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Receptor for Advanced Glycation End-Products and Environmental Exposure Related Obstructive Airways Disease: a Systematic Review

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Abstract

Background: Our group has identified the receptor for advanced glycation end-products (RAGE) as a predictor of World Trade Center particulate matter associated lung Injury. The aim of this systematic review is to assess the relationship between RAGE and obstructive airways disease (OAD) secondary to environmental exposure.

Methods: A comprehensive search using PubMed and EMBASE was performed on 01/05/2018 utilizing keywords focusing on environmental exposure, obstructive airways disease, RAGE and was registered with PROSPERO(2018-CRD42018093834). We included original human research studies in English, focusing on pulmonary end-points associated with RAGE and environmental exposure.

Results: A total of 213 studies were identified on the initial search. After removing the duplicates and applying inclusion/exclusions, we screened the titles and abstracts of 61 studies. Finally, 19 full text articles were included. The exposures discussed in these articles include, particulate matter (n=2) and cigarette smoke (n=17).

Conclusion: RAGE is a mediator of inflammation associated end-organ dysfunction such as obstructive airways disease. Soluble RAGE a decoy receptor may have a protective effect in some pulmonary processes. Overall, RAGE is biologically relevant in environmental exposure

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associated lung disease. Future investigations should focus on further understanding the role and therapeutic potential of RAGE in particulate matter exposure associated lung disease.

Keywords

Occupational exposure; particulate matter; airway hyperreactivity; murine models; lung injury

BACKGROUND

Obstructive airway disease (OAD) due to environmental exposure is a global health concern. [1–3] Mounting evidence supports the role of receptor for advanced glycation end-products (RAGE), also known as the advanced glycation end-product receptor (AGER), in the development of OAD.[4–6]

RAGE is a member of the immunoglobulin superfamily and has several isoforms which recognize pathogens and endogenous ligands. RAGE is at the highest baseline level in the lungs, where it is expressed by alveolar type epithelial cells, alveolar macrophages, and the smooth muscle cells of the airways.[7, 8] The membrane bound form is a key mediator of inflammation, metabolic dysfunction, and vascular injury. [9–11]

Given its proinflammatory role and abundance in the lungs, RAGE has been shown as an important biomarker of airflow obstruction in various diseases such as cystic fibrosis, asthma, COPD and particulate matter (PM)-associated OAD.[12–16] Furthermore, RAGE has been implicated in a murine smoke-exposure model of emphysema.[17]

In human subjects with OAD, explanted lungs were noted to have increased expression and bronchoalveolar lavage (BAL) levels of RAGE.[4, 18] The association between RAGE and OAD has also been studied at the genomic level. Single nucleotide polymorphisms within the AGER locus have been linked to forced expiratory volume in one second (FEV_1) in two genome-wide association studies (GWAS). [19, 20] AGER-associated loci using *in vitro* models have been investigated to further our understanding of possible mechanisms. The promoter variant AGER-429 T/C (rs1800625) is associated with severity of airflow obstruction in cystic fibrosis and cells with this functional variant have elevated RAGE expression.[21–23]

While the membrane bound form of RAGE has been implicated in airway inflammation and obstruction, the circulating soluble form (s)RAGE has been shown to act as a decoy receptor. Studies show that OAD, particularly COPD, is associated with reduced levels of circulating sRAGE.[13, 24] The utility of sRAGE as a diagnostic biomarker in OAD is currently being investigated.[14, 25] The exact correlation of sRAGE and lung disease appears to vary depending on the pulmonary insult. There is evidence that sRAGE is involved in pathogenesis of acute lung injury (ALI). One study showed that sRAGE was inversely correlated with the rate of alveolar fluid clearance.[26] In a direct ALI model elevated sRAGE levels were seen in BAL samples 24 hours after lipopolysaccharide-induced injury. Furthermore, treatment with mouse recombinant sRAGE one-hour post–injury, attenuated neutrophilic infiltration, inflammatory mediator production, and alveolar capillary

permeability.[27] A subsequent study showed that RAGE was only elevated in BAL fluid of mice with direct ALI compared to an indirect ALI model.[28]

The role of RAGE has been examined in several occupational lung diseases as well as pulmonary fibrosis. Some studies have suggested a protective effect, as evidenced by low expression of RAGE and sRAGE in human and mouse models of pulmonary fibrosis.[29, 30] Consistent with this hypothesis, mice deficient in Ager ($Ager^{-/-}$) develop rapidly progressive fibrosis with asbestos exposure.[31] In contrast, another study showed that $Ager^{-/-}$ mice exhibited less fibrosis when exposed to bleomycin as compared to wild-type controls.[32] Furthermore, $Ager^{-/-}$ mice do not demonstrate any difference in the severity of fibrosis with silica exposure.[31] In models of atopic asthma, $Ager^{-/-}$ mice did not demonstrate airway hypersensitivity, eosinophilic inflammation and airway remodeling. In fact, Ager inhibition in wild type mice significantly reduced inflammation.[15]

Finally, our group has identified elevated serum lysophosphatidic acid (LPA), a product of low-density lipoprotein (LDL) and a known ligand of RAGE and sRAGE, as World Trade Center-Lung Injury (WTC-LI) biomarkers in the Fire Department of New York (FDNY)-cohort.[33–35] We have therefore focused this systematic review on RAGE, a biologically plausible mediator and biomarker of environmentally associated OAD.

