REVIEW

The etiologic origins for chronic obstructive pulmonary disease

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Abstract: COPD, characterized by long-term poorly irreversible airway limitation and persistent respiratory symptoms, has resulted in enormous challenges to human health worldwide, with increasing rates of prevalence, death, and disability. Although its origin was thought to be in the interactions of genetic with environmental factors, the effects of environmental factors on the disease during different life stages remain little known. Without clear mechanisms and radical cure for it, early screening and prevention of COPD seem to be important. In this review, we will discuss the etiologic origins for poor lung function and COPD caused by specific adverse effects during corresponding life stages, as well as try to find new insights and potential prevention strategies for this disease.
Keywords: chronic obstructive pulmonary disease, COPD, early origins, risk factors, air pollution, cigarette smoking

Introduction

COPD, characterized by long-term poorly irreversible airway limitation and persistent respiratory symptoms, is a common and preventable disease.[1] According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, three criteria are needed to diagnose the disease: (1) a post-bronchodilator FEV_1:FVC ratioof less than 70%, (2) "appropriate symptoms" such as dyspnea, sputum production, chronic cough, or wheezing, (3) "significant exposures to noxious environmental stimuli.[2] This disease has at least three phenotypes: emphysema, chronic bronchitis, and small airway remodeling and obstruction,[3] and environmental and genetic factors are involved in the pathogenesis and development of the disease. Cigarette smoking is main cause of the disease, whereas only 10–20% of smokers develop COPD,[4] and approximately 25–45% of occurrence of COPD is attributed to nonsmoking risk.[5] As shown in Table 1 (The Global Burden of Disease study 2017),[6] COPD attributed to active smoking, ambient particulate matter pollution, occupational particulate matter/gases/fumes, ambient ozone pollution, household air pollution from solid fuels, secondhand smoke, and lead exposure was responsible for about 3.46 million of global all-age deaths and 79.78 million of disability-adjusted life-years (DALYs) in 2017. Active smoking and ambient particulate matter pollution were the main causes of deaths and DALYs for COPD (Figure 1). Although the global age-standardized death rates and DALY rates for COPD attributing to each of the above risk factors between 2007 and 2017 was reduced, this epidemical tendency forecasting is not optimistic as the growth and aging of population. Nowadays COPD is the fourth leading cause of death worldwide and will become the third leading cause of death by 2030,[7] thus it will be an urgent health problem to be solved. Without

Table 1 Global all-age attributable deaths and DALYs, and percentage change of age-standardized death rates and DALY rates caused of COPD by environment exposure between 2007 and 2017

Exposure risk	2007 deaths (million)	2017 deaths (million)	Change in age-standardized death rate during 2007–2017 (%)	2007 DALYs (million)	2017 DALYs (million)	Change in age-standardized DALYs rate during 2007–2017 (%)
Active smoking	1.13	1.23	−19.1%	26.10	28.20	−18.4%
Ambient particulate matter pollution	0.519	0.633	−10·5%	12.80	15.70	−6.0%
Occupational particulate matter, gases, and fumes	0.425	0.481	−16.1%	10.40	11.90	−12.7%
Ambient ozone pollution	0.392	0.472	−11.6%	6.33	7.37	−12.2%
Household air pollution from solid fuels	0.421	0.362	−36.3%	10.800	9.37	−33.5%
Secondhand smoke	0.244	0.266	−20.0%	6.23	6.91	−15.3%
Lead exposure	0.009	0.011	−3.3%	0.286	0.327	−11.0%

Notes: This data comes from part ofthe article Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1923–1994.[6]

Figure 1 The proportion of all-age deaths and DALYs for COPD attributed to active cigarette smoking, ambient particulate matter pollution, occupational particulate matter/gases/fumes, ambient ozone pollution, household air pollution from solid fuel, and secondhand smoke in 2007 and 2017.
Notes: This data comes from part of the article Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1923–1994.[6] R 3.5.2 version was used to plot.
Abbreviation: DALYs, disability-adjusted life-years.

curative therapies for COPD, palliation of airway obstruction, symptoms and exacerbation are the main clinical managements currently. Therefore, addressing the predisposing factors of COPD and prevent its development seemto be an appropriate intervention strategy for control of the disease in public health. Understanding the effects of risk factors correlated with the development of this disease on population at their different life stages is necessary so that more preventive strategies may be developed. In this review, we will provide a broad overview of etiologic origins for COPD, and try to find some potential preventive strategies and new insights for COPD studies.

The genetic, epigenetic, and transcriptional origins of COPDand poor lung function
The genetic origins
COPD and poor lung function (FEV$_1$, FEV$_1$/FVC) may already be determined before the birth for some patients.

COPD shows independent family aggregation,[8–10] and COPD family history shows 18.6% of the population-attributable risk, with more severe diseases, worse quality of life, and more frequent exacerbations.[11] In addition, asthma with family aggregation is observed to be the indirect risk of COPD.[12] Similarly, inter-individual difference in lung function is partly defined by genetic reasons. The infants with the lowest quartile of functional residual capacity of the FEV_1/FVC ratio and FEV_1 were lower than that with the highest quartile up to age 22.[13] Heritability of FEV_1/FVC was higher than that of either FEV_1 or FVC, and a significant difference in lung function exists between males and females. Males have higher FEV_1 and FVC, while females have higher FEV_1/FVC.[14] The genome-wide association study (GWAS), whole genome sequencing (WGS), and fine-mapping studies have consistently discovered and well-replicated many COPD associated genes (COPD genes) and loci in various populations. As summarized in Table 2,[15–68] a panel of genes associated with COPD and poor lung function, nicotine addiction, and lung injury-repair response are indicated.

