compromised pulmonary and systemic conditions related to smokeexposure. Specifically, data are discussed relative to impaired lung physiology, cancer mechanisms, maternal-fetal complications, cardiometabolic, and joint disorders in the context of smoke exposure exacerbations. As a general unifying mechanism, the receptor for advanced glycation end-products(RAGE) and its signaling axis is increasingly considered central to smoke-related pathogenesis. RAGEis a multi-ligand cell surface receptor whose expression increases following cigarette smoke exposure. RAGE signaling participates in the underpinning of inflammatory mechanisms mediated by requisite cytokines, chemokines, and remodeling enzymes. Understanding the biological contributions of RAGEduring cigarette smoke-induced inflammation may provide critically important insight into the pathology of lung disease and systemic complications that combine during the demise of those exposed.	/pubmed/28304347	Lewis JB, Hirschi KM, Arroyo JA, Bikman BT, Kooyman DL, Reynolds PR.	Int J Mol Sci. 2017 Mar 17;18(3). pii: E652. doi: 10.3390/ijms18030652. Review.	Int J Mol Sci. 2017	PubMed	citation	PMID:28304347 | PMCID:PMC5372664	pubmed	28304347

15	0	radon exposure and lung cancer mortality						1			Accounting for Berkson and Classical Measurement Error in Radon Exposure Using a Bayesian Structural Approach in the Analysis of Lung Cancer Mortality in the French Cohort of Uranium Miners.	Many occupational cohort studies on underground miners have demonstrated that radon exposure is associated with an increased risk of lung cancer mortality. However, despite the deleterious consequences of exposure measurement error on statistical inference, these analyses traditionally do not account for exposure uncertainty. This might be due to the challenging nature of measurement error resulting from imperfect surrogate measures of radon exposure. Indeed, we are typically faced with exposure uncertainty in a time-varying exposure variable where both the type and the magnitude of error may depend on period of exposure. To address the challenge of accounting for multiplicative and heteroscedastic measurement error that may be of Berkson or classical nature, depending on the year of exposure, we opted for a Bayesian structural approach, which is arguably the most flexible method to account for uncertainty in exposure assessment. We assessed the association between occupational radon exposure and lung cancer mortality in the French cohort of uranium miners and found the impact of uncorrelated multiplicative measurement error to be of marginal importance. However, our findings indicate that the retrospective nature of exposure assessment that occurred in the earliest years of mining of this cohort as well as many other cohorts of underground miners might lead to an attenuation of the exposure-risk relationship. More research is needed to address further uncertainties in the calculation of lung dose, since this step will likely introduce important sources of shared uncertainty.	/pubmed/28118116	Hoffmann S, Rage E, Laurier D, Laroche P, Guihenneuc C, Ancelet S.	Radiat Res. 2017 Feb;187(2):196-209. doi: 10.1667/RR14467.1. Epub 2017 Jan 24.	Radiat Res. 2017	PubMed	citation	PMID:28118116	pubmed	28118116
16	0	In Vitro				1					Multi-walled carbon nanotube induces nitrative DNA damage in human lung epithelial cells via HMGB1-RAGE interaction and Toll-like receptor 9 activation.	BACKGROUND: Carbon nanotube (CNT) is used for various industrial purposes, but exhibits carcinogenic effects in experimental animals. Chronic inflammation in the respiratory system may participate in CNT-induced carcinogenesis. 8-Nitroguanine (8-nitroG) is a mutagenic DNA lesion formed during inflammation. We have previously reported that multi-walled CNT (MWCNT) induced 8-nitroG formation in lung epithelial cells and this process involved endocytosis. To clarify the mechanism of CNT-induced carcinogenesis, we examined the role of Toll-like receptor (TLR) 9, which resides in endosomes and lysosomes, in 8-nitroG formation in human lung epithelial cell lines. METHODS: We performed immunocytochemistry to examine 8-nitroG formation in A549 and HBEpC cells treated with MWCNT with a length of 1-2 μm (CNT-S) or 5-15 μm (CNT-L) and a diameter of 20-40 nm. We examined inhibitory effects of endocytosis inhibitors, small interfering RNA (siRNA) for TLR9, and antibodies against high-mobility group box-1 (HMGB1) and receptor for advanced glycation end-products (RAGE) on 8-nitroG formation. The release of HMGB1 and double-stranded DNA (dsDNA) into the culture supernatant from MWCNT-treated cells was examined by ELISA and fluorometric analysis, respectively. The association of these molecules was examined by double immunofluorescent staining and co-immunoprecipitation. RESULTS: CNT-L significantly increased 8-nitroG formation at 0.05 μg/ml in A549 cells and its intensity reached a maximum at 1 μg/ml. CNT-L tended to induce stronger cytotoxicity and 8-nitroG formation than CNT-S. Endocytosis inhibitors, TLR9 siRNA and antibodies against HMGB1 and RAGE largely reduced MWCNT-induced 8-nitroG formation. MWCNT increased the release of HMGB1 and dsDNA from A549 cells into culture supernatant. The culture supernatant of MWCNT-exposed cells induced 8-nitroG formation in fresh A549 cells. Double immunofluorescent staining and co-immunoprecipitation showed that TLR9 was associated with HMGB1 and RAGE in lysosomes of MWCNT-treated cells. CONCLUSIONS: MWCNT induces injury or necrosis of lung epithelial cells, which release HMGB1 and DNA into the extracellular space. The HMGB1-DNA complex binds to RAGE on neighboring cells and then CpG DNA	/pubmed/27026438	Hiraku Y, Guo F, Ma N, Yamada T, Wang S, Kawanishi S, Murata M.	Part Fibre Toxicol. 2016 Mar 29;13:16. doi: 10.1186/s12989-016-0127-7.	Part Fibre Toxicol. 2016	PubMed	citation	PMID:27026438 | PMCID:PMC4812657	pubmed	27026438

											is recognized by TLR9 in lysosomes, leading to generation of nitric oxide and 8-nitroG formation. This is the first study demonstrating that TLR9 and related molecules participate in MWCNT-induced genotoxicity and may contribute to carcinogenesis.									
17	0	review		1							Association between HMGB1 and COPD: A Systematic Review.	HMGB1 is an alarmin, a protein that warns and activates inflammation. Chronic obstructive pulmonary disease (COPD) is characterised by a progressive airflow obstruction and airway inflammation. Current anti-inflammatory therapies are poorly effective in maintaining lung function and symptoms of COPD. This underlines the need for finding new molecular targets involved in disease pathogenesis in order to block pathology progression. This review aims to analyse latest advances on HMGB1 role, utilisation, and potential application in COPD. To this purpose we reviewed experimental studies that investigated this alarmin as marker as well as a potential treatment in chronic obstructive pulmonary disease. This systematic review was conducted according to PRISMA guidelines. In almost all the studies, it emerged that HMGB1 levels are augmented in smokers and in patients affected by COPD. It emerged that cigarette smoking, the most well-known causative factor of COPD, induces neutrophils death and necrosis. The necrosis of neutrophil cells leads to HMGB1 release, which recruits other neutrophils in a self-maintaining process. According to the results reported in the paper both inhibiting HMGB1 and its receptor (RAGE) and blocking neutrophils necrosis (inducted by cigarette smoking) could be the aim for further studies.	/pubmed/26798204	Gangemi S, Casciaro M, Trapani G, Quartuccio S, Navarra M, Pioggia G, Imbalzano E.	Mediators Inflamm. 2015;2015:164913. doi: 10.1155/2015/164913. Epub 2015 Dec 21. Review.	Mediators Inflamm. 2015	PubMed	citation	PMID:26798204 | PMCID:PMC4698778	pubmed	26798204
18	0	not studies exposure assoc. OAD					1				Relationship between gene expression and lung function in Idiopathic Interstitial Pneumonias.	BACKGROUND: Idiopathic interstitial pneumonias (IIPs) are a group of heterogeneous, somewhat unpredictable diseases characterized by progressive scarring of the interstitium. Since lung function is a key determinant of survival, we reasoned that the transcriptional profile in IIP lung tissue would be associated with measures of lung function, and could enhance prognostic approaches to IIPs. RESULTS: Using gene expression profiling of 167 lung tissue specimens with IIP diagnosis and 50 control lungs, we identified genes whose expression is associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as categorical (severe vs mild disease) or continuous variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), including those with established role in fibrosis (ADAMTS4, ADAMTS9, AGER, HIF-1α, SERPINA3, SERPINE2, and SELE) as well as novel IIP candidate genes such as rhotekin 2 (RTKN2) and peptidase inhibitor 15 (PI15). Protein-protein interactome analysis of 553 genes whose expression is significantly associated with lung function when modeled as continuous variables demonstrates that more severe presentation of IIPs is characterized by an increase in cell cycle progression and apoptosis, increased hypoxia, and dampened innate immune response. Our findings were validated in an independent cohort of 131 IIPs and 40 controls at the mRNA level and for one gene (RTKN2) at the protein level by immunohistochemistry in a subset of samples. CONCLUSIONS: We identified commonalities and differences in gene expression among different subtypes of IIPs. Disease progression, as characterized by lower measures of FVC and DLCO, results in marked changes in expression of novel and established genes and pathways involved in IIPs. These genes and pathways represent strong candidates for biomarker studies and potential therapeutic targets for IIP severity.	/pubmed/26503507	Steele MP, Luna LG, Coldren CD, Murphy E, Hennessy CE, Heinz D, Evans CM, Groshong S, Cool C, Cosgrove GP, Brown KK, Fingerlin TE, Schwarz MI, Schwartz DA, Yang IV.	BMC Genomics. 2015 Oct 26;16:869. doi: 10.1186/s12864-015-2102-3.	BMC Genomics. 2015	PubMed	citation	PMID:26503507 | PMCID:PMC4621862	pubmed	26503507

19	0	in vitro and mouse				1					Increased S100A4 expression in the vasculature of human COPD lungs and murine model of smoke-induced emphysema.	BACKGROUND: Chronic obstructive lung disease (COPD) is a common cause of death in industrialized countries often induced by exposure to tobacco smoke. A substantial number of patients with COPD also suffer from pulmonary hypertension that may be caused by hypoxia or other hypoxia-independent stimuli - inducing pulmonary vascular remodeling. The Ca(2+) binding protein, S100A4 is known to play a role in non-COPD-driven vascular remodeling of intrapulmonary arteries. Therefore, we have investigated the potential involvement of S100A4 in COPD induced vascular remodeling. METHODS: Lung tissue was obtained from explanted lungs of five COPD patients and five non-transplanted donor lungs. Additionally, mice lungs of a tobacco-smoke-induced lung emphysema model (exposure for 3 and 8 month) and controls were investigated. Real-time RT-PCR analysis of S100A4 and RAGE mRNA was performed from laser-microdissected intrapulmonary arteries. S100A4 immunohistochemistry was semi-quantitatively evaluated. Mobility shift assay and siRNA knock-down were used to prove hypoxia responsive elements (HRE) and HIF binding within the S100A4 promoter. RESULTS: Laser-microdissection in combination with real-time PCR analysis revealed higher expression of S100A4 mRNA in intrapulmonary arteries of COPD patients compared to donors. These findings were mirrored by semi-quantitative analysis of S100A4 immunostaining. Analogous to human lungs, in mice with tobacco-smoke-induced emphysema an up-regulation of S100A4 mRNA and protein was observed in intrapulmonary arteries. Putative HREs could be identified in the promoter region of the human S100A4 gene and their functionality was confirmed by mobility shift assay. Knock-down of HIF1/2 by siRNA attenuated hypoxia-dependent increase in S100A4 mRNA levels in human primary pulmonary artery smooth muscle cells. Interestingly, RAGE mRNA expression was enhanced in pulmonary arteries of tobacco-smoke exposed mice but not in pulmonary arteries of COPD patients. CONCLUSIONS: As enhanced S100A4 expression was observed in remodeled intrapulmonary arteries of COPD patients, targeting S100A4 could serve as potential therapeutic option for prevention of vascular remodeling in COPD patients.	/pubmed/26483185	Reimann S, Fink L, Wilhelm J, Hoffmann J, Bednorz M, Seimetz M, Dessureault I, Troesser R, Ghanim B, Klepetko W, Seeger W, Weissmann N, Kwapiszewska G.	Respir Res. 2015 Oct 20;16:127. doi: 10.1186/s12931-015-0284-5.	Respir Res. 2015	PubMed	citation	PMID:26483185 | PMCID:PMC4612429	pubmed	26483185