METHODS

Review Strategy:

A systematic review of the literature was performed adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[36, 37] Our Population, Intervention, Control, Outcome (PICO) question was “In adult patients with obstructive airways disease(P), we performed a systematic review to identify(I) the role of the advanced glycation end-products receptor in subjects whose OAD is secondary to an environmental exposure(O)?” Given the design of our systematic review, no comparison control (C) was needed. PubMed and EMBASE were searched on 01/05/2018. The details of the protocol of our systematic review were registered on PROSPERO (2018CRD42018093834) and can be accessed at www.crd.york.ac.uk/prospero/display_record.php?RecordID=93834.

Search Terms:

Databases were searched for the following:

> (Particulate matter OR air pollutants OR air pollution OR occupational pollution OR environmental pollution OR ambient air OR pollution OR particle size OR air filters OR smoking OR cigarette smoke) **AND** (advanced glycation end products receptor or rage or ager) **AND** (lung OR respiratory OR lung diseases OR obstructive lung disease OR obstructive airway disease OR obstructive airways disease OR asthma OR chronic bronchitis OR COPD OR chronic obstructive pulmonary disease OR emphysema)

For the purposes of this review, we defined: *obstructive airways diseases* to include asthma, emphysema, chronic bronchitis and chronic obstructive pulmonary disease (COPD);

environmental exposures included cigarette smoke, particulate matter/dust, air or other occupational pollution. We chose to include cigarette use as an environmental exposure since there is literature that passive smoking or environmental tobacco smoke is associated with an increased risk of COPD similar to direct tobacco use.[38–40]

We included studies which: (1) discussed advanced glycation end products receptor or any of its isoforms in the setting of OAD due to environmental exposures and (2) assessed OAD development after environmental exposure. We excluded studies that (1) were not original research; (2) not written in English language; (3) focused on non-human subjects or in-vitro work; or were (4) conducted in a pediatric population.

Data Extraction:

Each article was screened for study design, patient characteristics, sample size, tools used, severity and prevalence of OAD. Results from each database search were filtered for human subjects and English language, and imported into EndNote X8. The references were then screened for duplicates using RefWorks (ProQuest LLC). Only original research papers were then reviewed for (title, abstract and full text) to ascertain eligibility. We also examined the references cited in the relevant articles. All results were screened by **SHH** and further independently evaluated by **AN** and **AO**. Disagreements were resolved by consensus, Supplemental Table 1–5.

RESULTS/SYNTHESIS

Study Inclusion, Characteristics and Sources of Bias.

A total of 213 studies were identified from PubMed, EMBASE and reference-list screening, Figure 1. After application of selection criteria, 61 research papers were assessed for inclusion. Out of these, 41 were excluded after the initial review. Finally, 19 original research articles were considered eligible to be included. There are two types of environmental exposures discussed in these articles, particulate matter (n=2) and cigarette smoke (n=17). Of these, six investigations discuss RAGE as a biomarker of OAD activity, seven evaluate the association of RAGE with OAD, four are GWAS discussing RAGE and its isoforms in COPD and smoking, and two discuss the role of RAGE in multiple end-organ outcomes. Data from all searches, screening and extraction are available, Table-1 **and** Supplemental Table-1.

RAGE in the Context of Particulate Matter Exposure.

Autophagy is critical in the pathogenesis of PM-related COPD, leading to diffusion impairment. One study investigated the association of clinically relevant biomarkers in PM_{10} exposed COPD patients (GOLD Stages III/IV) in a retrospective study in Taiwan. The one-year average PM_{10} exposure was positively correlated with IL-6, Ubiquitin and Beclin-1 levels, while negatively correlated with D_{LCO}, circulating RAGE level and oxygen saturation (ΔSaO_2).[41] Recently, our group studied the role of sRAGE in the WTC-PM exposed firefighters as well as in a murine model of PM exposure. sRAGE is associated with WTC-LI in humans and mice alike, and in the murine model, absence of RAGE was protective against loss of lung function and airway hyperreactivity due to WTC-PM exposure. [6]

RAGE as a Biomarker of Emphysema.

Studies have evaluated sRAGE as a potential diagnostic biomarker in order to avoid chest imaging and possibly detect emphysema at earlier stages.[18, 42–44] A prior systematic review concluded that sRAGE is a strong biomarker of emphysema, but only in patients with airflow limitation. [14] Furthermore, peripheral plasma samples of individuals from the COPDGene population have been assessed for specific biomarker's association with emphysema noted on CT imaging (Percent low lung attenuation ≤ −910 HU). Patients with more emphysema had lower sRAGE and ICAM1 levels. [45] These results were further validated in the Treatment of Emphysema with a Gamma-Selective Retinoid Agonist (TESRA) cohort, Table 1. [45]

RAGE Correlates with Severity of Emphysema.

