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Inside this issue: Environmental and Occupational factors

Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. 2

Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomized, crossover study. 3

Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China. 3

Airway responsiveness to methacholine and incidence of COPD: an international prospective cohort study. 4

Pollution and respiratory disease: can diet or supplements help? A review. 5

Ambient air pollution and chronic bronchitis in a cohort of U.S. women. 8

Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction. 9

Occupational exposures and subclinical interstitial lung disease. The MESA (Multi-Ethnic Study of Atherosclerosis) air and lung studies. 10

Temporal changes in mortality attributed to heat extremes for 57 cities in Northeast Asia. 11

Long-term air pollution exposure, genome-wide DNA methylation and lung function in the LifeLines cohort study. 11

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Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015.

Cohen AJ, et al.

Lancet 2017; 389:1907-18.

https://ncbi.nlm.nih.gov/pmc/articles/PMC5439030/

Exposure to ambient air pollution increases mortality and morbidity. Global Burden of Disease 2015 identified air pollution as a leading cause of global disease burden especially in low and middle-income countries. Cohen, et al. addressed trends of the global burden of disease due to ambient air pollution from 1990 to 2015 in this article. They estimated global population-weighted mean concentrations of PM2.5 and ozone and the relative risk of mortality from ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), lung cancer, and lower respiratory infections from epidemiological studies using non-linear exposure-response functions spanning the global range of exposure.

They found that deaths attributable to ambient PM2.5 increased from 3.5 million in 1990 to 4.2 million in 2015. PM2.5 caused 103.1 million disability-adjusted life-years (DALY) in 2015 which is also an increase from 1990. Exposure to ozone caused an additional 254,000 deaths and a loss of 4.1 million DALYs from COPD in 2015. Global deaths and DALYs attributable to ozone exposure increased from 1990 to 2015 as a result of increases in both levels of ozone and COPD mortality.

Trends in PM2.5-attributable mortality reflect the influence not only of changing air quality, but also of demography and underlying mortality rates. Of note, south and east Asia contributed 59% of the 4.2 million global deaths attributable to ambient PM2.5 in 2015. The absolute numbers of attributable deaths and DALYs increased as a result of increases in pollution and the absolute numbers of deaths from non-communicable diseases, especially in China and India. They addressed that magnitude of the excess relative risk from PM2.5 exposure at high levels of PN2.5 remains uncertain because large-scale cohort studies are absent in the most polluted countries.

This study suggests that major reductions in pollution levels via policy action including air quality management programmes focused on major sources will be needed to prevent increase in disease burden.

Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomized, crossover study.

Sinharay R, et al.

Lancet 2018; 391:339-49

https://ncbi.nlm.nih.gov/pmc/articles/PMC5803182/

Sinharay R, et al. assessed the effects on respiratory and cardiovascular responses of walking down a busy street in London with high levels of pollution compared with walking in a traffic-free area of an urban park with lower pollution levels in older adults. In this randomized, crossover study, they recruited COPD or stable ischemic heart disease patients and age-matched healthy volunteers. Participants were randomly assigned to do a 2 hour walk either along Oxford street in London or in Hyde Park.

They found that in healthy volunteers, walking in Hyde Park associated with an increase in lung function up to 26 hours after the walk, while there were no significant changes in FEV1 or FVC from baseline after walking on Oxford Street. Both COPD and ischemic heart disease participants experienced the beneficial effects of walking in terms of improvement of FEV1 although less than in healthy volunteers. Reduction of FEV1 and FVC were associated with an increase in during-walk exposure to NO_2, ultrafine particles and PM2.5 in COPD participants. There was also an increase in small airways obstruction in association with pollutants and walking on busy road was associated with more respiratory symptoms in COPD participants. In all participants, walking in Hyde Park led to a decrease in pulse wave velocity and augmentation index which, are measures of arterial stiffness and these beneficial responses were also attenuated after walking on Oxford Street.

This study suggests that healthy participants and patients with COPD and ischemic heart disease should avoid highly polluted areas to walk in and also policies should be aimed to control ambient levels of air pollution along busy street as short-term exposure to traffic pollution showed negative health effects.

Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China.

Liu S, et al.

Thorax 2017; 72:788-95

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5738534/

Ambient air pollution may play an important role in the early development of respiratory disorders. Liu, et al. conducted a cross-section study in southern China to examine the association between ambient particulate matter (PM) and lung functions in adults. They recruited residents aged over 20 years from seven randomly selected clusters from cities across Guangdong province and examined with a standardized questionnaire and spirometry. They measured the average air pollution exposure level using 1-year atmosphere PMs sampled in the participating clusters.

A total of 5993 participants were included for analysis and COPD prevalence and atmospheric PM concentration varied significantly among the seven clusters in the study. They found that increased year-round daily mean PM concentrations are associated with increased COPD prevalence (adjusted OR 2.416 for >35 and <75ug/m3 and 2.530 for > 75 ug/m3 compared with the level of <35ug/m3 for PM2.5) and decreased respiratory function (26ml decrease in FEV1 and 28ml decrease in FVC and a 0.09% decrease in FEV1/FVC ratio as 10 ug/m3 increase in PM2.5) in Guangdong, China. The associations of COPD with PM10 were consistent with PM2.5 but slightly weaker. They also found that the increased daily mean PM levels were associated with an increased risk of COPD symptoms and other chronic pulmonary diseases.

While studies on associations between ambient air pollution and COPD development were inconclusive, this study add evidence for strong association of higher PM concentrations with increased COPD prevalence and decline lung function in relatively highly polluted cities. This study suggests we need environmental regulation strategy based on scientific data to improve health outcomes.

Airway responsiveness to methacholine and incidence of COPD: an international prospective cohort study.

Marcon A., et al.

Thorax. 2018, May 2.

http://dx.doi.org/10.1136/thoraxjnl-2017-211289

There has been debate that increased airway responsiveness can predict the risk of the prevalence of COPD or not. Therefore, the authors prospectively studied whether airway responsiveness is associated with the risk of developing COPD, using pooled data from two multicenter population-based cohort studies with similar designs and study protocols that collected data from three time points using similar methods (European Community Respiratory Health Survey and Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults). The authors classified subjects by their level of airway responsiveness using quintiles of methacholine dose–response slope at the first

examination (1991–1994), then, excluded subjects with airflow obstruction at the second examination (1999–2003) and analyzed an incidence of COPD using the criteria of post-bronchodilator FEV_1/FVC below the lower limit of normal at the third examination (2010–2014) as a function of responsiveness, adjusting for sex, age, education, body mass index, history of asthma, smoking, occupational exposures and indicators of airway caliber. Among 4,205 subjects during a median time of 9 years, 108 new cases of COPD were observed. Compared with the least responsive group (incidence rate 0.6 per 1,000/year), adjusted incidence rate ratios for COPD ranged from 1.7 (95% CI; 0.52 to 6.13) to 8.91 (95% CI; 3.67 to 21.66) for increasing airway responsiveness. Between smokers and non-smokers, similar dose–response associations were observed, and stronger associations were found among subjects without a history of asthma or asthma-like symptoms.

This study analyzed COPD incidence, defined using post-bronchodilator lung function data, in large population samples that were prospectively followed up over 20 years. The results of this study showed that higher airway responsiveness measured during young adult life was prospectively associated with an increased risk of COPD after 20 years. The authors showed that increased airway responsiveness is an independent risk factor for COPD, and young adults with high airway responsiveness are at greater risk for developing COPD in later life. This study showed stronger prospective evidence that increased responsiveness can precede the development of COPD, using continuous indicators of airway responsiveness in young adulthood (1991–1994), excluded subjects who had airflow obstruction 10 years later (1999–2003) and assessed the outcomes during the last available follow-up period (up to 2010–2013). The results of this study suggest that increased airway hyperresponsiveness precedes and is an independent risk factor for COPD, and measuring airway responsiveness could be helpful to identify subjects at risk for COPD. According to the results of this study, whether early treatment of patients with high responsiveness can slow down disease progression of COPD is a next clinical interest.