20	0	in vitro/lung cancer				1					Expression and DNA methylation status of the Rap2B gene in human bronchial epithelial cells treated by cigarette smoke condensate.	BACKGROUND: The relationship between lung cancer and smoking has been demonstrated. The Rap2B gene is usually overexpressed in lung cancers. This study was aimed to investigate the Rap2B gene expression and its promoter methylation in human bronchial epithelial cells (16HBE) treated by cigarette smoke condensate (CSC). METHODS: 16HBE cells were treated with CSC (1/8 IC50). Soft ager assay, tumorigenicity test, chromosome aberrations analysis were used to identify the transformed cells. The expression level of mRNA and protein of Rap2B was detected using real time PCR and Western blotting, respectively. The genome DNA methylation level was detected using combined bisulfite restriction analysis (COBRA) and the methylation status of the target fragment in Rap2B gene promoter was determined by bisulfite sequencing PCR (BSP). RESULTS: The 16HBE cells were successfully malignant transformed after the chronic exposure to CSC. The expression of Rap2B gradually increased in the process of malignant transformation. Meanwhile, global DNA was hypomethylated. However, no obvious change was observed in the methylation level of Rap2B gene promoter in transformed 16HBE cells. CONCLUSIONS: Rap2B gene may play an important role in the process of lung cancer and global DNA hypomethylation might be an early event in tumorigenesis.	/pubmed/26308105	Zhang S, Zhou M, Jiang G, Gong C, Cui D, Luo L, Wu D, Huang H, Zhang Q, Yang L.	Inhal Toxicol. 2015;27(10):502-9. doi: 10.3109/08958378.2015.1076546. Epub 2015 Aug 26.	Inhal Toxicol. 2015	PubMed	citation	PMID:26308105	pubmed	26308105
21	0	PEDS			1						Lung inflammation biomarkers and lung function in children chronically exposed to arsenic.	Evidence suggests that exposure to arsenic in drinking water during early childhood or in utero has been associated with an increase in respiratory symptoms or diseases in the adulthood, however only a few studies have been carried out during those sensitive windows of exposure. Recently our group demonstrated that the exposure to arsenic during early childhood or in utero in children was associated with impairment in the lung function and suggested that this adverse effect could be due to a chronic inflammation response to the metalloid. Therefore, we designed this cross-sectional study in a cohort of children associating lung inflammatory biomarkers and lung function with urinary As levels. A total of 275 healthy children were partitioned into four study groups according with their arsenic urinary levels. Inflammation biomarkers were measured in sputum by ELISA and the lung function was evaluated by spirometry. Fifty eight percent of the studied children were found to have a restrictive spirometric pattern. In the two highest exposed groups, the soluble receptor for advanced glycation end products' (sRAGE) sputum level was significantly lower and matrix metalloproteinase-9 (MMP-9) concentration was higher. When the biomarkers were correlated to the urinary arsenic species, negative associations were found between dimethylarsinic (DMA), monomethylarsonic percentage (%MMA) and dimethylarsinic percentage (%DMA) with sRAGE and positive associations between %DMA with MMP-9 and with the MMP-9/tissue inhibitor of metalloproteinase (TIMP-1) ratio. In conclusion, chronic arsenic exposure of children negatively correlates with sRAGE, and positively correlated with MMP-9 and MMP-9/TIMP-1 levels, and increases the frequency of an abnormal spirometric pattern. Arsenic-induced alterations in inflammatory biomarkers may contribute to the development of restrictive lung diseases.	/pubmed/26048584	Olivas-CalderÃ³n E, Recio-Vega R, Gandolfi AJ, Lantz RC, GonzÃ¡lez-Cortes T, Gonzalez-De Alba C, Froines JR, Espinosa-Fematt JA.	Toxicol Appl Pharmacol. 2015 Sep 1;287(2):161-7. doi: 10.1016/j.taap.2015.06.001. Epub 2015 Jun 3.	Toxicol Appl Pharmacol. 2015	PubMed	citation	PMID:26048584 | PMCID:PMC4751871	pubmed	26048584

22	0	letter		1							RAGE-ligands axis: A new 'driving force' for cigarette smoke-induced airway inflammation in COPD?	Receptor for advanced glycation end products (RAGE) was recently shown to contribute to cigarette smoke (CS)-induced airway inflammation in chronic obstructive pulmonary disease (COPD). In this study, RAGE small interfering ribonucleic acid (RNA) transfection attenuated increased messenger RNA levels of common RAGE ligands HMGB1, S100A8, S100A9 and S100A12, but not S100B following exposure to CS extract. Our findings and those from recent studies suggest a positive feedback involving RAGE and its ligands as a new 'driving force' for CS-induced airway inflammation in COPD.	/pubmed/25998568	Li M, Guo L, Wang H, Wang T, Shen Y, Liao Z, Wen F, Chen L.	Respirology. 2015 Aug;20(6):998-9. doi: 10.1111/resp.12557. Epub 2015 May 22.	Respirology. 2015	PubMed	citation	PMID:25998568	pubmed	25998568
23	0	radiation exposure and lung cancer						1			Mortality analyses in the updated French cohort of uranium miners (1946-2007).	PURPOSE: The objectives are to analyze mortality risks in the extended follow-up of the French uranium miners' cohort and to examine their potential relation to occupational exposure to ionizing radiation (IR). METHODS: The total cohort includes 5,086 uranium miners employed in the CEA-COGEMA group and followed up from 1946 to 2007. Vital status, causes of death, and cumulative radon exposures were recorded. The post-55 subcohort includes 3,377 miners first employed after 1955, for whom long-lived radionuclides (LLR) and external gamma-ray exposure were also recorded. External mortality analyses were performed by computing standardized mortality ratios (SMR). Excess relative risks (ERRs) due to IR exposures were estimated from Poisson regression models. RESULTS: The miners included in the total cohort were followed up for 35.4 years and exposed to 36.6 working level months (WLM) on average. There was no evidence of a difference in overall mortality between miners and the general French male population. Miners had a statistically significant excess mortality rate from lung cancer (SMR = 1.34 [95% CI 1.16-1.53]) and from kidney cancer (SMR = 1.60 [1.03-2.39]). Cumulative radon exposure was significantly associated with lung cancer risk (ERR/100 WLM = 0.71 [0.31-1.30]) and cerebrovascular risk (ERR/100 WLM = 0.41 [0.04-1.03]). In the post-55 subcohort, this excess mortality from lung cancer remained associated with exposure to radon, and also with exposure to LLR and external gamma rays. CONCLUSIONS: The analyses in the extended follow-up strengthen the results previously observed among French uranium miners about their excess risk of mortality and its association with their occupational IR exposure.	/pubmed/25410273	Rage E, CaÃ«r-Lorho S, Drubay D, Ancelet S, Laroche P, Laurier D.	Int Arch Occup Environ Health. 2015 Aug;88(6):717-30. doi: 10.1007/s00420-014-0998-6. Epub 2014 Nov 20.	Int Arch Occup Environ Health. 2015	PubMed	citation	PMID:25410273	pubmed	25410273
24	0	radiation exposure and lung cancer						1			Chest X-ray screening examinations among French uranium miners: exposure estimation and impact on radon-associated lung cancer risk.	BACKGROUND: Medical surveillance of uranium miners can include periodic chest X-ray examinations. This study aimed to assess the X-ray exposure due to occupational health monitoring in the French cohort of uranium miners, and to test whether consideration of this additional radiation exposure impacts the excess risk of lung cancer death associated with radon exposure. METHOD: X-ray exposure due to occupational health monitoring was estimated retrospectively based on review of a sample of miners' medical records and bibliographic data. Four exposure scenarios were designed, differing in their assumptions about the type of procedures performed, their frequency, and the lung dose delivered. Radon exposure and lung doses from exposure to α-particle emitters and external γ rays have previously been individually assessed. Exposure-risk and dose-risk relations were estimated by Poisson regression with a linear excess relative risk (ERR) model. RESULTS: The cohort included 5086 miners with a mean follow-up duration of 30.1 years. The mean number of chest X-ray examinations ranged from 15.1 in the lowest to 34 in the highest-exposure scenario, and produced a mean cumulative lung dose ranging from 4.6 to 34.2	/pubmed/25017574	Laborde-CastÃ©rot H, Laurier D, CaÃ«r-Lorho S, Etard C, Acker A, Rage E.	Occup Environ Med. 2014 Sep;71(9):611-8. doi: 10.1136/oemed-2013-101937. Epub 2014 Jun 23.	Occup Environ Med. 2014	PubMed	citation	PMID:25017574	pubmed	25017574

											mGy. The role of occupation-related imaging screening X-ray procedures in total equivalent lung dose appeared insignificant compared to α-emitter exposure. X-ray exposure was not associated with lung cancer mortality risk. The ERR associated with radon remained significantly positive when X-ray exposure was included in the multivariate analysis. CONCLUSIONS: X-ray exposure did not confound the exposure-risk relation between radon and lung cancer.									
25	0	not studies exposure assoc. OAD					1				Receptor for advanced glycation end-products regulates lung fluid balance via protein kinase C-gp91(phox) signaling to epithelial sodium channels.	The receptor for advanced glycation end-products (RAGE), a multiligand member of the Ig family, may play a crucial role in the regulation of lung fluid balance. We quantified soluble RAGE (sRAGE), a decoy isoform, and advanced glycation end-products (AGEs) from the bronchoalveolar lavage fluid of smokers and nonsmokers, and tested the hypothesis that AGEs regulate lung fluid balance through protein kinase C (PKC)-gp91(phox) signaling to the epithelial sodium channel (ENaC). Human bronchoalveolar lavage samples from smokers showed increased AGEs (9.02 ± 3.03 μg versus 2.48 ± 0.53 μg), lower sRAGE (1,205 ± 292 pg/ml versus 1,910 ± 263 pg/ml), and lower volume(s) of epithelial lining fluid (97 ± 14 ml versus 133 ± 17 ml). sRAGE levels did not predict ELF volumes in nonsmokers; however, in smokers, higher volumes of ELF were predicted with higher levels of sRAGE. Single-channel patch clamp analysis of rat alveolar epithelial type 1 cells showed that AGEs increased ENaC activity measured as the product of the number of channels (N) and the open probability (Po) (NPo) from 0.19 ± 0.08 to 0.83 ± 0.22 (P = 0.017) and the subsequent addition of 4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-N-oxyl decreased ENaC NPo to 0.15 ± 0.07 (P = 0.01). In type 2 cells, human AGEs increased ENaC NPo from 0.12 ± 0.05 to 0.53 ± 0.16 (P = 0.025) and the addition of 4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-N-oxyl decreased ENaC NPo to 0.10 ± 0.03 (P = 0.013). Using molecular and biochemical techniques, we observed that inhibition of RAGE and PKC activity attenuated AGE-induced activation of ENaC. AGEs induced phosphorylation of p47(phox) and increased gp91(phox)-dependent reactive oxygen species production, a response that was abrogated with RAGE or PKC inhibition. Finally, tracheal instillation of AGEs promoted clearance of lung fluid, whereas concomitant inhibition of RAGE, PKC, and gp91(phox) abrogated the response.	/pubmed/24978055	Downs CA, Kreiner LH, Johnson NM, Brown LA, Helms MN.	Am J Respir Cell Mol Biol. 2015 Jan;52(1):75-87. doi: 10.1165/rcmb.2014-0002OC.	Am J Respir Cell Mol Biol. 2015	PubMed	citation	PMID:24978055 | PMCID:PMC5455303	pubmed	24978055
26	0	not studies exposure assoc. OAD					1				Comparative analyses of volatile organic compounds (VOCs) from patients, tumors and transformed cell lines for the validation of lung cancer-derived breath markers.	Breath analysis for the purpose of non-invasive diagnosis of lung cancer has yielded numerous candidate compounds with still questionable clinical relevance. To arrive at suitable volatile organic compounds our approach combined the analysis of different sources: isolated tumor samples compared to healthy lung tissues, and exhaled breath from lung cancer patients and healthy controls. Candidate compounds were further compared to substances previously identified in the comparison of transformed and normal lung epithelial cell lines. For human studies, a breath sampling device was developed enabling automated and CO2-controlled collection of the end-tidal air. All samples were first preconcentrated on multibed sorption tubes and analyzed with gas chromatography mass spectrometry (GC-MS). Significantly ($p < 0.05$) higher concentrations in all three types of cancer samples studied were observed for ethanol and n-octane. Additional metabolites (inter alia 2-methylpentane, n-hexane) significantly released by lung cancer cells were observed at higher levels in cancer lung tissues and breath samples (compared to respective healthy controls) with statistical significance ($p < 0.05$) only in breath samples. The results obtained confirmed the cancer-related origin of volatile metabolites, e.g. ethanol and octane that were both detected at significantly ($p < 0.05$) elevated concentrations in all three kinds of cancer samples studied. This work is an important step towards identification of volatile breath markers of lung cancer through the demonstration of cancer-related origin of certain volatile metabolites.	/pubmed/24862102	Filipiak W, Filipiak A, Sponring A, Schmid T, Zelger B, Ager C, Klodzinska E, Denz H, Pizzini A, Lucciarini P, Jamnig H, Troppmair J, Amann A.	J Breath Res. 2014 Jun;8(2):027111. doi: 10.1088/1752-7155/8/2/027111. Epub 2014 May 27.	J Breath Res. 2014	PubMed	citation	PMID:24862102	pubmed	24862102