The early abnormal lung development including airway and alveolar development might underlie the susceptibility to COPD and impaired lung function.[3] The normal expression of *NKX2-1*, the first symbol of lung development, plays a critical role in morphogenesis of the anterior foregut and the lung and in differentiation of lung epithelial cells.[26,27] The mice lung with its heterozygous mutation failed to undergo normal branching embryogenesis and was unable to sustain normal gas exchange function, and subsequently causes immediate postnatal lethality.[26] The hedgehog (hh) pathway transmits signals to embryonic cells and is one of the key pathways of animal development.[69] The functional loss in *HHIP* may lead to impaired branching morphogenesis and lung hypoplasia in mice.[31,38] Retinoic acid receptor-beta (*RARB*) plays a key role in septation mature and alveoli formation of mice lung. *RARB* knockout mice showed premature septation, and they formed alveoli two times faster than that of wild-type mice during the period of septation.[43] The transcription factor *SOX5*, a susceptibility gene for COPD, is critical for proper in utero lung morphogenesis. *SOX5* deficiency mice exhibited delayed lung development before the saccular stage.[23] Another COPD gene *TGFB2* involves cellular growth, differentiation, and apoptosis, as well as other cellular functions from development to tissue homeostasis, also plays an important role in normal lung development, airway remodeling, and the immune system.[28,30–35] The roles of matrix metalloproteinase

(MMP) family and tissue inhibitors of MMPs (TIMPs), and *CD147* in the lung development, lung repair responses to injury, and occurrence of multiple lung diseases including COPD and emphysema were well reviewed by Hendrix and Kheradmand.[44] During lung development, *MMP1/2/3/7/9/12/14/21, CD147*, and *TIMP1/2/3* play important roles. These genes have different expression levels in different cell types of the lung during different developmental stages.[70,71] The lack of *MMP14* in mice may decrease alveolar enlarged airspaces and surface area, as well as delay angiogenesis.[49,50] In addition, *CD147, MMP7*, and *MMP14* might be involved in lung injury-repair response.[46,51–53] *ADAM33* also plays different roles in different developmental stages, including antenatal airway lung morphogenesis and airway wall modeling,[15,16] and contributes to asthma and bronchial hyperresponsiveness in early life and in adults.[16,21] The interaction of *ADAM33* with prenatal smoking exposure could lead to reduced lung function and development of asthma at the age of 8.[22] Moreover, polymorphisms of this gene, especially in its functionally relevant 5′ end, were related to the preschool children with increased airway resistance and impaired lung function and COPD susceptibility.[20] Taken together, many GWAS-identified COPD genes play key roles in lung development and lung injury-repair response, and their abnormal expression modulated by variation or disturbance of maternal environmental exposure before the birth of individuals may pave the way for COPD development and poor lung function.

In addition, many COPD genes contribute to COPD development and poor lung function in childhood and adulthood of individuals through cross talking with environmental exposure factors. As shown in Table 2, many other COPD genes were showed to be associated with FEV_1/FVC, FVC, and FEV_1 of the population in different life stages. The polymorphisms at positions Arg16Gly/Gln27Glu within *ADRB2* were found to be associated with airway responsiveness at the age of 6, with higher spirometry at the age of 6 and 11, as well as with the presence of COPD, asthma, and other respiratory symptoms in middle-aged and older adults,[61] whereas associated with worse lung function and less likelihood of the asthma diagnosis at the age of 11.[62] *CC-16* was showed to accelerate decline in lung function in childhood and adulthood, as well as promote the progress of moderate airflow limitation in adults.[65] A follow-up study on fetal-births indicated that several detoxification genes including *EPHX1, CYP1A1*, and *GSTT1*, which are implicated in the development of emphysema and COPD, may modify the impact of cigarette smoke exposure and ambient air