Pollution and respiratory disease: can diet or supplements help? A review.

Whyand T, et al.

Respir Res. 2018;19:79

https://doi.org/10.1186/s12931-018-0785-0

Air pollution is now the world's largest environmental health risk factor, and air pollution causes and exacerbates chronic respiratory diseases such as COPD, bronchial asthma and respiratory cancers. The authors reviewed the evidence for alterations in diet, including vitamin supplementation

in the effects of air pollution on asthma and other chronic respiratory diseases. The authors conducted a search of several combinations of some keywords such as air pollution, diet, antioxidants, fats, lung disease, lung cancer, obesity and Mediterranean diet in 2017 to March 2018 using PubMed, in addition to a search of original research and review papers from the past twenty years, dating back to 1997 resulted in 109 relevant papers of mainly original research.

The authors overview the risk of pollutants such as phthalates, particulate matter, polycyclic aromatic hydrocarbons, ozone, nitrogen dioxide, persistent organic pollutants and mixed pollutants. In relation to nutrient protection, they reviewed several health hazardous effects of vitamin A and carotenoids, vitamin C, E and D, curcumin, N-acetylcysteine, fats (omega-3 oils or n-3 polyunsaturated fats; PUFAs), choline. Shortly, higher intake of two dietary sources of vitamin A (pre-formed vitamin A; retinol, and provitamin A; carotenoids) such as tomatoes, carrots, and leafy vegetables has been associated with lower prevalence of asthma in women. A meta-analysis of five observational studies of β-carotene as the pro-vitamin A carotenoids showed that high dietary intake of β-carotene was not significantly associated with asthma or FEV1. Low intakes of vitamin C and E are associated with a higher prevalence of asthma, lower dietary intake (but not serum level) of vitamin E was significantly associated with increased asthma severity in a meta-analysis of 24 observational studies. Four RCTs reported potential protective effects of vitamin E against the negative effects of O3 that vitamin E-containing antioxidants reduce O3-induced bronchoconstriction in asthmatic or non-asthmatic subjects. Serum vitamin C, uric acid and vitamin E, but not vitamin A modified the effect of PM10 on exacerbations of asthma and COPD. Reduced serum vitamin D concentrations have been associated with severe asthma exacerbations in children, and increased odds of one or more severe asthma exacerbations in the previous year even in non-atopic children. Reduced vitamin D concentrations are also associated with increased airway smooth muscle mass, decreased lung function, and worse disease control in children with severe, therapy-resistant asthma. The results of meta-analysis in predominantly mild to moderate asthma patients suggest that vitamin D may reduce the risk of severe asthma exacerbation. The phytochemical curcumin from turmeric is a potent anti-inflammatory, anti-tumor, antifungal and antioxidant agent, and may have some protective role against the DNA damage caused by arsenic and protect against pulmonary fibrosis. Curcumin can prevent cadmium-induced tumor necrosis factor- alpha (TNF-α), IL-6 and IL-8 inflammatory secretion by human airway epithelial cells. Curcumin may stimulate the suppressor of cytokine signaling (SOCS) -3/JAK2/STAT signaling pathways, suppress chemokines and affect corticosteroid sensitivity through modulating histone deacetylase 2 (HDAC2) expression and its effect on histone modification in COPD patients. People taking dietary curcumin through eating curry had better pulmonary function (FEV1). Supplementation of N-acetylcysteine (NAC) may attenuate airway hyperresponsiveness following inhalation of diesel exhaust compared with filtered air, and long-term NAC