27	0	radiation assoc. renal cancer						1			Kidney cancer mortality and ionizing radiation among French and German uranium miners.	The investigation of potential adverse health effects of occupational exposures to ionizing radiation, on uranium miners, is an important area of research. Radon is a well-known carcinogen for lung, but the link between radiation exposure and other diseases remains controversial, particularly for kidney cancer. The aims of this study were therefore to perform external kidney cancer mortality analyses and to assess the relationship between occupational radiation exposure and kidney cancer mortality, using competing risks methodology, from two uranium miners cohorts. The French (n = 3,377) and German (n = 58,986) cohorts of uranium miners included 11 and 174 deaths from kidney cancer. For each cohort, the excess of kidney cancer mortality has been assessed by standardized mortality ratio (SMR) corrected for the probability of known causes of death. The associations between cumulative occupational radiation exposures (radon, external gamma radiation and long-lived radionuclides) or kidney equivalent doses and both the cause-specific hazard and the probability of occurrence of kidney cancer death have been estimated with Cox and Fine and Gray models adjusted to date of birth and considering the attained age as the timescale. No significant excess of kidney cancer mortality has been observed neither in the French cohort (SMR = 1.49, 95 % confidence interval [0.73; 2.67]) nor in the German cohort (SMR = 0.91 [0.77; 1.06]). Moreover, no significant association between kidney cancer mortality and any type of occupational radiation exposure or kidney equivalent dose has been observed. Future analyses based on further follow-up updates and/or large pooled cohorts should allow us to confirm or not the absence of association.	/pubmed/24858911	Drubay D, Ancelet S, Acker A, Kreuzer M, Laurier D, Rage E.	Radiat Environ Biophys. 2014 Aug;53(3):505-13. doi: 10.1007/s00411-014-0547-4. Epub 2014 May 24.	Radiat Environ Biophys. 2014	PubMed	citation	PMID:24858911	pubmed	24858911
28	0	PEDS			1						Transient early wheeze and lung function in early childhood associated with chronic obstructive pulmonary disease genes.	BACKGROUND: It has been hypothesized that a disturbed early lung development underlies the susceptibility to chronic obstructive pulmonary disease (COPD). Little is known about whether subjects genetically predisposed to COPD show their first symptoms or reduced lung function in childhood. OBJECTIVE: We investigated whether replicated genes for COPD associate with transient early wheeze (TEW) and lung function levels in 6- to 8-year-old children and whether cigarette smoke exposure in utero and after birth (environmental tobacco smoke [ETS]) modifies these effects. METHODS: The association of COPD-related genotypes of 20 single nucleotide polymorphisms in 15 genes with TEW, FEV1, forced vital capacity (FVC), and FEV1/FVC ratio was studied in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort (n = 1996) and replicated in the Child, parents and health: lifestyle and genetic constitution (KOALA) and Avon Longitudinal Study of Parents and Children (ALSPAC) cohorts. RESULTS: AGER showed replicated association with FEV1/FVC ratio. TNS1 associated with more TEW in PIAMA and lower FEV1 in ALSPAC. TNS1 interacted with ETS in PIAMA, showing lower FEV1 in exposed children. HHIP rs1828591 interacted with cigarette smoke exposure in utero in PIAMA and with ETS in ALSPAC, with lower lung function in nonexposed children. SERPINE2, FAM13A, and MMP12 associated with higher FEV1 and FVC, and SERPINE2, HHIP, and TGFB1 interacted with cigarette smoke exposure in utero in PIAMA only, showing adverse effects of exposure on FEV1 being limited to children with genotypes conferring the lowest risk of COPD. CONCLUSION: Our findings indicate relevant involvement of at least 3 COPD genes in lung development and lung growth by demonstrating associations pointing toward reduced airway caliber in early childhood. Furthermore, our results suggest that COPD genes are involved in the infant's lung response to smoke exposure in utero and in early life.	/pubmed/23886569	Kerkhof M, Boezen HM, Granell R, Wijga AH, Brunekreef B, Smit HA, de Jongste JC, Thijs C, Mommers M, Penders J, Henderson J, Koppelman GH, Postma DS.	J Allergy Clin Immunol. 2014 Jan;133(1):68-76.e1-4. doi: 10.1016/j.jaci.2013.06.004. Epub 2013 Jul 22.	J Allergy Clin Immunol. 2014	PubMed	citation	PMID:23886569	pubmed	23886569

29	0	not studies exposure assoc. OAD					1				Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap.	The pathophysiological features of chronic obstructive pulmonary disease (COPD)-asthma overlap are poorly understood and there has been no study of plasma or sputum biomarkers in overlap patients. In order to clarify the similarity and differences between overlap and COPD or asthma, we have investigated four potential biomarkers of COPD: surfactant protein A (SP-A), soluble receptor for advanced glycation end-products (sRAGE), myeloperoxidase (MPO) and neutrophil gelatinase-associated lipocalin (NGAL). SP-A and sRAGE are pneumocyte-derived markers. MPO and NGAL are neutrophil-derived molecules, but NGAL can also be expressed by respiratory epithelial cells. Plasma levels of SP-A and sRAGE and induced sputum levels of MPO and NGAL were measured by enzyme immunoassay/ELISA in 134 subjects: nonsmokers (n=26), smokers (n=23), asthma (n=32), COPD(n=39) and COPD-asthma overlap patients (n=14). In patients with COPD-asthma overlap, sputum MPO and plasma SP-A were significantly elevated whereas plasma sRAGE levels were reduced compared with asthma patients. Only sputum NGAL was significantly elevated in COPD-asthma overlap compared with COPD (p=0.00016) and could be used to differentiate patients with overlap from those with COPD. Increased induced sputum levels of NGAL might be a characteristic feature of overlap, suggesting enhanced neutrophilic airway inflammation and/or airway epithelial injury in COPD-asthma overlap.	/pubmed/23794464	Iwamoto H, Gao J, Koskela J, Kinnula V, Kobayashi H, Laitinen T, Mazur W.	Eur Respir J. 2014 Feb;43(2):421-9. doi: 10.1183/09031936.00024313. Epub 2013 Jun 21.	Eur Respir J. 2014	PubMed	citation	PMID:23794464	pubmed	23794464
30	0	Opinion		1							Receptor for advanced glycation end products: a new theraputic target for chronic obstructive pulmonary disease?	Receptor for advanced glycation end products (RAGE), a multiligand receptor, has been suggested to be implicated in inflammatory response. However, its role in chronic obstructive pulmonary disease(COPD) has not been well elucidated. Recently, several studies reported RAGE and its common ligands were upregulated in airways and lung tissues from COPD smokers. Moreover, inhibition of RAGEactivation significantly attenuated cigarette smoke extract or bacteria-induced pulmonary inflammation. Based on these findings, a conclusion could be made that ligand-activated RAGE may play a key role in COPD and thus RAGE could be a new therapeutic target for COPD.	/pubmed/23287523	Chen L, Liu L, Wang T, Shen YC, Wen FQ.	Arch Med Res. 2013 Jan;44(1):75-6. doi: 10.1016/j.arcmed.2012.12.003. Epub 2013 Jan 1.	Arch Med Res. 2013	PubMed	citation	PMID:23287523	pubmed	23287523
31	0	radiation exposure and lung cancer						1			The performance of functional methods for correcting non-Gaussian measurement error within Poisson regression: corrected excess risk of lung cancer mortality in relation to radon exposure among French uranium miners.	A broad variety of methods for measurement error (ME) correction have been developed, but these methods have rarely been applied possibly because their ability to correct ME is poorly understood. We carried out a simulation study to assess the performance of three error-correction methods: two variants of regression calibration (the substitution method and the estimation calibration method) and the simulation extrapolation (SIMEX) method. Features of the simulated cohorts were borrowed from the French Uranium Miners' Cohort in which exposure to radon had been documented from 1946 to 1999. In the absence of ME correction, we observed a severe attenuation of the true effect of radon exposure, with a negative relative bias of the order of 60% on the excess relative risk of lung cancer death. In the main scenario considered, that is, when ME characteristics previously determined as most plausible from the French Uranium Miners' Cohort were used both to generate exposure data and to correct for ME at the analysis stage, all three error-correction methods showed a noticeable but partial reduction of the attenuation bias, with a slight advantage for the SIMEX method. However, the performance of the three correction methods highly depended on the accurate determination of the characteristics of ME. In particular, we encountered severe overestimation in some scenarios with the SIMEX method, and we observed lack of correction with the three methods in some other scenarios. For illustration, we also applied and compared the proposed methods on the real data set from the French Uranium Miners' Cohort study.	/pubmed/22996087	Allodji RS, ThiÃ©baut AC, Leuraud K, Rage E, Henry S, Laurier D, BÃ©nichou J.	Stat Med. 2012 Dec 30;31(30):4428-43. doi: 10.1002/sim.5618. Epub 2012 Sep 21.	Stat Med. 2012	PubMed	citation	PMID:22996087	pubmed	22996087
32	1	copd and smoking									Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity.	The identification and validation of biomarkers to support the assessment of novel therapeutics for COPD continues to be an important area of research. The aim of the current study was to identify systemic protein biomarkers correlated with measures of COPD severity, as well as specific protein signatures associated with comorbidities such as metabolic syndrome. 142 protein analytes were measured in serum of 140 patients with stable COPD, 15 smokers without COPD and 30 non-smoking controls. Seven analytes (sRAGE, EN-RAGE, NGAL, Fibrinogen, MPO, TGF-α and HB-EGF)	/pubmed/22701684	Cockayne DA, Cheng DT, Waschki B, Sridhar S, Ravindran P, Hilton H, Kourteva G, Bitter H, Pillai SG, Visvanathan S,	PLoS One. 2012;7(6):e38629. doi: 10.1371/journal.pone.0038629. Epub 2012 Jun 12.	PLoS One. 2012	PubMed	citation	PMID:22701684 | PMCID:PMC3373533	pubmed	22701684

											showed significant differences between severe/very severe COPD, mild/moderate COPD, smoking and non-smoking control groups. Within the COPD subjects, univariate and multivariate analyses identified analytes significantly associated with FEV(1), FEV(1)/FVC and DLCO. Most notably, a set of 5 analytes (HB-EGF, Fibrinogen, MCP-4, sRAGE and Sortilin) predicted 21% of the variability in DLCO values. To determine common functions/pathways, analytes were clustered in a correlation network by similarity of expression profile. While analytes related to neutrophil function (EN-RAGE, NGAL, MPO) grouped together to form a cluster associated with FEV(1) related parameters, analytes related to the EGFR pathway (HB-EGF, TGF-α) formed another cluster associated with both DLCO and FEV(1) related parameters. Associations of Fibrinogen with DLCO and MPO with FEV(1)/FVC were stronger in patients without metabolic syndrome (r = -0.52, p = 0.005 and r = -0.61, p = 0.023, respectively) compared to patients with coexisting metabolic syndrome (r = -0.25, p = 0.47 and r = -0.15, p = 0.96, respectively), and may be driving overall associations in the general cohort. In summary, our study has identified known and novel serum protein biomarkers and has demonstrated specific associations with COPD disease severity, FEV(1), FEV(1)/FVC and DLCO. These data highlight systemic inflammatory pathways, neutrophil activation and epithelial tissue injury/repair processes as key pathways associated with COPD.		MÃ¼ller KC, Holz O, Magnussen H, Watz H, Fine JS.							
33	0	review		1							RAGE: a new frontier in chronic airways disease.	Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous inflammatory disorders of the respiratory tract characterized by airflow obstruction. It is now clear that the environmental factors that drive airway pathology in asthma and COPD, including allergens, viruses, ozone and cigarette smoke, activate innate immune receptors known as pattern-recognition receptors, either directly or indirectly by causing the release of endogenous ligands. Thus, there is now intense research activity focused around understanding the mechanisms by which pattern-recognition receptors sustain the airway inflammatory response, and how these mechanisms might be targeted therapeutically. One pattern-recognition receptor that has recently come to attention in chronic airways disease is the receptor for advanced glycation end products (RAGE). RAGE is a member of the immunoglobulin superfamily of cell surface receptors that recognizes pathogen- and host-derived endogenous ligands to initiate the immune response to tissue injury, infection and inflammation. Although the role of RAGE in lung physiology and pathophysiology is not well understood, recent genome-wide association studies have linked RAGE gene polymorphisms with airflow obstruction. In addition, accumulating data from animal and clinical investigations reveal increased expression of RAGE and its ligands, together with reduced expression of soluble RAGE, an endogenous inhibitor of RAGE signalling, in chronic airways disease. In this review, we discuss recent studies of the ligand-RAGE axis in asthma and COPD, highlight important areas for future research and discuss how this axis might potentially be harnessed for therapeutic benefit in these conditions.	/pubmed/22506507	Sukkar MB, Ullah MA, Gan WJ, Wark PA, Chung KF, Hughes JM, Armour CL, Phipps S.	Br J Pharmacol. 2012 Nov;167(6):1161-76. doi: 10.1111/j.1476-5381.2012.01984.x. Review.	Br J Pharmacol. 2012	PubMed	citation	PMID:22506507 | PMCID:PMC3504985	pubmed	22506507
34	1	copd, not environmental exposure									CHRNA3/5, IREB2, and ADCY2 are associated with severe chronic obstructive pulmonary disease in Poland.	We examined the association between single-nucleotide polymorphisms (SNPs) previously associated with chronic obstructive pulmonary disease (COPD) and/or lung function with COPD and COPD-related phenotypes in a novel cohort of patients with severe to very severe COPD. We examined 315 cases of COPD and 330 Caucasian control smokers from Poland. We included three SNPs previously associated with COPD: rs7671167 (FAM13A), rs13180 (IREB2), and rs8034191 (CHRNA 3/5), and four SNPs associated with lung function in a genome-wide association study of general population samples: rs2070600 (AGER), rs11134242 (ADCY2), rs4316710 (THSD4), and rs17096090 (INTS12). We tested for associations with severe COPD and COPD-related phenotypes, including lung function, smoking behavior, and body mass index. Subjects with COPD were older (average age 62 versus 58 years, P < 0.01), with more pack-years of smoking (45 versus 33 pack-years, P < 0.01). CHRNA3/5 (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.5-2.4; P = 7.4 × 10(-7)), IREB2 (OR, 0.69; 95% CI, 0.5-0.9; P = 3.4 × 10(-3)), and ADCY2 (OR, 1.35; 95% CI, 1.1-1.7; P = 0.01) demonstrated significant associations with COPD. FAM13A (OR, 0.8;	/pubmed/22461431	Hardin M, Zielinski J, Wan ES, Hersh CP, Castaldi PJ, Schwinder E, Hawrylkiewicz I, Sliwinski P, Cho MH, Silverman EK.	Am J Respir Cell Mol Biol. 2012 Aug;47(2):203-8. doi: 10.1165/rcmb.2012-0011OC. Epub 2012 Mar 29.	Am J Respir Cell Mol Biol. 2012	PubMed	citation	PMID:22461431 | PMCID:PMC3423462	pubmed	22461431