In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort of COPD patients, the change in CT lung density and severity of emphysema over the study period was correlated with a number of circulating biomarkers. At baseline, patients with higher levels of sRAGE and SP-D had less emphysema, while lower levels of CCL-18 correlated with more severe disease. Elevated sRAGE, fibrinogen, and IL-6 levels at baseline were associated with less progression of emphysema. [46]

In another study, serum samples of patients with stable COPD, smokers without COPD, and non-smoking controls, were compared for specific biomarkers. Extracellular RAGE-binding protein (EN-RAGE) and sRAGE levels were significantly different between those groups as well as in various stages of COPD. Overall, sRAGE levels were reduced in COPD patients and were more associated with variability in D_{LCO} values. On the contrary, EN-RAGE levels were significantly elevated in severe COPD and more associated with FEV_1 and FEV_1/FVC values. These findings suggest that sRAGE and EN-RAGE may affect different lung function measures (airway obstruction or diffusion capacity), Tables 1 **and** 2. [47]

Role of sRAGE in WTC Particulate Matter Exposed Firefighters.

Our group has identified RAGE as a biomarker of WTC-PM induced FEV_1 decline. Using a case-cohort design, we studied a cohort of never-smoking male FDNY firefighters exposed to WTC dust with normal pre-9/11 lung function. The odds of developing WTC-LI increased by 1.2, 1.8 and 1.0 in firefighters with sRAGE ≥ 97pg/mL, CRP ≥ 2.4mg/L, and MMP-9 ≥ 397ng/mL, respectively. We concluded that increased sRAGE is associated with WTC-LI, Tables 1 **and** 2. [6]

RAGE is a Biomarker of Vascular Injury.

A pilot study examined patients with COPD, smokers without COPD, and nonsmokers who had renal biopsy or nephrectomy. They measured AGE-RAGE and tissue oxidative stress levels in the pulmonary and renal endothelial cells and showed that they were indeed elevated in the COPD group. They also revealed similar findings in the cigarette smoke-exposed mice. The investigators concluded that COPD patients and cigarette smoke-exposed mice have pulmonary and renal endothelial cell injury associated with the tissue oxidative stress-AGE-RAGE pathway.[48]

Correlation of RAGE and Nitric Oxide (NO) Generation.

The role of RAGE in cigarette smoke-induced NO generation was studied by assessing the bronchial epithelia of smokers with COPD and compared to healthy smokers and nonsmokers with COPD. RAGE overexpression was noted only in smokers with COPD and positively correlated with NO levels, smoking status, and lung function decline. Human bronchial epithelial cells that were cultured in cigarette smoke extract had low sRAGE levels but enhanced RAGE and NO levels. Interestingly, increased NO level and NO synthase activity were all reversed by pretreatment of anti-RAGE antibody. [49]

Accumulation of RAGE in Different Body Compartments.

One study assessed AGE and sRAGE levels in plasma, sputum, bronchial biopsies, and skin and tested whether differential tissue accumulation is associated with COPD [50]. Skin autofluorescence of AGE and sRAGE in blood and sputum was measured by ELISA, and by immunohistochemistry in the bronchial biopsies. COPD patients had increased accumulation of AGE in the skin compared to non-COPD smokers and never smokers. This difference in expression was not seen in bronchial tissues of different groups. Lower FEV_1% of predicted and FEV_1/FVC ratio were independently associated with a higher AGE levels in skin [50]. sRAGE levels were significantly lower in the plasma of COPD patients compared to young and old healthy subjects. These levels were also negatively correlated with the severity of COPD. Patients with lower sRAGE levels had lower FEV_1, lower D_{LCO} and higher AGE accumulation in the skin. They hypothesized that sRAGE has a protective effect and functions as a decoy-receptor, preventing accumulation of AGE in the skin.[50]

RAGE as a biomarker of cardiovascular disease (CVD) in COPD.

The results of studies assessing sRAGE and CVD are heterogeneous. One study looked specifically at COPD patients and non-COPD smokers with calculated cardiovascular (CV) risk prediction scores.[51] The CV risk prediction scores and sRAGE levels were the same in both groups. They found no associations between sRAGE and diabetes or aortic pulse wave velocity.[51] In the absence of ischemic heart disease or diabetes, COPD patients had significantly lower levels of sRAGE which is consistent with prior literature.

sRAGE as a Marker of Longitudinal Loss of Lung Function.

A longitudinal cohort study of non-smokers, smokers without COPD, and smokers with COPD in Northern Finland was performed with measurements of HMGB1, a ligand of RAGE, sRAGE, and lung function testing. There were no significant differences in the HMGB1 levels between the study groups, but patients with severe airflow obstruction had higher levels than others.[52] This result is consistent with prior findings. Lower sRAGE levels were associated with longitudinal decline of FEV_1/FVC in all groups, Table 2. This was particularly evident in smokers with COPD as lower sRAGE levels predicted longitudinal decline in FEV_1.

Genetic Polymorphism of RAGE in COPD.