Table 2 Genes involved in COPD

Gene (https://www.genenames.org/)	Chromosome	Trait related to COPD diagnosis	Other trait	References
ADAM33 (ADAM metallopeptidase domain 33)	20p13	COPD risk, FEV_1 and FEV_1/FVC,	Lung development, asthma, and bronchial hyperresponsiveness,	15–22
SOX5 (SRY-box 5)	12p12.1	COPD risk	Lung development and/or repair processes	23
TNS1 (Tensin 1)	2q35	COPD risk, FEV_1, and FVC	TEW, cell migration, cartilage development	24
SERPINE2 (serpin family E member 2)	2q36.1	COPD risk, FEV_1, and FVC	Lung development	15,24
NKX2-1 (NK2 homeobox 1)	14q13.3	COPD risk, lung function	Lung development	26,27
TGFB2 (transforming growth factor beta 2)	1q41	COPD risk, FEV_1/FVC	Lung development, airway remodeling, and the immune system	28,30–35
HHIP (hedgehog interacting protein)	4q31.21	COPD risk, FEV_1, and FVC	TEW, lung development	24,36,37,2,52
PTCH1 (patched 1)	9q22.32	COPD risk, FEV_1/FVC, FVC	Lung development	2,39,53
CELSR1(cadherin EGF LAG seven-pass G-type receptor 1)	22q13.31	COPD risk	Fetal lung development	41
RARB (retinoic acid receptor beta)	3p24.2	COPD risk, FEV_1/FVC	Lung development	30,42,43
MMP1 (matrix metallopeptidase 1)	11q22.2	COPD risk	Lung development	44,45
MMP2 (matrix metallopeptidase 2)	16q12.2	COPD risk	Lung development	44
MMP3 (matrix metallopeptidase 3)	11q22.2	COPD risk	Lung development	44
MMP7 (matrix metallopeptidase 7)	11q22.2	COPD risk	Lung development, lung injury-repair response	4,44,46
MMP9 (matrix metallopeptidase 9)	20q13.12	COPD risk	Lung development	44,45
MMP12 (matrix metallopeptidase 12)	11q22.2	COPD risk, FVC, and FEV_1/FVC	Lung development	24,44,45,48
MMP14 (matrix metallopeptidase 14)	14q11.2	COPD risk	Lung development, lung injury-repair response	44,49–51
MMP21 (matrix metallopeptidase 21)	10q26.2	COPD risk	Lung development	44
TIMP1 (TIMP metallopeptidase inhibitor 1)	Xp11.3	COPD risk	Lung development	44
TIMP2 (TIMP metallopeptidase inhibitor 2)	17q25.3	COPD risk	Lung development	44
TIMP3 (TIMP metallopeptidase inhibitor 3)	22q12.3	COPD risk	Lung development	44
CD147(basigin)	19p13.3	COPD risk	Lung development, lung injury-repair response	44,52,53
HTR2A (5-hydroxytryptamine receptor 2A)	13q14.2	COPD risk	Nicotine addiction	4,54,55
CYP2A6 (cytochrome P450 family 2 subfamily A member 6)	19q13.2	COPD risk, FEV_1/FVC, and FEV_1	Nicotine addiction	4,56
CHRNA3/4/5/7 (cholinergic receptor nicotinic alpha 3/4/5/7subunit)	15q25.1/20q13.33/15q25.1/15q13.3	COPD risk, FEV_1/FVC, and FEV_1	Nicotine addiction	4,42,56,57
AGPHD1 (hydroxylysine kinase)	15q25.1	COPD risk	Nicotine addiction	57
TNF (tumor necrosis factor)	6p21.33	COPD risk		58
KIF25 (kinesin family member 25)	6q27	FEV_1/FVC		59
HAL (histidine ammonia-lyase)	12q23.1	FEV_1/FVC		59
KCNE2 (potassium voltage-gated channel subfamily E regulatory subunit 2)	21q22.11	FEV_1/FVC		59
GPR126 (adhesion G protein-coupled receptor G6)	6q24.2	FEV_1/FVC		59
KIF4B (kinesin family member 4B)	5q33.2	FEV_1/FVC		59

(*Continued*)

Table 2 (Continued).

Gene (https://www.genenames.org/)	Chromosome	Trait related to COPD diagnosis	Other trait	References
ZSWIM7 (zinc finger SWIM-type containing 7)	17p12	FEV_1		59
MFAP2 (microfibril associated protein 2)	1p36.13	FEV_1/FVC		30
HDAC4 (histone deacetylase 4)	2q37.3	FEV_1/FVC		30
MECOM (MDS1 and EVI1 complex locus)	3q26.2	FEV_1		30
SPATA9 (spermatogenesis associated 9)	5q15	FEV_1/FVC		30
ARMC2 (armadillo repeat containing 2)	6q21	FEV_1/FVC		30
NCR3 (natural cytotoxicity triggering receptor 3)	6p21.33	FEV_1/FVC		30
ZKSCAN3 (zinc finger with KRAB and SCAN domains 3)	6p22.1	FEV_1		30
CDC123 (cell division cycle 123)	10p14-p13	FEV_1/FVC, and FEV_1		30
LRMDA (leucine rich melanocyte differentiation associated)	10q22.2-q22.3	FEV_1		30
LRP1 (LDL receptor related protein 1)	12q13.3	FEV_1/FVC		30
CCDC38 (coiled-coil domain containing 38)	12q23.1	FEV_1/FVC		30
MMP15 (matrix metallopeptidase 15)	16q21	FEV_1/FVC		30
CFDP1 (craniofacial development protein 1)	16q23.1	FEV_1/FVC		30
KCNE2 (potassium voltage-gated channel subfamily E regulatory subunit 2)	21q22.11	FEV_1/FVC		30
AGER (advanced glycosylation end-product specific receptor)	6p21.32	COPD risk, and FEV_1/FVC		24
FAM13A (family with sequence similarity 13 member A)	4q22.1	COPD risk, FEV_1, and FVC		24,36
SERPINA1 (serpin family A member 1)	14q32.13	COPD risk, emphysema risk, FEV_1/FVC, and FEV_1		29,60
EP400NL (EP400 pseudogene 1)	12q24.33	Airflow limitation		59
PDZD2 (PDZ domain containing 2)	5p13.3	COPD risk		59
CDRT15P1 (CMT1A duplicated region transcript 15 pseudogene 1)	17p12	COPD risk		59
EFEMP1 (EGF containing fibulin extracellular matrix protein 1)	2p16.1	FVC		40
BMP6 (bone morphogenetic protein 6)	6p24.3	FVC		40
MIR129-2–HSD17B12	11p11.2	FVC		40
PRDM11 (PR/SET domain 11)	11p11.2	FVC		40
WWOX (WW domain containing oxidoreductase)	16q23.1-q23.2	FVC		40
KCNJ2 (potassium voltage-gated channel subfamily J member 2)	17q24.3	FVC		40
GSTCD (glutathione S-transferase C-terminal domain containing)	4q24	FVC		40
ADRB2 (adrenoceptor beta 2)	5q32	COPD risk, FEV_1, and FEV_1/FVC	Airway responsiveness	61,62,63
CC-16 (secretoglobin family 1A member 1)	11q12.3	COPD risk, lung function		47,64,65
EPHX1 (epoxide hydrolase 1)	1q42.12	COPD risk		66,67
CYP1A1 (cytochrome P450 family 1 subfamily A member 1)	15q24.1	COPD risk		68
GSTT1 (glutathione S-transferase theta 1)	22q11.23	COPD risk		66