											95% CI, 0.7-1.0; P = 0.11) approached statistical significance. FAM13A and ADCY2 also demonstrated a significant association with lung function. Thus, in severe to very severe COPD, we demonstrate a replication of association between two SNPs previously associated with COPD (CHRNA3/5 and IREB2), as well as an association with COPD of one locus initially associated with lung function (ADCY2).									
35	0	radiation exposure and lung cancer						1			Risk of lung cancer mortality in relation to lung doses among French uranium miners: follow-up 1956-1999.	The aim of this study was to assess the risk of lung cancer death associated with cumulative lung doses from exposure to α-particle emitters, including radon gas, radon short-lived progeny, and long-lived radionuclides, and to external γ rays among French uranium miners. The French "post-55" sub-cohort included 3,377 uranium miners hired from 1956, followed up through the end of 1999, and contributing to 89,405 person-years. Lung doses were calculated with the ICRP Human Respiratory Tract Model (Publication 66) for 3,271 exposed miners. The mean "absorbed lung dose" due to α-particle radiation was 78 mGy, and that due to the contribution from other types of radiation (γ and β-particle radiation) was 56 mGy. Radon short-lived progeny accounted for 97% of the α-particle absorbed dose. Out of the 627 deaths, the cause of death was identified for 97.4%, and 66 cases were due to lung cancer. A significant excess relative risk (ERR) of lung cancer death was associated with the total absorbed lung dose (ERR/Gy = 2.94, 95% CI 0.80, 7.53) and the α-particle absorbed dose (4.48, 95% CI 1.27, 10.89). Assuming a value of 20 for the relative biological effectiveness (RBE) of α particles for lung cancer induction, the ERR/Gy-Eq for the total weighted lung dose was 0.22 (95% CI: 0.06, 0.53).	/pubmed/22206233	Rage E, Vacquier B, Blanchardon E, Allodji RS, Marsh JW, CaÃ«r-Lorho S, Acker A, Laurier D.	Radiat Res. 2012 Mar;177(3):288-97. Epub 2011 Dec 29.	Radiat Res. 2012	PubMed	citation	PMID:22206233	pubmed	22206233
36	0	radiation exposure and lung cancer						1			The influence of multiple types of occupational exposure to radon, gamma rays and long-lived radionuclides on mortality risk in the French "post-55" sub-cohort of uranium miners: 1956-1999.	The adverse health effects of radon on uranium miners, especially on their lungs, are well documented, but few studies have considered the effects of other radiation exposures. This study examined the mortality risks associated with exposure to radon, external γ rays and long-lived radionuclides (LLR) in the French "post-55" sub-cohort, which includes uranium miners first employed between 1956 and 1990 for whom all three types of exposure were assessed individually. Exposure-risk relationships were estimated with linear excess relative risk models and a 5-year lag time. The post-55 sub-cohort includes 3377 miners, contributing 89,405 person-years, followed up through the end of 1999 with a mean follow-up of 26.5 years. Mean cumulative exposure was 17.8 WLM for radon, 54.7 mSv for γ rays, and 1,632 Bq.m(-3).h for LLR. Among the 611 deaths observed, 66 were due to lung cancer. Annual individual exposures were significantly correlated. Increased mortality was observed for lung cancer (SMR = 1.30; 95% CI: 1.01, 1.65) and for brain and central nervous system (CNS) cancer (SMR = 2.00; 95% CI: 1.09, 3.35). Cumulative exposure to radon, γ rays and LLR was associated only with a significant risk of lung cancer. These new results could suggest an association between lung cancer and exposure to γ rays and LLR. They must nonetheless be interpreted with caution because of the correlation between the types of exposure. The calculation of organ doses received by each of these exposures would reduce the collinearity.	/pubmed/21936607	Vacquier B, Rage E, Leuraud K, CaÃ«r-Lorho S, Houot J, Acker A, Laurier D.	Radiat Res. 2011 Dec;176(6):796-806. Epub 2011 Sep 21.	Radiat Res. 2011	PubMed	citation	PMID:21936607	pubmed	21936607
37	1	copd, not environmental exposure									Soluble receptor for advanced glycation end products in COPD: relationship with emphysema and chronic cor pulmonale: a case-control study.	BACKGROUND: The receptor for advanced glycation end products (RAGE) is a multiligand signal transduction receptor that can initiate and perpetuate inflammation. Its soluble isoform (sRAGE) acts as a decoy receptor for RAGE ligands, and is thought to afford protection against inflammation. With the present study, we aimed at determining whether circulating sRAGE is correlated with emphysema and chronic cor pulmonale in chronic obstructive pulmonary disease (COPD). METHODS: In 200 COPD patients and 201 age- and sex-matched controls, we measured lung function by spirometry, and sRAGE by ELISA method. We also measured the plasma levels of two RAGE ligands, N-epsilon-carboxymethyl lysine and S100A12, by ELISA method. In the COPD patients, we assessed the prevalence and severity of emphysema by computed tomography (CT), and the prevalence of chronic cor pulmonale by echocardiography. Multiple quantile regression was used to assess the effects of emphysema, chronic cor pulmonale,	/pubmed/21450080	Miniati M, Monti S, Basta G, Cocci F, Fornai E, Bottai M.	Respir Res. 2011 Mar 30;12:37. doi: 10.1186/1465-9921-12-37.	Respir Res. 2011	PubMed	citation	PMID:21450080 | PMCID:PMC3072955	pubmed	21450080

											smoking history, and comorbid conditions on the three quartiles of sRAGE. RESULTS: sRAGE was significantly lower (p = 0.007) in COPD patients (median 652 pg/mL, interquartile range 484 to 1076 pg/mL) than in controls (median 869 pg/mL, interquartile range 601 to 1240 pg/mL), and was correlated with the severity of emphysema (p < 0.001), the lower the level of sRAGE the greater the degree of emphysema on CT. The relationship remained statistically significant after adjusting for smoking history and comorbid conditions. In addition, sRAGE was significantly lower in COPD patients with chronic cor pulmonale than in those without (p = 0.002). Such difference remained statistically significant after adjusting for smoking history, comorbidities, and emphysema severity. There was no significant difference in the plasma levels of the two RAGE ligands between cases and controls. CONCLUSIONS: sRAGE is significantly lower in patients with COPD than in age- and sex-matched individuals without airflow obstruction. Emphysema and chronic cor pulmonale are independent predictors of reduced sRAGE in COPD.									
38	0							1			Analysis of volatile organic compounds (VOCs) in the headspace of NCI-H1666 lung cancer cells.	Analysis of volatile organic compounds (VOCs) provides an elegant approach for cancer screening and disease monitoring, whose use is currently limited by a lack of validated cancer-derived metabolites, which may serve as biomarkers. The aim of the experiments presented here was to investigate the release and consumption of VOCs from the non small cell lung cancer cell line NCI-H1666, which was originally derived from a bronchoalveolar carcinoma.Following detachment by trypsinization suspended cells were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell culture were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOC-analysis was performed by thermodesorption-gas chromatography mass spectrometry (TD-GC-MS). In contrast to our previous studies experiments with NCI-H1666 cells only confirmed the consumption of several aldehydes, n-butyl acetate and the ethers methyl tert-butyl ether and ethyl tert-butyl ether, but no unequivocal release of VOCs was observed. Together with our previously published work these data indicate that the consumption of certain VOCs is commonly observed while their release shows cell line-restricted patterns, whose underlying causes are unknown.	/pubmed/21263191	Sponring A, Filipiak W, Ager C, Schubert J, Miekisch W, Amann A, Troppmair J.	Cancer Biomark. 2010;7(3):153-61. doi: 10.3233/CBM-2010-0182.	Cancer Biomark. 2010	PubMed	citation	PMID:21263191	pubmed	21263191
39	1	not discussing environmental exposure assoc OAD									Proteomic studies on receptor for advanced glycation end product variants in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease.	PURPOSE: Proteomic screening revealed declined levels of the receptor for advanced glycation end products (RAGE) in human idiopathic pulmonary fibrosis (IPF). This study was undertaken to investigate the different RAGE isoforms in two lung diseases with destruction of the lung parenchyma, i.e. IPF and chronic obstructive pulmonary disease (COPD). EXPERIMENTAL DESIGN: RAGE was analyzed by 2-DE, MS and Western blotting using lung tissues from non-smokers, smokers, patients with IPF, COPD and α-1-antitrypsin deficiency (AAT) and by ELISA from the bronchoalveolar lavage fluid samples. RESULTS: RAGE, detected by 2-DE in the control lung, was confirmed to be glycosylated, soluble, C-truncated RAGE with characteristics indicative of the presence of endogenous secretory RAGE (esRAGE). Further studies revealed a decrease of the full length-RAGE (FL-RAGE) and its C-terminal processed variant (cRAGE) in the lung tissues of IPF and COPD patients but not in AAT. The esRAGE level was reduced in IPF but was unchanged in COPD. CONCLUSIONS AND CLINICAL RELEVANCE: This study shows an involvement of the three RAGE variants (FL-RAGE, cRAGE, esRAGE) in IPF. The decline of FL-RAGE and cRAGE, but	/pubmed/21137019	Ohlmeier S, Mazur W, Salmenkivi K, MyllÃ¤rniemi M, Bergmann U, Kinnula VL.	Proteomics Clin Appl. 2010 Jan;4(1):97-105. doi: 10.1002/prca.200900128. Epub 2010 Jan 7.	Proteomics Clin Appl. 2010	PubMed	citation	PMID:21137019	pubmed	21137019

											not esRAGE, in COPD lungs is evidence of involvement of specific RAGE variants also in this disease.									
40	0	in vitro on COPD lung tissues				1					Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD.	Advanced Glycation End products (AGEs) are the products of nonenzymatic glycation and oxidation of proteins and lipids. Formation of AGEs is increased in response to hyperglycaemia, reactive oxygen species and ageing. AGEs are proinflammatory and can modify the extracellular matrix. RAGE (Receptor for Advanced Glycation End Products) mediates some of the effects of AGEs. METHODS: Formalin-fixed lung tissue from patients who had lobectomy for bronchial carcinoma was used to investigate the presence of AGEs and RAGE. Subjects were divided into those with COPD and controls. Immunostaining for AGEs and RAGE was performed and the intensity of staining measured. RESULTS: Subjects with COPD and controls were similar in age and smoking history but FEV(1)% predicted was lower for COPD than controls. Intensity of staining for AGEs was greater in the airways (p = 0.025) and alveolar walls (p = 0.004) in COPD. Intensity of staining for RAGE was also significantly increased in alveolar walls (p = 0.03) but not the airways. FEV(1)% predicted was correlated with the intensity of staining for AGEs in the airways and alveoli. CONCLUSIONS: The increased staining for both AGEs and RAGE in COPD lung raises the possibility that the RAGE-AGEs interaction may have a role in the pathogenesis of COPD.	/pubmed/21112201	Wu L, Ma L, Nicholson LF, Black PN.	Respir Med. 2011 Mar;105(3):329-36. doi: 10.1016/j.rmed.2010.11.001. Epub 2010 Nov 26.	Respir Med. 2011	PubMed	citation	PMID:21112201	pubmed	21112201
41	0	no human subjects				1					Diesel particulate matter induces receptor for advanced glycation end-products (RAGE) expression in pulmonary epithelial cells, and RAGE signaling influences NF-Î²B-mediated inflammation.	BACKGROUND: Receptors for advanced glycation end-products (RAGE) are cell-surface receptors expressed by alveolar type I (ATI) epithelial cells and are implicated in mechanisms of alveolar development and sustained pulmonary inflammation. OBJECTIVES: In the present study, we tested the hypothesis that diesel particulate matter (DPM) up-regulates RAGE in rat ATI-like R3/1 cells and human primary small airway epithelial cells (SAECs), leading to an inflammatory response. METHODS AND RESULTS: Using real-time reverse transcriptase polymerase chain reaction and immunoblotting, we found that RAGE mRNA and protein are up-regulated in cells exposed to DPM for 2 hr. Use of a luciferase reporter containing nuclear factor-κB (NF-κB) response elements revealed decreased NF-κB activation in cells transfected with small interfering RNA (siRNA) for RAGE (siRAGE) before DPM exposure compared with cells transfected with scrambled control siRNA (siControl). In addition, immunostaining revealed diminished nuclear translocation of NF-κB in DPM-exposed cells transfected with siRAGE compared with cells transfected with siControl before DPM stimulation. Enzyme-linked immunosorbent assay demonstrated that in R3/1 cells DPM induced secretion of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), two cytokines induced by NF-κB and associated with leukocyte chemotaxis during an inflammatory response. Incorporating siRAGE was sufficient to significantly decrease DPM-induced MCP-1 and IL-8 secretion compared with cells transfected with siControl. CONCLUSIONS: These data offer novel insights into potential mechanisms whereby RAGE influences pulmonary inflammation exacerbated by DPM exposure. Further research may demonstrate that molecules involved in RAGE signaling are potential targets in lessening the degree of particulate matter-induced exacerbations of inflammatory lung disease.	/pubmed/21087909	Reynolds PR, Wasley KM, Allison CH.	Environ Health Perspect. 2011 Mar;119(3):332-6. doi: 10.1289/ehp.1002520. Epub 2010 Nov 18.	Environ Health Perspect. 2011	PubMed	citation	PMID:21087909 | PMCID:PMC3059995	pubmed	21087909