The genetic polymorphism of RAGE is less well studied in COPD compared to inflammatory diseases such as Crohn’s disease. There are 1517 single nucleotide

polymorphisms (SNPs) detected in the RAGE gene, but are mostly nonsense mutations.[53] Three functional SNPs in the promoter region (−429T/C and −374T/A) and one SNP in exon 3 (G82S) of the AGER gene have been studied. One study in a Chinese population showed that G82S polymorphism was significantly higher is COPD patients and associated with higher risk of developing COPD in current smokers.[53] In another study of a Polish population with severe COPD, a number of SNPs associated with lung function were investigated including AGER, ADCY2, THSD4. They identified associations between CHRNA3/5, IREB2, FAM13A and COPD, as well as ADCY2 with severe COPD.[54] A GWAS on two quantitative emphysema and airway imaging phenotypes using the COPDGene, ECLIPSE, National Emphysema Treatment Trial (NETT), and GenKOLS cohorts, found five loci of interest. AGER was associated with COPD and spirometric measures related to airflow obstruction as well as emphysema and sRAGE levels.[55] Furthermore, the Ser82 RAGE variant was associated with higher FEV_1, FEV_1/FVC and lower serum sRAGE levels in United Kingdom (UK) smokers. The investigators also found that HMGB1 activation of the RAGE-Ser82 receptor resulted in lower sRAGE levels.

RAGE a biomarker of Asthma.

Although asthma was not the clinical focus of any of the studies that met all inclusion/exclusion criteria of our systematic review, the development of an asthmatic phenotype may occur in the context of an environmental exposure. In review of this literature we found that patients with neutrophilic asthma and COPD had significantly lower levels of sRAGE in BAL, plasma and serum relative to healthy controls and those with non-neutrophilic asthma and COPD. HMGB1, a potent mediator of neutrophilic inflammatory response and a RAGE ligand, was slightly increased in neutrophilic patients. Consistent with our understanding of the role of sRAGE, lack of inhibition of downstream inflammatory effects of RAGE may play a role in development of neutrophilic asthma.[13] The role of RAGE has also been implicated in the pathophysiology of eosinophilic asthma. In a murine model, wild-type (WT) and RAGE knockout (KO) mice were exposed to house dust mite (HDM) extract and sensitized with ovalbumin. HDM exposed WT mice exhibited increased airway resistance and small airway tissue damping in response to methacholine challenge relative to RAGE knockouts. Absence of RAGE was associated with absence of inflammatory infiltrates, lack of elevated mucin expression or goblet cell hyperplasia. IL-5, IL-13 and eotaxin were significantly elevated in HDM exposed WT mice and to a lesser degree in RAGE knockout mice.[15] In another murine study, WT and RAGE KO mice were sensitized with ovalbumin. The WT mice exhibited significantly elevated levels interferon-gamma and IL-5, when compared to RAGE KO mice, Table 2. [16]

DISCUSSION

Our systematic review identified 19 original articles where the role of RAGE is found to be important in the development of environmental exposure related OAD. These studies had significant differences in the populations, methods, and outcomes that were studied, Table 1. However, these studies allow us to further define the role of RAGE in the development of OAD related to a heterogeneous environmental exposure. These studies suggest that RAGE may be a multifaceted contributor to OAD development.

Particulate matter exposure causes systemic inflammation, endothelial dysfunction, and subsequent end-organ damage leading to OAD.[56–58] These effects are particularly evident as loss of lung function associated with the WTC particulate matter exposure.[59–70] There is mounting evidence that RAGE is a biologically plausible mediator of inflammation and vascular injury, and is associated with conditions such as metabolic syndrome and OAD.

In most organs, RAGE is expressed at low baseline levels and increases with disease activity as seen in the lungs of COPD patients.[4] The highest expression of RAGE occurs in the lungs but its deleterious effects are not just limited to this organ. For instance, AGE-RAGE levels are elevated in the pulmonary and renal endothelial cells of patients with COPD.[48] Accumulation of AGEs in different organs appears to vary and correlates with the levels of circulating sRAGE. A prior study showed that accumulation of AGEs in the skin is directly correlated with low circulating sRAGE levels in COPD patients. This has led to the hypothesis that sRAGE acts a decoy receptor and appears to be protective against the inflammatory effect of membrane bound RAGE. Patients with higher particulate matter exposure and associated COPD have lower levels of sRAGE. These levels also correlate well with severity of COPD and predict longitudinal decline in FEV_1, Table 1/2.

A finer understanding of the RAGE pathway and its role in inflammation associated OAD may allow us to identify therapeutic targets to halt progression of diseases such COPD. In one study, administration of sRAGE or deletion of RAGE gene mitigated LPA-RAGE interaction and disease development.[34] RAGE has been the focus of targeted therapeutic trials.[9, 71–73]