therapy may reduce risk of patients with COPD exacerbation, QOL of COPD patients. Inhibitory effects of C20:5 and C22:6 ω-3 fatty acids on cyclooxygenase activity, eicosanoid synthesis from amino acids, IgE production reduce airway inflammation and bronchoconstriction in asthmatic patients. Omega-3 and some omega 6 oils also act to reduce inflammation, rebuilding fatty acid homeostasis in cellular membranes, modifying eicosanoid metabolic pathways, thus reducing clinical symptoms in patients with asthma that are allergic to pollutants and other allergens. A Mediterranean diet, largely attributed to the content of dietary fiber, antioxidants, protein, moderate amounts of fat predominantly from mono-unsaturated (MUFA) and omega-3 PUFA. Reduction of dietary saturated fat intake was associated with a reduction in neutrophilic airway inflammation in asthmatic patients, and higher fat and lower fiber intakes have been associated with increased eosinophilic airway inflammation in adult patients with severe asthma. Choline supplement (1500 mg twice) significantly reduced IL-4, IL-5 and TNF-alpha level as compared to baseline or standard pharmacotherapy after 6 months in asthmatic patients.

According to the results of their review, carotenoids, vitamin D and vitamin E may help protect against pollution damage which can trigger asthma, COPD and lung cancer initiation. Vitamin C, curcumin, choline and omega-3 fatty acids may also play some protective roles. They also introduce dietary recommendations from the British Thoracic Society and the Scottish Intercollegiate Guidelines Network, 2016, that describes; weight reduction is recommended in obese patients to promote general health and to reduce subsequent respiratory symptoms consistent with asthma. (Grade C), obese and overweight children should be offered weight-loss programs to reduce the likelihood of respiratory symptoms suggestive of asthma (Grade C), weight-loss interventions (including dietary and exercise-based programs) can be considered for overweight and obese adults and children with asthma to improve asthma control (Grade B). There are no official recommendations for using diet or supplements to help prevent COPD and lung cancer.

Ambient air pollution and chronic bronchitis in a cohort of U.S. women.

Hooper LG., et al.

Environ Health Perspect. 2018;126(2):027005
https://doi.org/10.1289/EHP2199

There is only limited information between exposure to air pollution and chronic bronchitis, chronic cough and sputum production. The authors evaluated the relationship between estimated annual average concentrations of PM_{10}, $PM_{2.5}$ and NO_2 at home addresses of participants in a prospective nationwide U.S. cohort study of more than 50,000 U.S. women participating in the National Institute of Environmental Health Sciences (NIEHS) Sister Study, including sisters diagnosed with breast cancer but no personal breast cancer diagnosis at time of baseline interview between August 2003 and March 2009. Incident and prevalent chronic bronchitis assessed by questionnaires asking the presence and duration of cough and phlegm independently derived from the British Medical Research Council adult respiratory symptom standardized questionnaire. Chronic bronchitis was defined according to the symptom-based definition of chronic productive cough for at least 3 months per year for at least 2 consecutive years. Among 47,357 subjects, 1,383 had prevalent chronic bronchitis at baseline, and 647 incidents occurred over the follow-up of 5.7 year in average. No associations with incident chronic bronchitis and air pollution were observed in all subjects. Prevalent chronic bronchitis was associated with PM_{10} with adjusted odds ratio (aOR) per interquartile range (IQR) difference of PM_{10} (5.8μg/m^3) was 1.07 (95% confidence interval; CI :1.01 to 1.13). In never-smokers, $PM_{2.5}$ and NO_2 were associated with prevalent chronic bronchitis (aOR=1.18 per IQR difference; 95%CI: 1.04 to 1.34,), and NO_2 was associated with prevalent chronic bronchitis (aOR=1:10; 95%CI: 1.01 to 1.20), cough (aOR=1.10; 95%CI: 1.05 to 1.16), and phlegm (aOR=1.07; 95%CI: 1.01 to 1.14); interaction p-values (nonsmokers vs. smokers) <0:05.

This study is the largest study to investigate the association between chronic bronchitis and long-term ambient air pollution exposure using a validated national exposure model, and provides evidence that chronic respiratory health effects such as cough and phlegm occur with long-term exposure to PM_{10} at levels below the previous national standards of the National Ambient Air Quality Standard for annual PM_{10} provided by the U.S. Environmental Protection Agency in 2006 (50 μg/m^3). Exposure to higher concentrations of PM_{10} was significantly associated with all prevalent chronic bronchitis, chronic cough, chronic phlegm, and chronic cough or phlegm. In addition, exposure to NO_2 was significantly associated with chronic cough and chronic cough or phlegm. The results of this study may have policy ramifications for air pollution regulation such as PM_{10}.

Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction.

Chen R, et al.

Environ Health Perspect. 2018;126(1):017007.
https://doi.org/10.1289/EHP1447

MicroRNAs (miRNAs) are a key factor in epigenetic regulation of gene expression, but miRNAs and the relationship between exposure to fine particulate matter ($PM_{2.5}$) air pollution and the potential contribution of miRNAs to cardiovascular effects are unknown so far. The authors designed a double-blind, randomized crossover study to evaluate the potential influence of $PM_{2.5}$ on the expression of cytokines and miRNAs that may regulate their expression relevant to systemic inflammation, coagulation, and vasoconstriction. The authors conducted a double-blind, randomized crossover trial with two distinctly different scenarios of $PM_{2.5}$ exposure by the alternative use of true and sham (severe particulate air pollution) air purifiers to healthy nonsmoking university students in Shanghai, China. The subjects were treated with true air purifier placed in the center of the room for nine consecutive days (two weekends and five weekdays), followed by a washout period (12 days), and then used a sham air purifier under the same conditions for another nine consecutive days. PM exposure levels were calculated. Immediately after completion of each intervention stage, venous peripheral blood samples were collected at the same time of day. The authors measured blood levels of 10 proinflammatory, procoagulant vasoconstrictor cytokines and mRNA expression for each of these 10 cytokines. In addition, one or two miRNAs targeting for each cytokine were measured. Linear mixed-effect models demonstrated that higher $PM_{2.5}$ exposure was positively associated with the expression of mRNA and/or protein of interleukin-1 (IL1), IL6, tumor necrosis factor (TNF), toll-like receptor 2 (TLR2), coagulation factor 3 (F3), and endothelin 1 (EDN1). Conversely, exposure to $PM_{2.5}$ was negatively associated with miRNAs (miR-21-5p, miR-187-3p, miR-146a-5p, miR-1-3p, and miR-199a-5p) predicted to target mRNAs of IL1, TNF, TLR2, and EDN1. The authors suggest the hypothesis that short-term exposure to $PM_{2.5}$ may contribute to the pathogenesis of cerebrovascular diseases by affecting the expression of circulating miRNAs, and they speculate that the results of their study are consistent with previous epidemiological studies showing circulating cytokines as sensitive markers of a short-term PM exposure. They speculate that $PM_{2.5}$ exposure increases proinflammatory cytokine expressions of IL-1, gene expressions of F3 that promotes coagulation, ET-1 that promotes vasoconstriction or endothelial dysfunction, contributing to exacerbating cardiovascular diseases. This study simultaneously evaluated circulating cytokines, mRNAs and miRNAs, and the results of this study may represent potential mediation or modulation of miRNAs in the cardiovascular effects of exposure to $PM_{2.5}$.

Occupational exposures and subclinical interstitial lung disease. The MESA (Multi-Ethnic Study of Atherosclerosis) air and lung studies.

Sack CS, et al.

Am J Respir Crit Care Med. 2017 Oct 15;196(8):1031-1039.