42	1	copd, not environmental exposure									Expression of high-mobility group box 1 and of receptor for advanced glycation end products in chronic obstructive pulmonary disease.	RATIONALE: Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation and remodeling. High-mobility group box 1 (HMGB1), a nuclear protein that is released during inflammation and repair, interacts with proinflammatory cytokines and with the receptor for advanced glycation end products (RAGE), which is highly expressed in the lung. OBJECTIVES: To determine whether HMGB1 is augmented in COPD and is associated with IL-1beta and RAGE. METHODS: HMGB1 was assessed in the bronchoalveolar lavage (BAL) of 20 never-smokers, 20 smokers, and 30 smokers with COPD and it was correlated with inflammatory and clinical parameters. In parallel, HMGB1 and RAGE immunolocalization was determined in bronchial and lung tissues. Last, binding of HMGB1 to IL-1beta in human macrophages and in BAL fluid was examined. MEASUREMENTS AND MAIN RESULTS: BAL levels of HMGB1 were higher in smokers with COPD than in smokers and never-smokers (P < 0.0001 for both comparisons), and similar differences were observed in epithelial cells and alveolar macrophages. BAL HMGB1 correlated positively with IL-1beta (r(s) = 0.438; P = 0.0006) and negatively with FEV(1) (r(s) = -0.570; P < 0.0001) and transfer factor of the lung for carbon monoxide (r(s) = -0.382; P = 0.0026). HMGB1-IL-1beta complexes were found in BAL supernatant and alveolar macrophages from smokers and patients with COPD, as well as in the human macrophage cell line, THP-1, where they enhanced the synthesis of tumor-necrosis factor-alpha. RAGE was overexpressed in the airway epithelium and smooth muscle of patients with COPD and it colocalized with HMGB1. CONCLUSIONS: Elevated HMGB1 expression in COPD airways may sustain inflammation and remodeling through its interaction with IL-1beta and RAGE.	/pubmed/20133931	Ferhani N, Letuve S, Kozhich A, Thibaudeau O, Grandsaigne M, Maret M, Dombret MC, Sims GP, Kolbeck R, Coyle AJ, Aubier M, Pretolani M.	Am J Respir Crit Care Med. 2010 May 1;181(9):917-27. doi: 10.1164/rccm.200903-0340OC. Epub 2010 Feb 4.	Am J Respir Crit Care Med. 2010	PubMed	citation	PMID:20133931	pubmed	20133931

43	0	lung cancer						1			Noninvasive detection of lung cancer by analysis of exhaled breath.	BACKGROUND: Lung cancer is one of the leading causes of death in Europe and the western world. At present, diagnosis of lung cancer very often happens late in the course of the disease since inexpensive, non-invasive and sufficiently sensitive and specific screening methods are not available. Even though the CT diagnostic methods are good, it must be assured that "screening benefit outweighs risk, across all individuals screened, not only those with lung cancer". An early non-invasive diagnosis of lung cancer would improve prognosis and enlarge treatment options. Analysis of exhaled breath would be an ideal diagnostic method, since it is non-invasive and totally painless. METHODS: Exhaled breath and inhaled room air samples were analyzed using proton transfer reaction mass spectrometry (PTR-MS) and solid phase microextraction with subsequent gas chromatography mass spectrometry (SPME-GCMS). For the PTR-MS measurements, 220 lung cancer patients and 441 healthy volunteers were recruited. For the GCMS measurements, we collected samples from 65 lung cancer patients and 31 healthy volunteers. Lung cancer patients were in different disease stages and under treatment with different regimes. Mixed expiratory and indoor air samples were collected in Tedlar bags, and either analyzed directly by PTR-MS or transferred to glass vials and analyzed by gas chromatography mass spectrometry (GCMS). Only those measurements of compounds were considered, which showed at least a 15% higher concentration in exhaled breath than in indoor air. Compounds related to smoking behavior such as acetonitrile and benzene were not used to differentiate between lung cancer patients and healthy volunteers. RESULTS: Isoprene, acetone and methanol are compounds appearing in everybody's exhaled breath. These three main compounds of exhaled breath show slightly lower concentrations in lung cancer patients as compared to healthy volunteers ($p < 0.01$ for isoprene and acetone, $p = 0.011$ for methanol; PTR-MS measurements). A comparison of the GCMS-results of 65 lung cancer patients with those of 31 healthy volunteers revealed differences in concentration for more than 50 compounds. Sensitivity for detection of lung cancer patients based on presence of (one of) 4 different compounds not arising in exhaled breath of healthy volunteers was 52% with a specificity of 100%. Using 15 (or 21) different compounds for distinction, sensitivity was 71% (80%) with a specificity of 100%. Potential marker compounds are alcohols, aldehydes, ketones and hydrocarbons. CONCLUSION: GCMS-SPME is a relatively insensitive method. Hence compounds not appearing in exhaled breath of healthy volunteers may be below the limit of detection (LOD). PTR-MS, on the other hand, does not need preconcentration and gives much more reliable quantitative results then GCMS-SPME. The shortcoming of PTR-MS is that it cannot identify compounds with certainty. Hence SPME-GCMS and PTR-MS complement each other, each method having its particular advantages and disadvantages. Exhaled breath analysis is promising to become a future non-invasive lung cancer screening method. In order to proceed towards this goal, precise identification of compounds observed in exhaled breath of lung cancer patients is necessary. Comparison with compounds released from lung cancer cell cultures, and additional information on exhaled breath composition in other cancer forms will be important.	/pubmed/19788722	Bajtarevic A, Ager C, Pienz M, Klieber M, Schwarz K, Ligor M, Ligor T, Filipiak W, Denz H, Fiegl M, Hilbe W, Weiss W, Lukas P, Jamnig H, Hackl M, Haidenberger A, Buszewski B, Miekisch W, Schubert J, Amann A.	BMC Cancer. 2009 Sep 29;9:348. doi: 10.1186/1471-2407-9-348.	BMC Cancer. 2009	PubMed	citation	PMID:19788722 | PMCID:PMC2761408	pubmed	19788722

44	0	does not discuss AGER							1		Changes in weather and the effects on pediatric asthma exacerbations.	BACKGROUND: Pediatric asthma exacerbations may correlate with changes in weather, yet this relationship is not well defined. OBJECTIVE: To determine the effects of fluctuations in climatic factors (temperature, humidity, and barometric pressure) on pediatric asthma exacerbations. METHODS: A retrospective study was performed at 1 large urban hospital during a 2-year period (January 1, 2004, to December 31, 2005). Children presenting to the emergency department (ED) for an asthma exacerbation were included. Data on climactic factors, pollutants, and aeroallergens were collected daily. The relationship of daily (intraday) or between-day (interday) changes in climactic factors and asthma ED visits was evaluated using time series analysis, controlling for seasonality, air pollution, and aeroallergen exposure. The effects of climactic factors were evaluated on the day of admission (T=0) and up to 5 days before admission (T-5 through T-1). RESULTS: There were 25,401 asthma ED visits. A 10% intraday increase in humidity on day T-1 or day T-2 was associated with approximately 1 additional ED visit for asthma (P < .001 and P = .01, respectively). Interday changes in humidity from day T - 3 to T-2 were also associated with more ED visits (P < .001). Interday changes in temperature from T-1 to T = 0 increased ED visits, with a 10 degrees F increase being associated with 1.8 additional visits (P = .006). No association was found with changes in barometric pressure. CONCLUSION: Fluctuations in humidity and temperature, but not barometric pressure, appear to influence ED visits for pediatric asthma. The additional ED visits occur 1 to 2 days after the fluctuation.	/pubmed/19788019	Mireku N, Wang Y, Ager J, Reddy RC, Baptist AP.	Ann Allergy Asthma Immunol. 2009 Sep;103(3):220-4. doi: 10.1016/S1081-1206(10)60185-8.	Ann Allergy Asthma Immunol. 2009	PubMed	citation	PMID:19788019	pubmed	19788019
45	0	does not discuss AGER							1		Association between modelled traffic-related air pollution and asthma score in the ECRHS.	The aim of our analysis was to study the association between air pollution and asthma among adults. For this goal, a previously developed "asthma score" was used. Persons aged 25-44 yrs were randomly selected (1991-1993) and followed up (2000-2002) within the European Community Respiratory Health Survey (ECRHS I and II, respectively). The asthma score was defined from 0 to 5, based on the positive answers to the following symptoms reported for the last 12 months: wheeze/breathlessness, chest tightness, dyspnoea at rest, dyspnoea after exercise and woken by dyspnoea. Participants' home addresses were linked to outdoor modelled NO2 estimates for 2001. Negative binomial regression was used to model the asthma score. The score from ECRHS II was positively associated with NO2 (ratio of the mean asthma score (RMS) 1.23, 95% CI 1.09-1.38, for an increase of 10 microg x m(-3)). After excluding participants with asthma and symptoms at baseline, the association remained (RMS 1.25, 95% CI 1.05-1.51), and was particularly high among those reporting a high score in ECRHS II. The latter probably reflects incident cases of asthma. Our results suggest that traffic-related pollution causes asthma symptoms and possibly asthma incidence in adults. The asthma score offers an alternative with which to investigate the course and aetiology of asthma in adults.	/pubmed/19443533	Jacquemin B, Sunyer J, Forsberg B, Aguilera I, Bouso L, Briggs D, de Marco R, GarcÃa-Esteban R, Heinrich J, Jarvis D, Maldonado JA, Payo F, Rage E, Vienneau D, KÃ¼nzli N.	Eur Respir J. 2009 Oct;34(4):834-42. doi: 10.1183/09031936.00138208. Epub 2009 May 14.	Eur Respir J. 2009	PubMed	citation	PMID:19443533	pubmed	19443533

46	0	exhaled breath analysis in lung cancer						1			Determination of volatile organic compounds in exhaled breath of patients with lung cancer using solid phase microextraction and gas chromatography mass spectrometry.	BACKGROUND: Analysis of exhaled breath is a promising diagnostic method. Sampling of exhaled breath is non-invasive and can be performed as often as considered desirable. There are indications that the concentration and presence of certain of volatile compounds in exhaled breath of lung cancer patients is different from concentrations in healthy volunteers. This might lead to a future diagnostic test for lung cancer. METHODS: Exhaled breath samples from 65 patients with different stages of lung cancer and undergoing different treatment regimes were analysed. Mixed expiratory and indoor air samples were collected. Solid phase microextraction (SPME) with carboxen/polydimethylsiloxane (CAR/PDMS) sorbent was applied. Compounds were analysed by means of gas chromatography (GC) and mass spectrometry (MS). RESULTS: The method we used allowed identification with the spectral library of 103 compounds showing at least 15% higher concentration in exhaled breath than in inhaled air. Among those 103 compounds, 84 were confirmed by determination of the retention time using standards based on the respective pure compound. Approximately, one third of the compounds detected were hydrocarbons. We found aromatic hydrocarbons, alcohols, aldehydes, ketones, esters, ethers, sulfur compounds, nitrogen-containing compounds and halogenated compounds. Acetonitrile and benzene were two of 10 compounds which correlated with smoking behaviour. A comparison of results from cancer patients with those of 31 healthy volunteers revealed differences in the concentration and presence of certain compounds. The sensitivity for detection of lung cancer patients based on eight different compounds not seen in exhaled breath of healthy volunteers was 51% and the specificity was 100%. These eight potential markers for detection of lung cancer are 1-propanol, 2-butanone, 3-butyn-2-ol, benzaldehyde, 2-methyl-pentane, 3-methyl-pentane, n-pentane and n-hexane. CONCLUSIONS: SPME is a relatively insensitive method and compounds not observed in exhaled breath may be present at a concentration lower than LOD. The main achievement of the present work is the validated identification of compounds observed in exhaled breath of lung cancer patients. This identification is indispensible for future work on the biochemical sources of these compounds and their metabolic pathways.	/pubmed/19397483	Ligor M, Ligor T, Bajtarevic A, Ager C, Pienz M, Klieber M, Denz H, Fiegl M, Hilbe W, Weiss W, Lukas P, Jamnig H, Hackl M, Buszewski B, Miekisch W, Schubert J, Amann A.	Clin Chem Lab Med. 2009;47(5):550-60. doi: 10.1515/CCLM.2009.133.	Clin Chem Lab Med. 2009	PubMed	citation	PMID:19397483	pubmed	19397483