Abbreviation: TEW, transient early wheeze.

pollutants such as PM2.5 and polycyclic aromatic hydrocarbons (PAHs) on acute bronchitis in their later life.[72–75] In some cases, nicotine addiction increases cigarette smoking, thus increases the COPD risk and impair lung function. Some genes associated with nicotine addiction were reviewed, including *CHRNA3/4/5/7, DRD4, SLC6A3, SLC6A4, NRXN1, HTR2A, CHRNA7, CYP2A6*,[47] of which, *HTR2A, CYP2A6,* and *CHRNA3/4/5/7* are involved in COPD pathogenesis depending partly on cigarette exposure due to a gene-by-environment interaction.[54,55–57] *HTR2A* may increase the risk for the early onset of cigarette smoking and the risk for relapsing after smoking cessation.[55] Furthermore, the gene cluster of *CHRNA3/CHRNA5/CHRNB4* plays an important role in the cigarette smoke-causing injury process. Smoking behavior may mediate the relationship between COPD and the rs1051730 mapped to *CHRNA3/5*.[76] However, the mechanism of *CHRNA3/5* increasing the respiratory diseases risk is controversial: either *CHRNA3/5* has an independent effect or the regulation of nicotine addiction on COPD development.[77,78]

Epigenetic origins

During the lung development, some epigenetic alterations including: DNA methylation, histone modifications, and noncoding RNAs are key regulators of the process. An individual's epigenetic alterations of genes that may originate from his parents or grandparents could subsequently persist well into childhood.[79–81] Developmental programming, occurring primarily via epigenetic alterations, can be induced by the intrauterine conditions such as cigarette smoking, nutrition and stress, and result in inter- and transgenerational epigenetic effects on genetic origins in mice and their offspring.[82,83] Reprogramming of the epigenome, genetic imprinting, retained nucleosomes may be the potential mechanism of inter- and transgenerational epigenetic effects.[82] Epidemiological and experimental evidence indicated that exposure to environmental factors during prenatal and early postnatal period upon the epigenome is critical in embryonic development and tissue differentiation may lead to permanent epigenetic modifications and contribute to the possibility of developing adult-onset disorders such as metabolic, cardiovascular, lung cancer, lung function, and COPD.[79,82,84,85] Epigenetic regulation is important in chronic remodeling of respiratory tracts.[86] DNA methylation is an established mechanism for COPD development,[87] which may be regulated by genetic polymorphisms.[82,88] As the key regulators of lung development, histones are usually modified by methylation, phosphorylation, acetylation, and

ubiquitination of specific amino acids. Especially, histone acetylation is crucial in regulation of lung development and function, and is implicated with asthma and COPD.[89–91] Histone acetyltransferases (HATs) mediates histone acetylation that increases gene expression, whereas histone deacetylases (HDACs) induces hypocetylation that promotes gene silencing.[89] Thus, the imbalance between HATs and HDACs activity caused by any adverse factors may lead to disorders of embryonic lung development, including the block in proximal airway development,[92] alveolar hyperplasia,[93] and disrupted alveolarization.[94] In addition, the methyltransferases Suv39H1 and Suv39H2 that result in transcriptional silencing through histone H3 lysine 9 methylationare are involved in all lung development processes.[95] Thus, the disturbance of necessary epigenetic alterations resulting from genetic variation or adverse risk factors during the prenatal and early postnatal period may influence the lung development of the fetus.

Postnatal environmental factors including cigarette smoking, aging and diet, as well as genetic risk factors such as genetic variation, can modulate the methylation modification of promoter CpG via DNA methyltransferases and methyl CpG binding protein 2, which affects the transcription and expression/activation of some key genes involved in pathogenesis of COPD and impaired lung function.[96–98] Different risk factors can induce distinctive DNA methylation profiling on genome of individuals including patients with COPD and healthy people.[98–100] Methylation at cg08257009 in the *SERPINA* gene cluster was found to be associated with FEV_1/FVC in adults.[101] Furthermore, one epigenome-wide association analysis (EWAS) in whole blood found that methylation at 15 CpG-sites was significantly associated with cigarette smoking and lung function, of which, 5 methylated CpG-sites (cg05575921, cg21161138, cg05951221, cg21566642, and cg06126421) showed significant associations between DNA methylation and gene expression in lung tissues.[102] Another EWAS of four SNP (rs8034191: T>C-HYKK, rs12914385:C>T-CHRNA3, rs13180: C>T-IREB2 and rs8042238:C>T-IREB2), previously related to COPD, showed a significant association with blood DNA methylation of those genes, of which, PSMA4 and IREB2 were also differentially methylated in COPD cases and controls. In addition, all four variants also showed a significant correlation with differential expression of the IREB2 3′UTR in lung tissues.[103]

Taken together, genetic and environmental factors, and their cross talking may influence the early lung development,

and result in COPD and poor lung function later via epigenetic modifications that modulate thiss activation and transcription of COPD genes.