RAGE is a key mediator of MetSyn which affects more than 30% of adults in the United States.[74–76] A diet high in caloric content is a key contributor to MetSyn. Several groups are actively studying the MetSyn and lung disease associated with environmental exposures. Several studies of WTC-exposed cohorts (a high particulate exposed group) have described a high incidence of obesity.[75, 77] In addition, we found that a multi-metabolite model was able to differentiate between those with WTC-LI and those without.[70] One of the key mediators of your metabolome is diet and we know that dietary interventions that have focused on weight loss in obstructed patients show improvement of both FEV_1 and FVC by as much as 22% in as little as 15 days.[78, 79] Using a very low calorie diet, investigators have been able to achieve a 20kg loss over a 6-month period; every 10% relative loss of weight, led to a significant improvement of FVC by 92 mL, and FEV_1 by 73mL.[80] As patients decreased their body mass index from 37 to 32kg/m^2, the mean morning FEV_1 and FVC significantly increased.[81] Improvement of lung function in obese subjects that undergo weight loss is due predominately to changes in lung mechanics. Associated biochemical changes that may play a role are active areas of investigation and are a focus of our future work. Additionally, recent studies show the effectiveness of calorie reduced and Mediterranean diets in reducing lipid levels.[82] While moderating fats can be essential to maintaining a healthy diet, there is extensive literature that explores the potential health benefits of fats high in a Mediterranean diet, such as n-3 and n-6 PUFAs. [83, 84]

Systematic reviews have inherent biases that we addressed through design of our search algorithm. Our systematic review is affected by selection, detection, performance, and

reporting bias. Selection bias was addressed by having a pre-determined inclusions and exclusions criteria and distinct definitions. Detection and performance bias were addressed by having at least two rounds of screening individually performed. Reporting bias was addressed through PubMed and EMBASE-search filters that included peer-reviewed published articles that were written in English and that focused on human subjects. Removing duplicates further limited reporting bias.

The development of OAD due to environmental exposure is a leading cause of morbidity and mortality worldwide. RAGE is involved in the inflammatory cascade of events that lead to development of obstructive airway disease. Soluble RAGE acts as a decoy receptor and may have a protective effect against development of OAD. Patients with lower levels of soluble RAGE may have more severe COPD and emphysema. By targeting RAGE mediated inflammation, we may mitigate progression of obstructive airways disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATIONS

AF	Autofluorescence
AAT	Alpha-1 Antitrypsin
ADCY2	Adenylate Cyclase 2
AGE	Advanced Glycation End Products
AGER	Advanced Glycation End Products Receptor
BAL	Bronchoalveolar Lavage
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CEL	N^{e}-(carboxyethyl) lysine
CHRNA	Cholinergic Receptor Nicotinic Alpha 1 Subunit
CML	N^{e}-(carboxymethyl) lysine
CN	China

COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CV	Cardiovascular
CT	Computed tomography
DE	Germany
D_LCO	Diffusing capacity of the lung for carbon monoxide
DNA	Deoxyribose Nucleic Acid
EC	Ethylenedicysteine
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
ELISA	Enzyme-linked immunosorbent assay
eGFR	Estimated Glomerular Filtration Rate
EN-RAGE	Extracellular RAGE-Binding Protein
esRAGE	Endogenous secretory RAGE
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
FR	France
GenKOLS	Genetics of COPD, Norway
GWAS	Genome Wide Association Studies
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBE	Human Bronchial Epithelial Cells
HMGB1	High Mobility Group Box 1
HU	Hounsfield unit
hsCRP	High Sensitivity C-Reactive Protein
IL-1β	Interleukin 1-beta
IL-6	Interleukin-6
IPF	Idiopathic Pulmonary Fibrosis
IREB2	Iron Responsive Element Binding Protein 2
IT	Italy

LPA	Lysophosphatidic Acid
LP15A	15th Percentile on Lung Attenuation Curve
MMP-9	Matrix Metalloproteinase 9
MS	Mass Spectrometry
NETT	National Emphysema Treatment Trial
NL	Netherlands
NO	Nitric Oxide
OAD	Obstructive Airways Disease
PCR-RFLP	Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
PD15	Lowest 15th Percentile of Frequency Distribution
PM	Particulate Matter
PM_{10}	Particulate Matter <10 μm in Aerodynamic Diameter
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWV	Pulse Wave Velocity
RAGE	Receptor for Advanced Glycation End-Products
ROC_{AUC}	Receiver Operating Characteristic Area Under the Curve
RV	Residual Volume
s	Soluble
SaO_2	Oxygen Saturation
SNP	Single Nucleotide Polymorphism
SP-D	surfactant protein D
TESRA	Treatment of Emphysema with a Gamma-Selective Retinoid Agonist
TLC	Total Lung Capacity
UACR	Urinary Albumin/Creatinine Ratio
UK	United Kingdom
US	United States
WB	Western Blot
WBC	White Blood Cell Count

WTC	World Trade Center
%LAA	Percent Low Lung Attenuation
2-DE	2-Dimentional Electrophoresis