47	0	does not discuss AGER							1		Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults.	BACKGROUND: Effects of air pollution exposure on IgE-mediated response in asthmatics are poorly investigated. The aim was to examine the relationship between air pollution concentrations and total IgE levels in adult asthmatics. METHODS: The present study relates to the 369 asthmatic adults from the French Epidemiological study on Genetics and Environment of Asthma (EGEA), with availability of data on both total serum IgE measurements and air pollution concentrations. Geo-statistical models were performed on 4 x 4 km grids to assess individual outdoor air pollution exposure. Annual outdoor concentrations of ozone (O(3)), nitrogen dioxide (NO(2)), sulphur dioxide (SO(2)), and particulate matter smaller than 10 microm size (PM(10)), and concentrations of summer ozone were assigned to subject's home address. RESULTS: The geometric mean of total IgE was 161 IU/ml and the average of O(3) exposure was 44.9 +/- 9.5 microg/m(3). Ozone concentrations were positively related to total IgE levels and an increase of 10 microg/m(3) of O(3) resulted in an increase of 20.4% (95% CI = 3.0-40.7) in total IgE levels. Adjustment for age, gender, smoking habits and previous life in the countryside did not change the results, and an increase of 19.1% (2.4-38.6) in total IgE was observed with O(3). Negative associations observed between NO(2) and total IgE levels disappeared after including O(3) in the models. Neither SO(2) nor PM(10) were correlated with total IgE levels. CONCLUSIONS: Results suggest that O(3) or related ambient pollutants may up-regulate total IgE levels among asthmatic adults.	/pubmed/19076539	Rage E, Jacquemin B, Nadif R, Oryszczyn MP, Siroux V, Aguilera I, Kauffmann F, KÃ¼nzli N; Epidemiological Study on the Genetics Environment of Asthma (EGEA)..	Allergy. 2009 Jan;64(1):40-6. doi: 10.1111/j.1398-9995.2008.01800.x. Epub 2008 Nov 28.	Allergy. 2009	PubMed	citation	PMID:19076539	pubmed	19076539
48	0	does not discuss AGER							1		Air pollution and asthma severity in adults.	BACKGROUND/OBJECTIVES: There is evidence that exposure to air pollution affects asthma, but the effect of air pollution on asthma severity has not been addressed. The aim was to assess the relation between asthma severity during the past 12 months and home outdoor concentrations of air pollution. METHODS: Asthma severity over the past 12 months was assessed in two complementary ways among 328 adult asthmatics from the French Epidemiological study on the Genetics and Environment of Asthma (EGEA) examined between 1991 and 1995. The four-class severity score integrated clinical events and type of treatment. The five-level asthma score is based only on the occurrence of symptoms. Nitrogen dioxide (NO(2)), sulphur dioxide (SO(2)) and ozone (O(3)) concentrations were assigned to each residence using two different methods. The first was based on the closest monitor data from 1991 to 1995. The second consisted of spatial models that used geostatistical interpolations and then assigned air pollutants to the geo-coded residences (1998). RESULTS: Higher asthma severity score was significantly related to the 8-hour average of ozone during April-September (O(3)-8 h) and the number of days (O(3)-days) with 8-hour ozone averages above 110 microg.m(-3) (for a 36-day increase, equivalent to the interquartile range, in O(3)-days, odds ratio 2.22 (95% confidence interval 1.61 to 3.07) for one class difference in score). Adjustment for age, sex, smoking habits, occupational exposure, and educational level did not alter results. Asthma severity was unrelated to NO(2). Both exposure assessment methods and severity scores resulted in very similar findings. SO(2) correlated with severity but reached statistical significance only for the model-based assignment of exposure. CONCLUSIONS: The observed associations between asthma severity and air	/pubmed/19017701	Rage E, Siroux V, KÃ¼nzli N, Pin I, Kauffmann F; Epidemiological Study on the Genetics and Environment of Asthma..	Occup Environ Med. 2009 Mar;66(3):182-8. doi: 10.1136/oem.2007.038349. Epub 2008 Nov 18.	Occup Environ Med. 2009	PubMed	citation	PMID:19017701 | PMCID:PMC2663354	pubmed	19017701

											pollution, in particular O(3), support the hypothesis that air pollution at levels far below current standards increases asthma severity.										
49	0	in vitro				1					Immortalization of human alveolar epithelial cells to investigate nanoparticle uptake.	Primary human alveolar type 2 (AT2) cells were immortalized by transduction with the catalytic subunit of telomerase and simian virus 40 large-tumor antigen. Characterization by immunochemical and morphologic methods demonstrated an AT1-like cell phenotype. Unlike primary AT2 cells, immortalized cells no longer expressed alkaline phosphatase, pro-surfactant protein C, and thyroid transcription factor-1, but expressed increased caveolin-1 and receptor for advanced glycation end products (RAGE). Live cell imaging using scanning ion conductance microscopy showed that the cuboidal primary AT2 cells were approximately 15 microm and enriched with surface microvilli, while the immortal AT1 cells were attenuated more than 40 microm, resembling these cells in situ. Transmission electron microscopy highlighted the attenuated morphology and showed endosomal vesicles in some immortal AT1 cells (but not primary AT2 cells) as found in situ. Particulate air pollution exacerbates cardiopulmonary disease. Interaction of ultrafine, nano-sized particles with the alveolar epithelium and/or translocation into the cardiovasculature may be a contributory factor. We hypothesized differential uptake of nanoparticles by AT1 and AT2 cells, depending on particle size and surface charge. Uptake of 50-nm and 1-microm fluorescent latex particles was investigated using confocal microscopy and scanning surface confocal microscopy of live cells. Fewer than 10% of primary AT2 cells internalized particles. In contrast, 75% immortal AT1 cells internalized negatively charged particles, while less than 55% of these cells internalized positively charged particles; charge, rather than size, mattered. The process was rapid: one-third of the total cell-associated negatively charged 50-nm particle fluorescence measured at 24 hours was internalized during the first hour. AT1 cells could be important in translocation of particles from the lung into the circulation.	/pubmed/18539954	Kemp SJ, Thorley AJ, Gorelik J, Seckl MJ, O'Hare MJ, Arcaro A, Korchev Y, Goldstraw P, Tetley TD.	Am J Respir Cell Mol Biol. 2008 Nov;39(5):591-7. doi: 10.1165/rcmb.2007-0334OC. Epub 2008 Jun 6.	Am J Respir Cell Mol Biol. 2008	PubMed	citation	PMID:18539954 | PMCID:PMC2643209	pubmed	18539954

50	0	NOT_LUNG				1					Expressive/suppressive anger-coping responses, gender, and types of mortality: a 17-year follow-up (Tecumseh, Michigan, 1971-1988).	OBJECTIVES: This study examined prospectively (1971-1988) the relationship between anger-coping responses, gender, and mortality (N = 91) in a representative sample of men (N = 324) and women (N = 372), aged 30 to 69, from the Tecumseh Community Health Study. METHODS: Anger-coping was measured by responses to hypothetical unfair anger-provoking situations. Cox proportional hazard regressions were used adjusted for seven health risk factors (age, smoking, relative weight, systolic blood pressure (SBP), bronchial problems, FEV1, and cardiovascular (CV) risk). RESULTS: Men's suppressed anger interacted significantly with SBP and also with bronchial problems to predict both all-cause and CV mortality. Women showed direct relationships between suppressed anger and early mortality (all-cause, CV, and cancer). Women also showed an interaction of spouse-suppressed anger and SBP for all-cause and CV mortality. Data suggest men who expressed their anger died earlier of cancer (N = 16) deaths. CONCLUSIONS: Suppressed anger at the time of an unjust attack may become chronic resentment (intermittent rage or hatred) about which little is known and requires research. The design for future research should experimentally measure both suppressed anger-coping responses (after an unfair attack) and morbidity (eg, blood pressure, bronchitis, immune disorder, etc.) to predict prospectively to earlier mortality.	/pubmed/12883109	Harburg E, Julius M, Kaciroti N, Gleiberman L, Schork MA.	Psychosom Med. 2003 Jul-Aug;65(4):588-97.	Psychosom Med. 2003	PubMed	citation	PMID:12883109	pubmed	12883109
51	0	lung cancer						1			Gene expression patterns of paired bronchioloalveolar carcinoma and benign lung tissue.	A variant of adenocarcinoma, bronchioloalveolar carcinoma (BAC), has increased in incidence since 1950 and now represents 2-14% of all lung cancers. There has been concomitant diminution in the proportion of squamous cell carcinoma, the most common form of primary lung cancer. The BAC form of adenocarcinoma occurs disproportionately in women, has an earlier age of onset than conventional pulmonary carcinoma, and is not linked to smoking. The increased incidence of BAC in both smokers and non-smokers suggests that BAC may have an environmental etiology other than smoking. To explore this possibility, we compared the patterns of gene expression in paired samples of tumor and normal lung tissue from 3 patients with a pathologic diagnosis of BAC. Characterization of the gene expression patterns of the paired tissue samples was performed by oligonucleotide microarray analysis of 12,000 known genes and expressed sequence tags (ESTs). We identified 12 genes that were up-regulated > or = 2-fold in all 3 tumors and 6 genes that were down-regulated in all 3 tumors to < or = 0.20 times the baseline. These findings suggest that large scale transcriptional profiling of BAC tumors may disclose a pattern of altered cellular expression in response to genetic changes, diseases, and environmental insult; such transcriptional profiling may aid in diagnosis and therapy.	/pubmed/11688848	Goodwin LO, Mason JM, Hajdu SI.	Ann Clin Lab Sci. 2001 Oct;31(4):369-75.	Ann Clin Lab Sci. 2001	PubMed	citation	PMID:11688848	pubmed	11688848

52	0	LUNG_CANCER						1			Autoimmunity to collagen in human lung cancer.	Autoantibodies have been described in human cancer patients as well as in animal models of malignancy. The extracellular matrix and especially basement membranes act as barriers for tumor cell invasion. Collagen, particularly types I, III, and IV, are major constituents of the extracellular matrix. We tested the hypothesis that autoimmunity to collagen antigens is present in lung cancer. Sera from 67 patients with lung cancer and 50 reference subjects were tested for anticollagen antibodies by using purified human collagen types I-V and for antibodies binding human cartilage aggrecan proteoglycan. Antibody levels were determined by using ELISA. The relationship of serum levels of these antibodies to patient survival, histology, treatment response, disease stage, and pack years of smoking was examined by using multiple regression and discriminant function analyses. A subgroup of 45 patients in whom a smoking history was available was analyzed separately. Within 1 month of the initiation of therapy, mean serum levels of antibodies binding fibrillar collagen types I-III and V were significantly higher ($P < 0.025$) than were those in control sera (43.2% of patients positive for one or more anticollagen antibodies). Antibodies binding aggrecan proteoglycan were not different between patients and control sera. In the lung cancer patients, the levels of serum antibodies binding types IV and V collagens contributed to the variance of progression-free survival days, survival days, and the duration of favorable response in opposite directions. Histological cell type contributed to the variance in the level of serum antibody binding collagen types IV and V. Lower levels of antibody binding type IV and higher levels of antibody binding type V were associated with small cell carcinoma. The pack-years of smoking only contributed to the variance in the level of serum antibody binding type V collagen. We conclude that autoantibodies to fibrillar collagen antigens are present frequently in lung cancer patients, and their levels may be related to histological cell type and to the duration of the response to treatment.	/pubmed/8548751	Fernandez-Madrid F, Karvonen RL, Kraut MJ, Czelusniak B, Ager JW.	Cancer Res. 1996 Jan 1;56(1):121-6.	Cancer Res. 1996	PubMed	citation	PMID:8548751	pubmed	8548751	
53	0	in vitro				1					Cigarettes smoke extract induces inflammatory gene expression in human bronchial epithelial cells.	AB Background Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder of the respiratory tract characterised by airflow obstruction. It is increasingly recognised that the innate immune pattern-recognition receptors may contribute to airway inflammation in COPD in response to environmental factors such as cigarette smoke (CS). One pattern-recognition receptor that has recently come to attention in chronic airway disease is the cell surface receptor for advanced glycation end products (RAGE). RAGE also exists as a soluble form (sRAGE) that primarily functions as receptor decoy and an endogenous inhibitor of RAGE signalling. Clinical studies show that smokers with or without COPD have significantly greater levels of RAGE expression in airway epithelial cells compared with never smokers. However, the role of RAGE in mediating CSinduced inflammatory gene expression has not been understood. We hypothesise that CS can induce RAGE expression, sRAGE reduction, and inflammatory gene expression in human bronchial epithelial cells (BEAS-2B). Method Confluent BEAS-2B cells were treated with different concentrations of Cigarette Smoke Extract (CSE) (1%, 2.5%, and 5%) for 24 hours. Western blotting was used to assess protein expression of RAGE in cell lysate. ELISA was used to measure interleukin 6 (IL-6), CXCL1 (GRO-a), CXCL5 (ENA- 78), CXCL8 (IL-8), CXCL10 (IP-10), CCL11 (eotaxin), and sRAGE in culture medium. Result We found that IL-6 and CXCL8 releases were markedly increased by CSE in a concentration-dependant manner, but CXCL-1, CXCL5, CXCL10 and CCL11 could not be detected in both untreated and CSE-treated cells. Interestingly, RAGE was highly expressed in untreated cells and CSE treatment did not further increase its expression. Furthermore, sRAGE was also undetectable in both untreated and CSE-treated cells. Conclusion These findings suggest that CSE can induce inflammatory gene expression in BEAS-2B cells. Further experiments are being conducted to explore the effect of CSE on other inflammatory gene expression and to investigate the role of RAGE in mediating CSE-mediated inflammatory response in BEAS-2B cells.	Click here for full text options	Alshehri M. Brand O. Alqarni A. Pasini A. Pang L.	Thorax. Conference: British Thoracic Society Winter Meeting, BTS 2017. United Kingdom. 72 (Supplement 3) (pp A146), 2017. Date of Publication: December 2017.	BMJ Publishing Group	Embase	Conference Abstract			