MicroRNAs origins

The increasing human/animal models and cell studies demonstrated that microRNAs (miRNAs) play a central regulatory role in various biological processes, including cellular proliferation, differentiation and apoptosis. MiRNAs play key roles in the lung development, and pulmonary diseases such as COPD, whereas the degree of translation into pulmonary diseases is still unclear. Recently, we reviewed the roles of miRNAs in COPD development induced by different environmental exposure as well as genetic predisposition encounter. Environmental exposure including air pollutants and cigarette smoking can induce dysregulated miRNA expression profiles, which cause adverse biological response such as oxidative stress, inflammation, and the imbalance between apoptosis and replenishment of structural cells in the lung by disturbing their regulation on COPD genes, and contribute to COPD development and poor lung function in susceptible individuals. In addition, functional SNP variant with miRNA genes can affect the mature form of corresponding miRNAs and disturb the regulation of them on COPD genes, thus leading to COPD susceptibility. Some key miRNAs, such as miR-34 a/b/c, miR-146a, miR-203, miR-218 and let-7 family, may serve as potential fluid biopsy-based markers for risk indicators of environmental exposure and COPD.[104]

The environmental origins of COPDand poor lung function

Although without absolute consistence with the pulmonary development phase division, it is traditionally divided into five histological stages from the embryonic stage to the alveolar stage (Table 3).[105,106] Two follow-up studies conducted on participants aged from 13 to 71 years showed that the plateau of FEV_1 is 20–23 years old for males, and 15 for females, whereas the decline in FEV_1 occurs at about 25 years old for both sexes, suggesting a longer plateau phase for FEV_1 in females than in males.[107,108] Moreover, the FEV_1/FVC ratio increased until 17 years old in males and then declines approximately linearly, whereas this ratio indicated a uniform decline in the age range in females.[107,108] Interestingly, although cigarette smoking can increase the rate of lung function decline in both sexes, it can only reduce the achieved peak of FEV_1 value in males, but not in females.[108] Those observations

suggest a congenital difference of lung function among sexes. The difference may originate from hereditary difference from the gender-biased environmental exposure ways between males and females.

Another follow-up study showed that the antenatal adverse factors and early childhood disadvantage factors lead to permanent lung function impairment, with a slightly greater decline in lung function but no catching up with age.[109] COPD risk increases with increasing early-life adverse factors, of which, the impacts resulting from childhood asthma, maternal and paternal asthma, maternal smoking, and respiratory infections are the same as strongly implicated in an accelerated decline rate of lung function as that of severe smoking. The tendency of decline in lung function increased with the accumulative degree of smoking exposure (healthy never smokers, quitting smoking before the age of 30, quitting smoking between 30 and 40 years, quitting smoking after the age of 40, continuous smokers),[107] suggesting that the different degrees of exposure to environmental factors might lead to different degrees of lung function impairment.

Maternal amniotic fluid

Maternal amniotic fluid has important impacts on fetal lung development and respiratory disease occurrence in offspring. Oligohydramnios can lead to fetal lung hypoplasia, while the extent depends on the degree and duration of little amniotic fluid, and the fetal lung development stages.[110,111] Fetal lung development may be regulated by amniotic fluid components such as pro-inflammatory mediators.[112] Plasminogen activator inhibitor 1 (PAI-1) is a main inhibitor of the fibrinolytic system and plays an important role in tissue remodeling,[113] and its reduction is associated with cough at 1 year of age and wheeze at 2 years of age.[114]

Preterm birth and birth weight gain

Preterm birth is the main risk for bronchopulmonary dysplasia (BPD) that accounts for the prevalence of the vast majority of chronic pulmonary diseases[115,116] and is a risk factor of permanent lung function decline.[117–120] Preterm birth is also associated with school-age and adult asthma,[112,118] wheeze and breath shortness,[121] COPD,[122] as well as bronchial hyperresponsiveness and decreased FEV_1.[120]

In addition, low birth weight may lead to persistent decline in lung function and different degree of airway obstruction, and increase risk of respiratory symptoms.[123–125] Interestingly, a meta-analysis report of

Table 3 The different risk factors during varied life periods of the lung

The risk factors		The life periods of the lung
1. Genetic susceptibility factors	①Family history of COPD, asthma, and emphysema and airway disease; ②The acquisition of pathogenic genes, etc	A: Before the pregnancy
2.1 Antenatal or postnatal environmental risk factors	①Maternal amniotic fluid ②Preterm birth and birth weight gain ③Maternal cigarette smoking ④Maternal air pollution exposure ⑤Delivery patterns ⑥Maternal obesity ⑦Maternal diet and drug use	B: The growth and development of the lung: from the foregut at 4 weeks of gestation to 15–25 years of age (1) Embryonic stage: 4–7 weeks of gestation (2) Pseudoglandular stage: 7–17 weeks of gestation (3) Canalicular stage: 16–25 weeks of gestation (4) Saccular stage: 24–38 weeks of gestation (5) Alveolar stage: before birth to childhood and adolescence
2.2 Early postnatal environmental risk factors	①Childhood air pollution exposure ②Childhood asthma ③Childhood respiratory infection ④Childhood cigarette smoking exposure ⑤Childhood obesity/ nutritional factors	
3. Adulthood environmental risk factors	①Adulthood cigarette smoking ②Adulthood air pollution exposure ③Occupational exposure	C: The aging periods of the lung: 25 year of age to COPD or death occurrence

147,000 European children observed an independent relationship between higher infant weight gain and the higher risk of school-age asthma and preschool wheezing.[112] The mechanism between birth weight and COPD needs further study.