https://www.atsjournals.org/doi/10.1164/rccm.201612-2431OC

Exposures to certain environmental particulates and antigens are causes of several types of interstitial lung disease (ILD), but the impact of occupational exposures on the burden of ILD is unknown so far. The authors used the cohort of community-dwelling adults enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort aged 45–84 years at recruitment. High-attenuation areas (HAA) was measured at baseline and on serial cardiac computed tomography (CT) scans in 5,702 participants, and the authors evaluated whether self-reported and objectively assigned (job-exposure matrix; JEM) occupational exposures to vapors, gas, dusts, and fumes (VGDF) that were associated with HAA and interstitial lung abnormalities (ILA). As the results of full-lung CT scanning for 10-year follow-up, ILA was detected in 2,312 participants. Linear mixed models and logistic regression adjusted for age, sex, race/ethnicity, education, employment status, tobacco use, and scanner technology were used, and each JEM score increment in VGDF exposure was associated with 2.64% greater HAA (95% confidence interval, 1.23–4.19%), and self-reported vapors/gas exposure was associated with increased odds of ILA among those currently employed (1.76-fold; 95% CI, 1.09–2.84) and those < 65 years old (1.97-fold; 95% CI, 1.16–3.35). There was no consistent associations of occupational exposures and progression of HAA over the follow-up period, but exposure based on JEM score was associated with increased HAA and demonstrated evidence of a dose–response relationship, with higher estimated exposure levels associated with increased HAA. In the subgroup of younger participants and those who were currently employed, there was the strongest trend toward increased ILA with occupational exposures.

This is the first study to show that occupational exposures (VGDF) is related to chest CT findings of lung inflammation and fibrosis. The results of this study may represent that environmental triggers to produce different pathologic responses in the susceptible host, even without specific exposures known as causes of ILD and chronic obstructive pulmonary disease such as welding fumes, cigarette smoke, VDGF.

Temporal changes in mortality attributed to heat extremes for 57 cities in Northeast Asia.

Lee W, et al.

Sci Total Environ 2018;616-617:703-9

https://doi.org/10.1016/j.scitotenv.2017.10.258

Recent studies have reported that heat-related mortality decreased by adaptation during decades, but it doesn't mean that the heat mortality burden is decreasing because the frequency of extreme heat events in increasing. To examine temporal changes in mortality attributed to heat extremes in North-east Asia, Lee, et al collected temperature and mortality data covering the years 1972-2012 from 57 cities of Taiwan, Korea, and Japan. The temporal changes in heat-mortality association were estimated with a time-varying distributed lag non-linear model. Attributable deaths were calculated considering temporal variations in exposure and relative risk. Then they pooled the estimates through meta-analysis.

They found that the mortality risk on extreme heat days declined during study period in all countries. But all-cause mortality risk attributed to heat increased during 2003-2012 compared with 1972-1981 as summer temperature in Japan have shown more heat extreme over time. The cause-specific (cardiovascular and respiratory) mortality displayed the same temporal trend as all-cause mortality. In Taiwan and Korea, relative risk and attributable risk fraction of extreme heat decreased for all three types of mortality during the study periods.

This study suggests that public health strategy to assess the total burden due to heat extremes related to climate change, should focus on the temporal variation in heat-mortality as well as changes in the distribution of heat extremes overtime.

Long-term air pollution exposure, genome-wide DNA methylation and lung function in the LifeLines cohort study.

de F C Lichtenfels AJ, et al.

Environ Health Perspect 2018;126:027004

https://ehp.niehs.nih.gov/ehp2045/

Long-term air pollution exposure is associated with lower lung function, but the mechanism leading

to declined lung function is not fully understood. de FC Lichtenfels, et al studied the association between long-term air pollution exposure and DNA methylation. They performed a genome-wide methylation study in 1,017 subjects from LifeLines cohort study to analyze the association of exposure to nitrogen dioxide (NO2) and particulate matter (PM) with DNA on in whole blood. They replicated the top hits in two independent samples from the population-based Cooperative Health Research in the Region of Ausburg studies (KORA).

They found significant associations between NO2 and DNA methylation for seven CpG sites with Bonferroni corrected threshold p value and 4,980 CpG sites with False Discovery Rate < 0.05. None of the Bonferroni significant CpGs were significantly replicated in the two KORA cohorts. Mediation analysis showed that one of seven top CpGs (near ARF5 gene) significantly mediated the association between NO2 exposure and FVC and 2 sites (near ARF5 and GNG2) significantly mediated the association between NO2 and FEV1/FVC. They found no associations for PM exposure.

This study suggests DNA methylation may partly mediate lung function decline by long-term NO2 exposure and future studies are needed to further elucidate the potential mechanisms underlying NO2-exposure related respiratory disease.

APSR Respiratory Updates is an initiative of the APSR Education Committee

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