54	0	duplicate	1								Advanced glycation endproducts and their receptor in different body compartments in COPD.	Background: Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by chronic airway inflammation and emphysema, and is caused by exposure to noxious particles or gases, e.g. cigarette smoke. Smoking and oxidative stress lead to accelerated formation and accumulation of advanced glycation end products (AGEs), causing local tissue damage either directly or by binding the receptor for AGEs (RAGE). This study assessed the association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. Methods: Healthy smoking and never-smoking controls (n = 191) and COPD patients (n = 97, GOLD stage I-IV) were included. Autofluorescence (SAF) was measured in the skin, AGEs (pentosidine, CML and CEL) and sRAGE in blood and sputum by ELISA, and in bronchial biopsies by immunohistochemistry. eQTL analysis was performed in bronchial biopsies. Results: COPD patients showed higher SAF values and lower plasma sRAGE levels compared to controls and these values associated with decreased lung function (p <0.001; adjusting for relevant covariates). Lower plasma sRAGE levels significantly and independently predicted higher SAF values (p < 0.001). One SNP (rs2071278) was identified within a region of 50 kB flanking the AGER gene, which was associated with the gene and protein expression levels of AGER and another SNP (rs2071278) which was associated with the accumulation of AGEs in the skin. Conclusion: In COPD, AGEs accumulate differentially in body compartments, i.e. they accumulate in the skin, but not in plasma, sputum and bronchial biopsies. The association between lower sRAGE and higher SAF levels supports the hypothesis that the protective mechanism of sRAGE as a decoy-receptor is impaired in COPD.	Click here for full text options	Hoonhorst S.J.M. Lo Tam Loi A.T. Pouwels S.D. Faiz A. Telenga E.D. van den Berge M. Koenderman L. Lammers J.-W.J. Boezen H.M. van Oosterhout A.J.M. Lodewijk M.E. Timens W. Postma D.S. ten Hacken N.H.T.	Respiratory Research. 17 (1) (no pagination), 2016. Article Number: 46. Date of Publication: 26 Apr 2016.	BioMed Central Ltd. (E-mail: info@biomedcentral.com)	Embase	Article				
55	0	duplicate	1								Relationship between gene expression and lung function in Idiopathic Interstitial Pneumonias.	Background: Idiopathic interstitial pneumonias (IIPs) are a group of heterogeneous, somewhat unpredictable diseases characterized by progressive scarring of the interstitium. Since lung function is a key determinant of survival, we reasoned that the transcriptional profile in IIP lung tissue would be associated with measures of lung function, and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with IIP diagnosis and 50 control lungs, we identified genes whose expression is associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as categorical (severe vs mild disease) or continuous variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), including those with established role in fibrosis (ADAMTS4, ADAMTS9, AGER, HIF-1aalpha, SERPINA3, SERPINE2, and SELE) as well as novel IIP candidate genes such as rhotekin 2 (RTKN2) and peptidase inhibitor 15 (PI15). Protein-protein interactome analysis of 553 genes whose expression is significantly associated with lung function when modeled as continuous variables demonstrates that more severe presentation of IIPs is characterized by an increase in cell cycle progression and apoptosis, increased hypoxia, and dampened innate immune response. Our findings were validated in an independent cohort of 131 IIPs and 40 controls at the mRNA level and for one gene (RTKN2) at the protein level by immunohistochemistry in a subset of samples. Conclusions: We identified commonalities and differences in gene expression among different subtypes of IIPs. Disease progression, as characterized by lower measures of FVC and DLCO, results in marked changes in expression of novel and established genes and pathways involved in IIPs. These genes and pathways represent strong candidates for biomarker studies and potential therapeutic targets for IIP severity.	Click here for full text options	Steele M.P. Luna L.G. Coldren C.D. Murphy E. Hennessy C.E. Heinz D. Evans C.M. Groshong S. Cool C. Cosgrove G.P. Brown K.K. Fingerlin T.E. Schwarz M.I. Schwartz D.A. Yang I.V.	BMC Genomics. 16 (1) (no pagination), 2015. Article Number: 869. Date of Publication: October 26, 2015.	BioMed Central Ltd. (E-mail: info@biomedcentral.com)	Embase	Article				

56	0	abstract		1							Sputum-plasma ratio of soluble receptor for advanced glycation end-products in patients with chronic obstructive pulmonary disease.	Background Chronic obstructive pulmonary disease (COPD) is associated with systemic inflammatory consequences. Receptor for advanced glycation end products (RAGE) acts as an important progression factor amplifying the immune and inflammatory responses in several pathophysiological conditions. The soluble form of RAGE (sRAGE) acts as a decoy for the receptor ligands and is thus thought to protect against excessive inflammation. Conflicting reports exist about sRAGE value in stable and exacerbating COPD. Objective To assess the sputum to plasma ratio of sRAGE in stable COPD patients. **Subjects and methods** The study included 44 adult patients of both sexes who were presented to Alexandria Main University Hospital between March and July 2015. Patients were categorized into three groups; 15 stable COPD patients (Group I), 15 smokers without COPD (Group II), and 14 healthy non-smokers (Group III). Measurement of sRAGE level in induced sputum and plasma was performed using ELISA technique. Results The study included 38 male patients and 6 female patients, whose median ages were 50, 42 and 35.5 years in Groups I, II, and III respectively ($p < 0.001$). Median FEV1% predicted were 35, 96, and 105% in Groups I, II, and III respectively ($p < 0.001$). No statistical significant difference was found among all groups regarding sRAGE level in induced sputum, plasma or sputum/plasma ratio ($p = 0.092, 0.372, 0.154$, respectively). Although levels of sRAGE is apparently higher in induced sputum rather than in plasma, it lacked significance ($r = 0.27$, $p = 0.08$). Furthermore, no significant correlation was found between either plasma or sputum sRAGE level and predicted FEV1% ($r = -0.11$, $p = 0.48$ and $r = -0.12$, $p = 0.28$, respectively). Conclusions sRAGE level either in induced sputum, plasma or sputum plasma ratio is not significantly different between stable COPD patients, smokers and healthy controls. Thus, sRAGE cannot be considered as a marker of either diagnosis or severity of COPD. Copyright © 2016 The Egyptian Society of Chest Diseases and Tuberculosis	Click here for full text options	Hassanein E.G. ElGanady A.A. Baess A.I. Issa Y.A. ElAkhtel E.M.	Egyptian Journal of Chest Diseases and Tuberculosis. 65 (3) (pp 573-578), 2016. Date of Publication: 01 Jul 2016.	Egyptian Society Of Chest Diseases And Tuberculosis (E-mail: info@egyptsct.org)	Embase	Article				
57	0	not human				1					Ex vivo elastase treatment disrupts parenchymal structure and enhances airway narrowing in precision cut lung slices.	Background Chronic obstructive pulmonary disease (COPD) is a chronic lung disease caused primarily by smoking. COPD patients suffer from a loss of lung function due to airway inflammation, airway remodelling and in some patients emphysema development. Alterations in the parenchymal structure, due to the presence of elastolytic enzymes and oxidative stress may affect airway mechanics in COPD. Here, we hypothesize that ex vivo treatment of lung slices with elastase or H2O2 enhances bronchoconstriction caused by a disrupted parenchymal structure. Aim To investigate the relationship between the parenchymal structure and airway narrowing in an ex vivo precision cut lung slice (PCLS) model after treatment with elastase or H2O2. Methods Lungs of C57Bl/6J mice (n=8) were sliced (250 mum) and treated ex vivo with elastase (2.5 mug/ml) or H2O2 (200 muM) for 16 hours. Following treatment, slices were washed twice with medium and incubated for another 24 hours after which the slices were collected. To determine airway narrowing, methacholine-induced contraction studies were performed. Parenchymal structure was assessed by confocal microscopy after which mean linear intercept (Lmi) was determined. Gene expression levels of markers of alveolar type I and II cell repair, known to be decreased in COPD, were assessed using RT-PCR. Results Following elastase, but not H2O2 treatment, slices showed a significant increase in Lmi (basal 75.91 mum vs elastase 90.18 mum ($p=0.04$) and H2O2 84.95 mum ($p=0.76$)), reflective of an altered parenchymal structure. In addition, elastase enhanced methacholine-induced airway narrowing as shown by a significant decrease in pEC50 (-5.78 vs -6.68 log M, $p=0.01$). H2O2 did not change pEC50 (-5.78 vs -5.99 log M, $p=0.64$), but showed a trend for increasing Emax (44.12 vs 67.35 % contraction, $p=0.06$). Elastase did not alter Emax significantly (44.12 vs 61.11 % contraction, $p=0.12$) Expression levels of alveolar type I and type II markers Aqp5 and RAGE were decreased ($p<0.05$) following elastase treatment, whereas H2O2 -treatment decreased the expression of RAGE, Con43, T1alpha, PAI1 and SFTPC mRNA ($p<0.05$). Conclusion Treatment of PCLS with elastase, but not with H2O2 enhances airway narrowing in response to methacholine. This is associated with decreased gene expression levels of several markers of alveolar repair and a larger Lmi. These findings support	Click here for full text options	Van Dijk E.M. Culha S. Bidan C. Menzen M. Gosens R.	FASEB Journal. Conference: Experimental Biology 2016, EB. San Diego, CA United States. Conference Publication: (var.pagings). 30 (no pagination), 2016. Date of Publication: April 2016.	FASEB	Embase	Conference Abstract			

											our hypothesis that the link between increased bronchoconstriction and a disrupted parenchymal structure can be mimicked using PCLS ex vivo. PCLS may be a promising model to study therapies aimed at lung repair.										
58	1										A genome-wide association study of emphysema and airway quantitative imaging phenotypes.	Rationale: Chronic obstructive pulmonary disease (COPD) is defined by the presence of airflow limitation on spirometry, yet subjects with COPD can have marked differences in computed tomography imaging. These differences may be driven by genetic factors. We hypothesized that a genome-wide association study (GWAS) of quantitative imaging would identify loci not previously identified in analyses of COPD or spirometry. In addition, we sought to determine whether previously described genome-wide significant COPD and spirometric loci were associated with emphysema or airway phenotypes. Objectives: To identify genetic determinants of quantitative imaging phenotypes. Methods: We performed a GWAS on two quantitative emphysema and two quantitative airway imaging phenotypes in the COPDGene (non-Hispanic white and African American), ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), NETT (National Emphysema Treatment Trial), and GenKOLS (Genetics of COPD, Norway) studies and on percentage gas trapping in COPDGene. We also examined specific loci reported as genomewide significant for spirometric phenotypes related to airflow limitation or COPD. Measurements and Main Results: The total sample size across all cohorts was 12,031, of whom 9,338 were from COPDGene. We identified five loci associated with emphysema-related phenotypes, one with airway-related phenotypes, and two with gas trapping. These loci included previously reported associations, including the HHIP, 15q25, and AGER loci, as well as novel associations near SERPINA10 and DLC1. All previously reported COPD and a significant number of spirometric GWAS loci were at least nominally ($P < 0.05$) associated with either emphysema or airway phenotypes. Conclusions: Genome-wide analysis may identify novel risk factors for quantitative imaging characteristics in COPD and also identify imaging features associated with previously identified lung function loci	Click here for full text options	Cho M.H. Castaldi P.J. Hersh C.P. Hobbs B.D. Barr R.G. Tal-Singer R. Bakke P. Gulsvik A. San Jose Estepar R. Van Beek E.J.R. Coxson H.O. Lynch D.A. Washko G.R. Laird N.M. Crapo J.D. Beaty T.H. Silverman E.K.	American Journal of Respiratory and Critical Care Medicine. 192 (5) (pp 559-569), 2015. Date of Publication: 01 Sep 2015.	American Thoracic Society (E-mail: malexander@thoracic.org)	Embase	Article				

59	0	duplicate	1								Receptor for advanced glycation end-products regulates lung fluid balance via protein kinase C-gp91^{phox} signaling to epithelial sodium channels.	AB The receptor for advanced glycation end-products (RAGE), a multiligand member of the Ig family, may play a crucial role in the regulation of lung fluid balance. We quantified soluble RAGE (sRAGE), a decoy isoform, and advanced glycation end-products (AGEs) from the bronchoalveolar lavage fluid of smokers and nonsmokers, and tested the hypothesis that AGEs regulate lung fluid balance through protein kinase C (PKC)-gp91phox signaling to the epithelial sodium channel (ENaC). Human bronchoalveolar lavage samples fromsmokers showed increasedAGEs (9.02 +/- 3.03 mug versus 2.48 +/- 0.53 mug), lower sRAGE (1,205 +/- 292 pg/ml versus 1,9106263 pg/ml), and lower volume(s) of epithelial lining fluid (97 +/- 14 ml versus 133 +/- 17 ml). sRAGE levels did not predict ELF volumes in nonsmokers; however, in smokers, higher volumes of ELF were predicted with higher levels of sRAGE. Single-channel patch clamp analysis of rat alveolar epithelial type 1 cells showed that AGEs increased ENaC activity measured as the product of the number of channels (N) and the open probability (Po) (NPo) from 0.19 +/- 0.08 to 0.83 +/- 0.22 (P = 0.017) and the subsequent addition of 4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-N-oxyl decreased ENaC NPo to 0.15 +/- 0.07 (P = 0.01). In type 2 cells, human AGEs increased ENaC NPo from 0.12 +/- 0.05 to 0.53 +/- 0.16 (P = 0.025) and the addition of 4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-N -oxyl decreased ENaC NPo to 0.10 +/- 0.03 (P = 0.013). Using molecular and biochemical techniques, we observed that inhibition of RAGE and PKC activity attenuated AGE-induced activation of ENaC. AGEs induced phosphorylation of p47phox and increased gp91phox dependent reactive oxygen species production, a response that was abrogated with RAGE or PKC inhibition. Finally, tracheal instillation of AGEs promoted clearance of lung fluid, whereas concomitant inhibition of RAGE, PKC, and gp91phox abrogated the response.	Click here for full text options	Downs C.A. Kreiner L.H. Johnson N.M. Brown L.A. Helms M.N.	American Journal of Respiratory Cell and Molecular Biology. 52 (1) (pp 75-87), 2015. Date of Publication: 01 Jan 2015.	American Thoracic Society (E-mail: malexander@thoracic.org)	Embase	Article				
60	0	lung cancer						1			Expression of the receptor for advanced glycation end-products and frequency of polymorphism in lung cancer.	AB Receptor for advanced glycation end products (RAGE) is associated with the pathogenesis of cancer progression. The pathological effects mediated through RAGE are physiologically inhibited by soluble RAGE (sRAGE). The aim of the present study was to identify the expression of the sRAGE, RAGE and RAGE ligands in serum samples and lung cancer tissue obtained from lung cancer patients. Using ELISA and immunohistochemistry, it was observed that the sRAGE levels were downregulated in the serum, the expression of RAGE was decreased in the lung cancer tissue and the RAGE ligands HMGB1 and S100 were upregulated in cancer tissue. Furthermore, the presence of several selected types of RAGE polymorphism that occur in lung cancers were measured in the tissue samples. An association between the -429T/C and 2184A/G polymorphisms of RAGE and the genesis and progression of lung cancer was identified. The comparison between various histological subtypes and stages of lung cancer was performed with the aim to clarify the biological role of the RAGE gene, and identify a biomarker to aid diagnosis and predict the prognosis for lung cancer patients.	Click here for full text options	Wang H. Li Y. Yu W. Ma L. Ji X. Xiao W.	Oncology Letters. 10 (1) (pp 51-60), 2015. Date of Publication: 01 Jul 2015.	Spandidos Publications (10 Vriaxidos Street, Athens 116 10, Greece)	Embase	Article				
61	0	lung cancer						1			Circulating soluble advanced glycation end product is inversely associated with the significant risk of developing cancer: evidence from a meta-analysis.	AB Currently, advanced glycation end product (RAGE) is receiving much attention in carcinogenesis research due to its involvement in cancer progression and metastasis. We therefore sought to examine the association of circulating soluble RAGE (sRAGE) with all types of cancer by a meta-analysis. The PubMed and EMBASE databases were searched before March 1, 2014. Data and study quality were assessed in duplicate. Effect estimates were expressed as weighted mean difference (WMD) and its 95 % confidence interval (CI). Altogether, nine eligible articles including 1,337 cancer patients and 1,839 controls were analyzed. The overall analysis indicated that circulating sRAGE was remarkably reduced by 222.07 pg/ml in cancer patients compared with controls (95 % CI: -373.77 to -70.37; P = 0.004), with heterogeneity and without publication bias. In subgroup analyses, this reduction was weakened yet still significant in prospective studies (WMD = -87.62; 95 % CI: -138.60 to -36.63; P = 0.001) with improved heterogeneity (I2 = 56.5 %; P = 0.056). Restricting analyses to the large studies (total number of subjects >=200) identified significant reduction of circulating sRAGE in cancer patients relative to controls (WMD = -231.34; 95 % CI: -450.10 to -12.58; P = 0.038). Further meta-regression analysis showed that smoking status explained some part of heterogeneity for the	Click here for full text options	He L. Bao H. Xue J. Zheng L. Zhang Q. Sun L. Pan H.	Tumor Biology. 35 (9) (pp 8749-8755), 2014. Date of Publication: 09 Oct 2014.	Kluwer Academic Publishers	Embase	Article				