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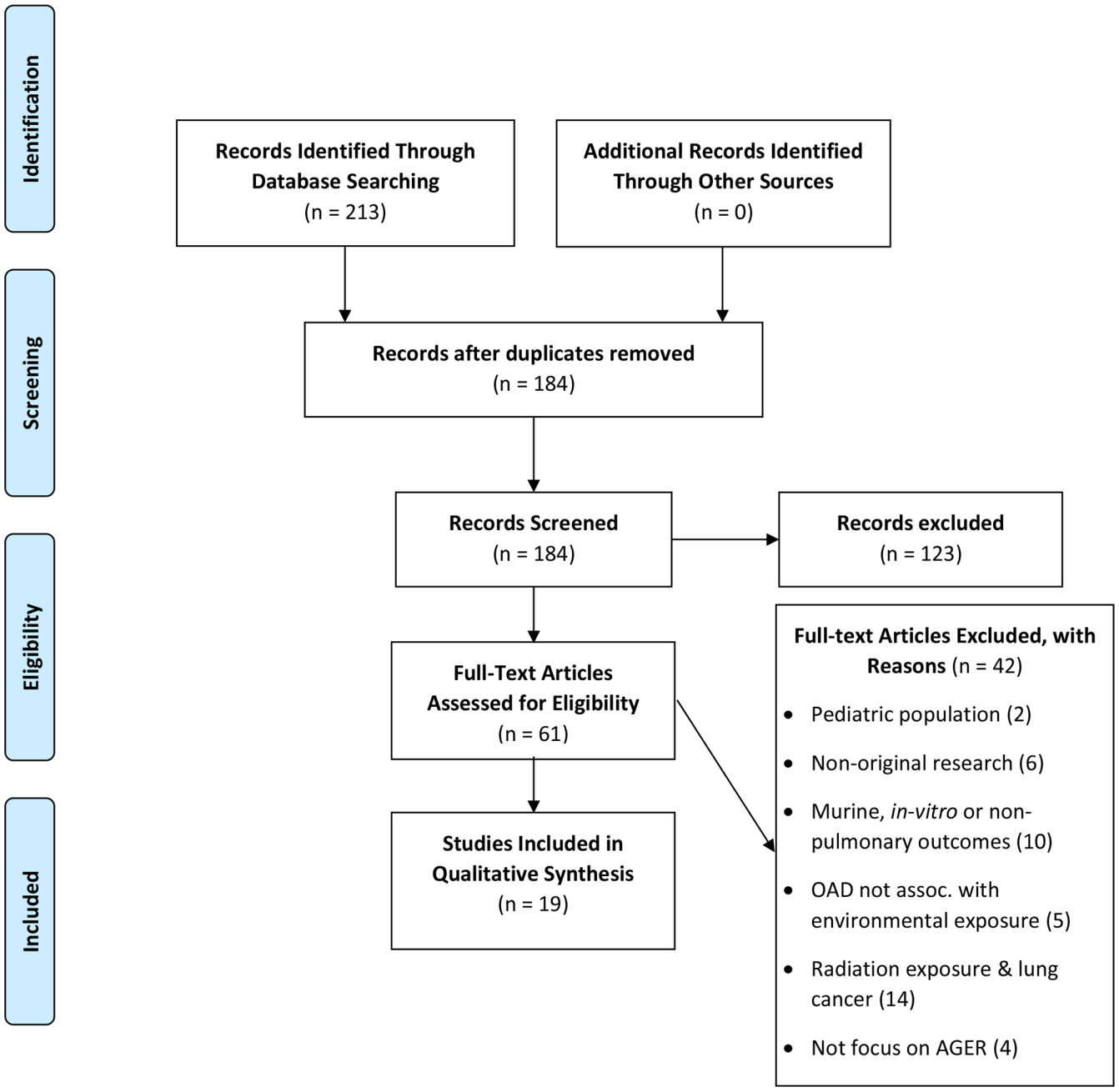

Figure 1: Flow Diagram as per PRISMA Guidelines.

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Table 1.