Maternal cigarette smoking

Antenatal adverse exposure may lead to the lung's response, making it more predisposed to subsequent injury.[116] Fetal exposure to maternal smoking during pregnancy is one of the most serious events for abnormal lung development,[126] it can increase the risk of poor lung function, COPD, asthma, and childhood wheeze.[122,127–130] The mechanisms might partly result from epigenetic alterations because of the global DNA methylation in umbilical-cord blood was observed to be associated with prenatal exposure to PAH,[131] which is the main harmful component of incomplete combustion of cigarettes.

Maternal air pollution exposure

Preconceptional and prenatal exposure to industrial and traffic air pollutants increases risk of childhood asthma, allergic rhinitis, and eczema.[132] Particulate matter smaller than 2.5 μm (PM2.5), composed of ammonium, nitrate and bromine, mainly results from traffic and biomass

combustion.[133] Maternal sulfur dioxide (SO_2) and PM2.5 exposure were found to be associated with preterm birth and low birth weight, and childhood asthma.[133–135] Residential PM2.5 exposure was showed to influence the expression of placental imprinted genes, suggesting a plausible line of investigation of how air pollution affects fetal growth and development.[136] Maternal PM10 exposure was reported to increase the risk of congenital anomaly, notably fetal growth and development, and is related to placental DNA methylation, such as the *LINE1* and *HSD11B2* genes.[137] In the pilot study of 44 mother-infant pairs, Kingsley et al[138] observed an association of prenatal perfluorooctanoic acid exposure with cord blood leukocyte DNA methylation in two CpG sites of *RASA3* that plays a key role in cell growth and differentiation.[139]

Delivery patterns

Delivery mode shapes individual microbiota's acquisition and establishment, which may influence children's health.[140] Maternal vaginal microbiota provides a natural first-class microbial exposure resembling the mother's vaginal microbiota's habitat on infant's body via natural labor. Whereas cesarean section that lacks a vaginal exposure leads to the first microbial community resembling the maternal skin microbiota.[140] Furthermore, cesarean section

could increase the risk of allergic rhinitis, asthma, and hospitalization for asthma.[141] These suggest that delivery patterns may lead to difference in normal physiology or contribute to respiratory diseases due to variations in the microbiota development. Previous studies commonly focused on the specific bacterial taxa of the gut, however, the role of respiratory tract flora in pulmonary disease occurrence is little known.

Maternal obesity

The role of maternal obesity in their children has been reviewed by Duijts et al.[142] Pre-pregnancy obesity, and higher gestational weight gain and maternal overweight or obesity during pregnancy is associated with the higher risk of respiratory diseases, such as wheezing and asthma in their offspring.[143,144,145] Thus, maternal obesity may be a risk of COPD, but further investigation is still needed.

Maternal diet and drug use

Maternal diet or drug use during pregnancy may regulate the risk of respiratory diseases in offspring, which may be caused by the interactions between maternal nutrition intake and genetic alterations, as well as by immune regulation, epigenetic modifications, and microbial changes. The overfull folic acid and free sugars intake in pregnant women were shown to increase the risk of asthma in offspring,[146,147] which may be due to the role of the nutrition in airway inflammation and hyperreactivity in late generations.[148] Hypercaloric diet (HFD) of pregnant dams could lead to metabolic abnormalities that may persist throughout development,[148] and inflammatory response in the pups' lungs.[149] The intake of HFD + antioxidant N-acetylcysteine (NAC) in pregnant dams was showed to delay the alveolarization of pups, although their branching morphogenesis is normal.[150] While maternal intake of some vitamins, microelements, and folic acid was found to have protective effects on some respiratory diseases in offspring[151] and may modulate epigenetic modifications on gene expression and airway epithelial cell signaling in fetal lung, which may affect intrauterine programming of growth and development.[152,153] Polymorphisms within some genes involve the regulation of maternal antioxidant intake on offspring respiratory disease.[154] Furthermore, intrauterine antibiotic exposure plays important roles in the health of offspring through interfering with normal metabolic and immune maturation,[155] affecting the fetal organogenesis and development by methylation alterations and placental

microbiome changes.[156,157] Prenatal cocaine exposure in the placenta might affect neurochemical effects, vasoconstrictive, and fetal programming. Maternal diet and drug use during pregnancy are an increasing focused topic, because they are modifiable causes of disease in offspring. However, these complex links and mechanisms between maternal intake and COPD are necessary to reveal.

Childhood air pollution exposure

Early life air pollution exposure including traffic-derived CO, NO, NO_2, PM2.5, PM10, SO_2, and black carbon appears to influence the development of airway diseases and increase risk of respiratory diseases, including COPD and asthma in later life.[158–161] A prospective birth cohort study during the first 6 years of life indicated that early childhood air pollution exposure to PM2.5 increased the risk of early respiratory diseases,[162] which was similar to another prospective study observation in children of Sweden.[163] PM2.5 can induce both chemical and physical damage by penetrating the alveoli into the systemic circulation, whereas PM10 usually causes physical damage to the lungs, such as the alveoli and larynx.[164] As we known, at least three mechanisms are thought to be involved in the causal processes: occurrence of oxidative stress, inflammation, and epigenetic alterations. Firstly, PM-induced excessive ROScauses oxidative stress that leads to cell function impairment and cell death.[165] Secondly, oxidative stress alters the expression of proteins related to inflammatory response in the airways.[166] Additionally, PM may induce epigenetic changes including aberrant DNA methylation and histone modifications of key genes like *LINE-1*, *IL-8* and *COX-2*, and influence the inflammatory response.[167–169]