												association of circulating sRAGE with cancer risk (regression coefficient: -67.02; P = 0.046). Our findings demonstrate a protective role of circulating sRAGE in the development of cancer, especially in patients without diabetes mellitus or with normal renal function.											
62	1	copd, not environmental									Changes of HMGB1 and sRAGE during the recovery of COPD exacerbation.	Background: Acute exacerbation of chronic obstructive pulmonary disease is associated with increased airway and systemic inflammation. However, the correlation between acute exacerbation/convalescence of chronic obstructive pulmonary disease (COPD) and simultaneous changes of high mobility group protein B1 (HMGB1) and soluble RAGE (sRAGE) levels has not been clearly clarified. The aim of this study was to assess these issues. **Methods:** A total of 44 COPD patients were recruited. Following a structured interview, plasma levels of HMGB1, sRAGE, fibrinogen and serum level of high-sensitivity C-reactive protein (hsCRP) were measured in patients with acute exacerbation of COPD (AECOPD) within 24 h of hospitalization and pre-discharge (convalescence). All patients were examined with spirometry in convalescence of COPD. Results: There was a significant decline in plasma HMGB1 (P<0.01), sRAGE (P<0.05), fibrinogen (P<0.01) and serum hsCRP (P<0.01) levels from acute exacerbation to convalescence phase of COPD. Changes of sRAGE was significantly correlated with changes of HMGB1 (r=0.4, P=0.007). COPD disease status correlated with the ratio of HMGB1/sRAGE, but not gender, age, course of disease, smoking history and FEV1% pred. Levels of HMGB1 and sRAGE were the highest in the current smoker group, and significantly decreased in ex-smoker group in both acute exacerbation and convalescence phase of COPD, however, their levels in never smoker group were higher than ex-smoker group in either phase of COPD. Conclusions: HMGB1 and sRAGE levels were dynamically changed between exacerbation and convalescence phase of COPD, HMGB1 and sRAGE were likely not only a potential marker in COPD exacerbation but also a therapeutic target for COPD treatment	Click here for full text options	Zhang Y. Li S. Wang G. Han D. Xie X. Wu Y. Xu J. Lu J. Li F. Li M.	Journal of Thoracic Disease. 6 (6) (pp 734-741), 2014. Date of Publication: 2014.	Pioneer Bioscience Publishing (E-mail: jtd@thepbpc.org)	Embase	Article				
63	0	duplicate	1								The association of plasma biomarkers with computed tomography-assessed emphysema phenotypes.	Rationale: Chronic obstructive pulmonary disease (COPD) is a phenotypically heterogeneous disease. In COPD, the presence of emphysema is associated with increased mortality and risk of lung cancer. High resolution computed tomography (HRCT) scans are useful in quantifying emphysema but are associated with radiation exposure and high incidence of false positive findings (i.e., nodules). Using a comprehensive biomarker panel, we sought to determine if there was a peripheral blood biomarker signature of emphysema. Methods: 114 plasma biomarkers were measured using a custom assay in 588 individuals enrolled in the COPDGene study. Quantitative emphysema measurements included percent low lung attenuation (%LAA)<= - 950 HU, <= -910 HU and mean lung attenuation at the 15th percentile on lung attenuation curve (LP15A). Multiple regression analysis was performed to determine plasma biomarkers associated with emphysema independent of covariates age, gender, smoking status, body mass index and FEV1. The findings were subsequently validated using baseline blood samples from a separate cohort of 388 subjects enrolled in the Treatment of Emphysema with a Selective Retinoid Agonist (TESRA) study. Results: Regression analysis identified multiple biomarkers associated with CT-assessed emphysema in COPDGene, including advanced glycosylation end-products receptor (AGER or RAGE, p < 0.001), intercellular adhesion molecule 1 (ICAM, p < 0.001), and chemokine ligand 20 (CCL20, p < 0.001). Validation in the TESRA cohort revealed significant associations with RAGE, ICAM1, and CCL20 with radiologic emphysema (p < 0.001 after meta-analysis). Other biomarkers that were associated with emphysema include CDH1, CDH 13 and SERPINA7, but were not available for validation in the TESRA study.	Click here for full text options	Carolan B.J. Hughes G. Morrow J. Hersh C.P. O'Neal W.K. Rennard S. Pillai S.G. Belloni P. Cockayne D.A. Comellas A.P. Han M. Zemans R.L. Kechris K. Bowler R.P.	Respiratory Research. 15 (1) (no pagination), 2014. Article Number: 127. Date of Publication: 12 Oct 2014.	BioMed Central Ltd. (E-mail: info@biomedcentral.com)	Embase	Article				

											Receiver operating characteristics analysis demonstrated a benefit of adding a biomarker panel to clinical covariates for detecting emphysema, especially in those without severe airflow limitation (AUC 0.85). Conclusions: Our findings, suggest that a panel of blood biomarkers including sRAGE, ICAM1 and CCL20 may serve as a useful surrogate measure of emphysema, and when combined with clinical covariates, may be useful clinically in predicting the presence of emphysema compared to just using covariates alone, especially in those with less severe COPD. Ultimately biomarkers may shed light on disease pathogenesis, providing targets for new treatments.										
64	0	copd, not environmental exposure					1				Association of five genetic variants with chronic obstructive pulmonary disease susceptibility and spirometric phenotypes in a Chinese Han population.	Background and objective Recent genome-wide association studies have shown associations between variants at five loci (TNS1, GSTCD, HTR4, AGER and THSD4) and chronic obstructive pulmonary disease (COPD) or lung function. However, their association with COPD has not been proven in Chinese Han population, nor have COPD-related phenotypes been studied. The objective of this study was to look for associations between five single nucleotide polymorphisms (SNP) in these novel candidate genes and COPD susceptibility or lung function in a Chinese Han population. **Methods** Allele and genotype data on 680 COPD patients and 687 healthy controls for sentinel SNP in these five loci were investigated. Allele frequencies and genotype distributions were compared between cases and controls, and odds ratios were calculated. Potential relationships between these SNP and COPD-related lung function were assessed. Results No significant associations were found between any of the SNP and COPD in cases and controls. The SNP (rs3995090) in HTR4 was associated with COPD (adjusted P = 0.022) in never-smokers, and the SNP (rs2070600) in AGER was associated with forced expiratory volume in 1 s (FEV1%) predicted (beta = -0.066, adjusted P = 0.016) and FEV1/forced vital capacity (beta = -0.071, adjusted P = 0.009) in all subjects. Conclusions The variant at HTR4 was associated with COPD in never-smokers, and the SNP in AGER was associated with pulmonary function in a Chinese Han population. We demonstrate that variants in HTR4 are associated with COPD in never-smokers, and SNP in AGER are associated with lung function in a Chinese Han population.	Click here for full text options	Yang J. Zhou H. Liang B. Xiao J. Su Z. Chen H. Ma C. Li D. Feng Y. Ou X.	Respirology. 19 (2) (pp 262-268), 2014. Date of Publication: February 2014.	Blackwell Publishing (550 Swanston Street, Carlton South VIC 3053, Australia)	Embase	Article				
65	1										Plasma sRAGE and N-(carboxymethyl) lysine in patients with CHF and/or COPD.	Background: Knowledge of the role of the receptor for advanced glycation end products (RAGE), particularly its soluble form (sRAGE), and of its advanced glycation end product (AGE) ligand, N-(carboxymethyl)lysine adducts (CML), is limited in chronic heart failure (CHF) and in chronic obstructive pulmonary disease (COPD). We evaluated whether the AGE/RAGE system is activated in stable CHF and COPD, and whether plasma sRAGE and CML levels are affected by clinical and functional parameters. **Materials and methods:** We measured plasma levels of sRAGE and CML using a sandwich enzyme-linked immunosorbent assay (ELISA) in 143 subjects, aged >= 65 years, divided into five groups: 58 with CHF, 23 with COPD, 27 with CHF+COPD and 35 controls (17 healthy smokers and 18 healthy nonsmokers). Individuals with diabetes were excluded from the study. Results: Plasma levels of sRAGE and CML were higher in CHF patients than in controls [sRAGE: 0.48 (0.37-0.83) vs. 0.42 (0.29-0.52) ng/mL, P = 0.01; CML: 1.95 (1.58-2.38) vs. 1.68 (1.43-2.00) ng/mL, P = 0.01]. By contrast, sRAGE and CML were not different between both COPD and CHF+COPD patients and controls (P > 0.05). N-terminal pro-brain natriuretic peptide (Nt-pro BNP) correlated with sRAGE, but not with CML, in the patient groups: CHF (r = 0.43, P < 0.001), COPD (r = 0.77, P < 0.0001) and CHF/COPD (r =	Click here for full text options	Boschetto P. Campo I. Stendardo M. Casimirri E. Tinelli C. Gorrini M. Ceconi C. Fucili A. Potena A. Papi A. Ballerin L.	European Journal of Clinical Investigation. 43 (6) (pp 562-569), 2013. Date of Publication: June 2013.	Blackwell Publishing Ltd (9600 Garsington Road, Oxford OX4 2XG, United Kingdom)	Embase	Article				

											0.43, P = 0.003). Conclusions: Plasma levels of sRAGE and CML are increased in CHF, but not in COPD patients. The robust association between NT-pro BNP, a diagnostic and prognostic marker in CHF, and sRAGE concentrations might suggest a possible BNP pathway of amplification of inflammation via the AGE/RAGE system		Fabbri L. Luisetti M.								
66	0	duplicate	1								Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD.	Advanced Glycation End products (AGEs) are the products of nonenzymatic glycation and oxidation of proteins and lipids. Formation of AGEs is increased in response to hyperglycaemia, reactive oxygen species and ageing. AGEs are proinflammatory and can modify the extracellular matrix. RAGE (Receptor for Advanced Glycation End Products) mediates some of the effects of AGEs. Methods: Formalin-fixed lung tissue from patients who had lobectomy for bronchial carcinoma was used to investigate the presence of AGEs and RAGE. Subjects were divided into those with COPD and controls. Immunostaining for AGEs and RAGE was performed and the intensity of staining measured. Results: Subjects with COPD and controls were similar in age and smoking history but FEV1% predicted was lower for COPD than controls. Intensity of staining for AGEs was greater in the airways (p = 0.025) and alveolar walls (p = 0.004) in COPD. Intensity of staining for RAGE was also significantly increased in alveolar walls (p = 0.03) but not the airways. FEV1% predicted was correlated with the intensity of staining for AGEs in the airways and alveoli. Conclusions: The increased staining for both AGEs and RAGE in COPD lung raises the possibility that the RAGE-AGEs interaction may have a role in the pathogenesis of COPD.	Click here for full text options	Wu L. Ma L. Nicholson L.F.B. Black P.N.	Respiratory Medicine. 105 (3) (pp 329-336), 2011. Date of Publication: March 2011.	W.B. Saunders Ltd (32 Jamestown Road, London NW1 7BY, United Kingdom)	Embase	Article				