Relevance of RAGE in OAD secondary to Environmental Exposure

	Study*	Country	Population/Exposure/ Design	Study Size	Specimen/Assay	End Points	Significant Findings
1	**Caraher** 2017 [6]	US	FDNY, WTC-PM, Case Cohort	185	Serum/Luminex	FEV_1	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.
2	**Lee** 2016 [41]	TN	COPD, PM_{10}, Retrospective Case Control	58	Serum, ELISA	FVC, FEV_1/FVC, RV/TLC, D_{LCO}, ΔSaO_2, 8-isoprostane, IL-6, RAGE, Carbonyl Oxidation, Ubiquitin, Proteasome, Beclin-1	Exposure to elevated levels of $PM_{10,}$ was associated with reduced circulating RAGE levels.
3	**Polverino** 2017 [48]	US	COPD, Cigarette Smoke, Longitudinal	82	Lung, IHC	UACRs, eGFR, AGE-RAGE in Pulmonary/Renal ECs	↑immunostaining of AGE and RAGE in endothelial cells of COPD cases.
4	**Hoonhorst** 2016 [50]	NL	COPD, Cigarette Smoke, Longitudinal	288	Blood/Sputum/ Bronchial Biopsies, ELISA/IHC	AGE, sRAGE, Lung Function	Low sRAGE is associated with COPD and impaired lung function.
5	**John** 2016 [51]	UK	COPD, Cigarette Smoke, Cross-sectional	291	Blood, IHC	PWV, BP, Skin AF, sRAGE, Lipids	CV risk prediction score and sRAGE levels were the same COPD and non-COPD smokers.
6	**Carolan** 2014 [45]	US	COPDGene, Cigarette Smoke, Cross-Sectional	588	Plasma, Custom Assay by Myriad-RBM	%LAA, LP15A, sRAGE	Patients with more emphysema had lower sRAGE and ICAM1 levels.
7	**Iwamoto** 2014 [52]	FL	COPD, Cigarette Smoke, Longitudinal	295	Plasma	FEV_1, FVC, FEV1/FVC, sRAGE	Lower sRAGE predicts greater progression of airflow obstruction.
8	**Chen** 2014 [49]	CH	COPD, Cigarette Smoke, *ex-vivo*	40	Lung, HBE/IHC/ Elisa/WB	FEV_1, FVC, FEV1/FVC, RAGE, NO Generation	Overexpression of RAGE contributes to smoking-induced NO generation in COPD.
9	**Coxson** 2013 [46]	Multiple	ECLIPSE, Cigarette Smoke, Longitudinal	1285	Serum, ELISA	Lung Density on CT Scan	Elevated sRAGE, fibrinogen, and IL-6 levels at baseline were associated with less progression of emphysema.
10	**Cockayne** 2012 [47]	DE	COPD, Cigarette Smoke, prospective observational study	185	Serum, Multiplex	FEV_1, FEV_1/FVC, D_{LCO}, 142 Analytes	sRAGE, EN-RAGE were 2 of 7 biomarkers that showed significant differences between severe/very severe COPD, mild/moderate COPD, smoking and non-smoking control groups; sRAGE and EN-RAGE affect different lung function measures
11	**Miniati** 2011 [85]	IT	COPD, Cigarette Smoke, Case-Control	401	Plasma, ELISA	FEV_1, FEV_1/FVC, D_{LCO}, Emphysema severity, sRAGE	sRAGE is significantly lower in patients with COPD than in age- and sex-matched individuals without obstruction. Emphysema is an independent predictor of reduced sRAGE in COPD.
12	**Ohlmeier** 2010 [44]	FL	IPF/UIP/COPD/ AAT	49	Lung, 2-DE, MS, WB, ELISA	RAGE	Three RAGE variants (FL-RAGE, cRAGE, esRAGE) are important in IPF. The decline of FL-RAGE and cRAGE, but

	Study*	Country	Population/Exposure/ Design	Study Size	Specimen/Assay	End Points	Significant Findings
							not esRAGE, in COPD lungs is evidence of involvement of specific RAGE variants also in this disease.
13	**Ferhani** 2010 [18]	FR	COPD, Cigarette Smoke, N/A	70	Lung, WB, ELISA, Luminex, IHC, BAL, EC, AM	HMGB1, IL-1β, RAGE	Elevated HMGB1 expression in COPD airways may sustain inflammation and remodeling through its interaction with IL-1b and RAGE.
14	**Zhang** 2014 [42]	CN	COPD, Cigarette Smoke, N/A	102	Plasma/Serum, ELISA	FEV_1, FEV_1/FVC, HMGB1, sRAGE, hsCRP, fibrinogen	HMGB1 and sRAGE levels were dynamically changed between exacerbation and convalescence phase of COPD.
15	**Boschetto** 2013 [43]	IT	COPD, CHF, COPD & CHF, Cigarette Smoke, N/A	143	Plasma, ELISA	sRAGE, CML, BNP	Plasma levels of sRAGE and CML are increased in CHF, but not in COPD patients.
16	**Cho** 2015 [55]	Multiple	COPDGene, ECLIPSE, NETT, GenKOLS, Cigarette Smoke, N/A	12,031	GWAS	Loci associated with emphysema	The AGER locus was related to an emphysematous phenotype.
17	**Hardin** 2012 [54]	PL	COPD, Cigarette Smoke, N/A	645	Blood, TaqMan	FEV_1, FEV_1/FVC, SNPs COPD and COPD associated phenotypes, SNPs previously associated with lung function in GWAS and COPD were assessed.	In patients with severe COPD, there is an association between 2 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)
18	**Li** 2014 [53]	CN	COPD, Cigarette Smoke, N/A	455	WBC Genomic DNA/ PCR-RFLP	FEV_1, FVC, FEV_1/FVC	G82S polymorphism in the RAGE gene is associated w/ increased risk of COPD; GS genotype of the G82S variant is a COPD Risk factor.
19	**Miller** 2016 [86]	UK	COPD, Cigarette Smoke, N/A	992	Lung/Serum, IHC, PCR, ELISA	Alveolar RAGE, AGER splicing, sRAGE	AGER splicing, Ser82 allele assoc. with ↑ FEV_1, FEV_1/FVC & ↓sRAGE

*First Author Year (Ref)