Childhood asthma

Childhood asthma is an established risk factor for low lung function and predisposition to COPD in adult.[109,170–176] Although the clear mechanism between COPD development stemming from childhood asthma history is poorly understood, the overlapped genetic variations between COPD and asthma were identified by previous GWAS.[172,177] Interestingly, Bui et al performed a cohort study in Tasmanian children (N=8,583) aged 7–45 years and found that the lowest quartile of FEV_1 at 7 years old in a selected subsample (N=1,389) was related to asthma-COPD overlap syndrome (ACOS) but not asthma or COPD alone, and observed the association of the lowest quartile of FEV_1/FVC ratio at 7 years with COPD (OR:

5.76; 95%CI: 1.9–17.4) and ACOS (OR: 16.3; 95%CI: 4.7–55.9), but not with asthma alone,[172] suggesting that screening for lung function in children may provide help in identifying the high-risk group of COPD. Interestingly, the assessment of airway hyperresponsiveness that correlates with airway inflammation, asthma, and remodelling may contribute to estimate of asthma control and future exacerbation risk, although this procedure is still a study tool for asthma.[178,179]

Childhood respiratory infection

Normal respiratory tract microbiome is important in immunological development and allergic inflammatory response, which modulates the COPD risk.[180,181] Childhood respiratory infection was demonstrated to be associated with lower lung function and increased COPD risk in later life.[122,182,183] Early respiratory infection including virus and bacterial flora is predominantly related to a series of respiratory diseases. Viral respiratory tract infections especially respiratory syncytial virus (RSV) and human rhinovirus (HRV) in infancy and early childhood may promote the risk of asthma and wheezing later.[184,185] Children with a history of HRV infection could contribute to the occurrence of asthma in preschool age.[186] Children who suffer from RSV-bronchiolitis could increase the risk of lower lung function, asthma, wheezing, hospitalization and respiratory morbidity in later life.[186–189] Even though the mechanisms between respiratory diseases and infection are poorly known, it may at least partly result from genetic factors. Some variants of the 17q21 locus were observed to be implicated in childhood asthma, and also associated with early-life infection and HRV-induced wheezing.[183,190] Protecting children from being "at risk" during infancy or early childhood is a way to prevent serious respiratory infection, meaning an effectively preventive strategy for respiratory diseases.

Childhood cigarette smoking exposure

Early childhood smoking exposure majorly comes from parental secondary smoking with less active smoking. Early family cigarette smoking exposure can easily impair lung function and increase the later risk of respiratory diseases in children.[191] Previous prospective cohort studies indicated that childhood cigarette smoking exposure from families leaded to reduced lung function, active smoking predisposition, airway obstruction susceptibility and early onset COPD, as well as prevalence of bronchodilator responsiveness, asthma and wheeze in later life.[192–194]

Parental smoking cessation and public-place banning cigarette smoke may be an effective measure for prevention of children's respiratory diseases and COPD occurrence in later life.

Childhood obesity/nutritional factors

Obesity is not only prevalent among adults but also occurs in children.[195] Childhood obesity is an increased risk of chronic respiratory diseases. Asthma is consistently one of the most common diseases among children. Presently, the relationship between childhood obesity and COPD are still largely unknown, but some evidence about the effects of childhood obesity on early asthma and airflow obstruction was found.[112,196–200] The leukotriene pathway and some overlapping genes between obesity and asthma including β2-adrenergic receptor (*ADRB2*), TNF-a, lymphotoxin-a (*LTA*), vitamin D receptor (*VDR*),[201] and protein kinase C alpha (*PAKCA*)[202] were demonstrated to play important roles in the obesity-asthma phenotype.[197] Additionally, age is a significant effect modifier of obesity and asthma. As asthma increases, the impact of obesity on asthma may decrease.[197] The etiologies for COPD and asthma caused by obesity partly root in obesity-induced circulating inflammation in the lung, and airway smooth muscle dysfunction.[197,203–207]

Nutritional factors may play an important role in the development, progression and administration of pulmonary diseases such as COPD and asthma.[208] High-fat diet pattern was shown to be associated with increased risk of childhood asthma and COPD,[209,210] likely by augmenting neutrophil airway inflammation and suppressing bronchodilator's recovery.[211] Furthermore, eating fast food is correlated with the prevalence of asthma, airway hyperresponsiveness, and wheezing in childhood.[212,213] Some antioxidants in lungs including uric acid, vitamins C and E, glutathione and beta-carotene are the first line of defending against the oxidants to increase risk of COPD, idiopathic pulmonary fibrosis and asthma.[214] Abnormal concentration of these antioxidants may increase risk of lower lung function, current wheezing, and asthma.[215,216] This may be explained by several potential biological mechanisms, including impaired pathogen elimination of respiratory airways,[217] abnormal regulation of Th17 cells,[218] as well as reduced maturation of airway smooth muscle cells and suppressor T cells.[197] Modifying dietary fat intake and reducing obesity may be helpful to control and manage asthma and COPD.