Definition of Abbreviations: FDNY Fire Department of New York**; TN** Taiwan**; CN** China**; DE** Germany**; CV** Cardiovascular**; ECLIPSE** Evaluation of COPD **Longitudinally** to Identify Predictive Surrogate Endpoints**; FL** Finland**; FR** France**; GWAS** Genome Wide Association Studies**; IT** Italy**; PL** Poland**; NL** Netherlands**; UK** United Kingdom**; US** United States**; WB** Western Blot**; SP-D** surfactant protein D**; COPD** Chronic Obstructive Pulmonary Disease**; WTC-PM:** World Trade Center-Particulate Matter**; PM_{10}** Particulate Matter <10 μm in Aerodynamic Diameter**; FEV_1** Forced Expiratory Volume in 1 second**; FVC** Forced Vital Capacity**; RV** Residual Volume**; TLC** Total Lung Capacity**; SaO_2** Oxygen Saturation**; DLCO** Diffusion Capacity for Carbon Monoxide**; sRAGE** Soluble Receptor for Advanced Glycation End Products**; RAGE** Receptor for Advanced Glycation End Products**; AGER** Advanced Glycation End Products Receptor**; CRP** C-Reactive Protein**; HBE** Human Bronchial Epithelial Cells**; ICAM1** intercellular adhesion molecule**; MMP-9** Matrix Metalloproteinase-9**; ROC_{AUC}** Receiver Operating Characteristic Area Under the Curve**; IL-6** Interleukin 6**; AGE** Advanced Glycation End Products**; UACR** Urinary Albumin/Creatinine Ratio**; eGFR** Estimated Glomerular Filtration Rate**; EC** Endothelial Cells**; AM** Alveolar Macrophages**; PWV** Pulse Wave Velocity**; BP** Blood Pressure**; IHC** Immunohistochemistry**; AF** Autofluorescence**; %LAA** Percent Low Lung Attenuation**; LP15A** 15^{th} Percentile on Lung Attenuation Curve**; NO** Nitric Oxide**; PD15** Lowest 15^{th} Percentile of Frequency Distribution of Lung Density**; EN-RAGE** Extracellular RAGE-Binding Protein**; 2-DE** 2-Dimentional Electrophoresis**; MS** Mass Spectrometry**; esRAGE** Endogenous secretory RAGE**; ELISA** Enzyme-Linked Immunosorbent Assay**; HMGB1** High Mobility Group Box 1**; IL-1β** Interleukin 1-beta**; hsCRP** High Sensitivity C-Reactive Protein**; CML** N-(carboxymethyl) lysine adducts**; BNP** Brain Natriuretic Peptide**; SNP** Single Nucleotide Polymorphism**; GWAS** Genome-Wide Association Studies**; CHRNA** Cholinergic Receptor Nicotinic Alpha 1 Subunit**; ADCY2** Adenylate Cyclase 2**; IREB2** Iron Responsive Element Binding Protein 2**; AAT** Alpha-1 Antitrypsin**; CHF** Congestive Heart Failure; **IPF** Idiopathic Pulmonary Fibrosis**; BAL** Bronchoalveolar Lavage**; NETT**

National Emphysema Treatment Trial**; IHC** Immunohistochemistry**; WBC** White Blood Cell Count**; DNA** Deoxyribose Nucleic Acid**; PCR-RFLP** Polymerase Chain Reaction-Restriction Fragment Length Polymorphism**; WTC-LI** World Trade Center Lung Injury**; CT** Computed tomography. **N/A** Not Applicable

Table 2.

Associations Between RAGE, sRAGE, and Disease State

Outcome	RAGE	sRAGE	Summary
Obstructive Airways Disease			• Lungs of patients with OAD (COPD and Cystic fibrosis) have increased levels of RAGE [4, 21] • OAD associated airway inflammation associated with lower levels of sRAGE in CF patients [22, 23] • None of the identified studies focused or included asthma as a clinical endpoint
Asthma			• Neutrophilic asthma un humans is associated with lower levels of sRAGE [13] • RAGE expression associated with increased downstream inflammatory effects reflective of an asthmatic profile. [15, 16]
COPD			• COPD is associated with RAGE over-expression [48] • sRAGE levels are reduced in COPD patients [50] • RAGE SNPs are positively associated with COPD [53, 54]
Cardiovascular Disease			• sRAGE and CVD outcome are inconsistent [51]
Emphysema			• Lower RAGE associated with more emphysema [45] • Higher sRAGE is associated with less emphysema and less disease progression [46]
World Trade Center Lung Injury			• Absence of RAGE is protective from loss of lung function in a murine model [6] • Increased sRAGE associated with WTC-LI development [6]
Pulmonary Fibrosis			• $AGER^{-/-}$ mice develop fibrosis in an asbestos exposure [31]
Nitric Oxide Generation			• COPD smokers had higher RAGE and NO levels [49] • *in vitro* cigarette smoke exposure led to low sRAGE, high RAGE and NO levels [49]
FEV_1 & FEV_1/FVC			• Ser82 RAGE variant associated with higher FEV_1 [86] • Lower sRAGE levels associated with longitudinal decline of FEV_1 in COPD smokers and of FEV_1/FVC in all subjects [52] • COPD patients with lower sRAGE levels had higher FEV_1 [50]

GREEN Positive Association; **RED** Negative Association; **GRAY** Inconsistent

COPD Chronic Obstructive Pulmonary Disorder; **FEV_1** Forced Expiratory Volume per one second; **FVC** Forced Vital Capacity; **WTC-LI** World Trade Center Lung Injury; **SNP** Single Nucleotide Polymorphism; **CVD** Cardiovascular Disease; **NO** Nitric Oxide; **OAD** Obstructive Airways Disease