Adulthood cigarette smoking exposure

Cigarette smoking and secondhand smoke exposure in adulthood contributes to the development of COPD and the increasing mortality of COPD, although persist smoking cessation.[191,210,219] The excess risk of developing COPD in high cigarette smoke exposure categories was estimated 60–400%.[220] Whilethere is controversy between smoking predisposition and gender,. one study showed that females have a higher susceptibility to cigarette smoking, another reported the same level of predisposition for both sexes.[219,221] The burden of COPD would increase in women as cigarette smoking prevalence increased, and as young women started smoking at an earlier agecigarette smoking.[161] The main causative processes at least involve oxidants-antioxidants, proteases-antiproteases, improper repair, and chronic inflammation of airways.[219] These processes result in alveolar wall destruction and mucus hypersecretion, functional disorder and death of biomolecules, destruction of extracellular matrix, and fibrosis of lung with submucosal, adventitial and smooth muscle thickening.[219] Therefore, inhibiting the pathogenesis of COPD should be a good strategy for the treatment and symptom improvement of the disease. Quitting smoking early is of great benefit in COPD development and the decline in lung function, especially before the age of 30 when the rate of lung function decline in those who had quitsmoking is indistinguishable from healthy nonsmokers.[107]

Adulthood air pollution exposure

Approximately 50% of all households and 90% of rural households use biomass fuel for heating and cooking, which accounts for over three billion people exposed to biomass smoke.[160,222] Even in modern homes in some developed countries, biomass fuel is unable to be replaced by the ever-increasing cost of clean fuels.[223] Women seem to suffer from more biomass smoke exposure because they could inhale over 25 million liters of highly polluted air during their lifetime when they spend an average of 60,000 hours cooking near a biomass stove.[224] Biomass fuel including fossil coal, animal dung, wood and crop residues has low efficiency due to less heat production and incomplete burning, and releases more than 200 established chemical compounds, including gaseous and particulate pollutants and strong oxidant properties. Over 90% of those chemical compounds could penetrate deep into the lungs and result in chronic inflammation and destructive changes in airways and alveoli.[160,224]

Compared with no exposure to biomass smoke, exposure to biomass fuel smoke was observed to be associated with 2.44-fold and 2.4-fold increased odds of COPD in both sexes and women, respectively.[225,226] Exposure to biomass smoke may be a greater risk factor for COPD compared with cigarette smoking exposure from a global perspective because of the number of people exposed to biomass smoke is three times more than smokers.[224,227] COPD patients exposed to biomass smoke share part similar profile of cell and airway inflammation with smokers.[228] Compared with control women cooking with clean fuels, women cooking with biomass have more severe airway inflammation and oxidative stress when evaluated with the induced sputum.[229] The ventilation improvement has been demonstrated to be effective in reducing indoor biomass smoke,[230] which might decrease the burden of COPD.

Outdoor air pollution is mainly caused bymotor vehicle and industrial emissions and is related to various respiratory impairments, particularly in children aged 10–18 years[231] and women.[232] The heavier traffic density was shown to be associated with the greater declines in lung function.[232] Long-term exposure to ambient PM2.5 is associated with the decline in lung functionand increases risk of COPD.[233,234] In addition, the COPD risk increases with the increase of PM10 levels,[235] whereas the prevalence of COPD and respiratory symptoms reduces with the decline in levels of PM10.[236] A population-based cohort study in Metropolitan Vancouver, Canada, reported that black carbon is responsible for the increase of COPD hospitalization and mortality, while wood smoke exposures increases the risk of COPD hospitalization.[237] The oxidative stress, hyperresponsiveness, inflammation, impaired cilia activity and amplification of viral infections in airways may explain the adverse effects of ambient air pollutants.[238]

Occupational exposure

Occupational exposure, such as gases/fumes, biomass smoke, dust exposure, animal and crop planting, chemical exposure, is strongly associated with COPD.[98,233,239,240] The recent National Health and Nutrition Examination Survey for the non-institutionalized civilian US indicated that prevalence of airflow obstruction varies by occupation and industry, and that mining, construction, manufacturing, prepress, bookbinders, installers, and repairers may influence airflow obstruction.[241] In addition, occupational exposure to gas, vapor, dust, or fumes was shown to be

associated with COPD, airflow limitation, and emphysema.[242,243] Compared to developed countries, occupational exposure is more serious in developing countries due to lack of adequate protection and lack of strict regulations in the workplace.[160] Therefore there would be a larger burden of COPD attributed to occupational exposure in developing countries compared to developed countries.

Conclusions

COPD is a heterogeneous and multifactorial disease. As shown in Table 1, COPD induced by active smoking, ambient particulate matter pollution, occupational particulate matter/gases/fumes, ambient ozone pollution, household air pollution from solid fuels, secondhand smoke, and lead exposure was responsible for about 3.46 million of global all-age deaths and 79.78 million of disability-adjusted life-years (DALYs) in 2017. Active smoking and ambient particulate matter pollution were the main causes of deaths and DALYs for COPD (Figure 1). The status of death and DALY for COPD is getting worse withpopulation growth and aging. Therefore, COPD emerges as an enormous challenge to global health.

Individuals may suffer special exposure factors during different life stages (Table 3). In turn, these special factors could exhibit their own effects at different life stages. As summarized in Figure 2 and Table 2, host family history of respiratory diseases such as COPD, asthma, and emphysema, which may share some overlapping predisposing genes, is an established risk factor for COPD development and poor lung function. Some COPD genes such as *ADAM33, SOX5, TNS1,*
SERPINE2, NKX2-1, TGFB2, HHIP, PTCH1, CELSR1, RARB, CD147, MMP1/2/3/7/9/12/14, and *TIMP1/2/3* are critical for lung development (organogenesis, alveolarization, branching morphogenesis, and angiogenesis) or/and lung repair responses to injury (airway inflammation, oxidative stress, impaired cilia activity, and amplification). Whereas, some COPD genes, including *HTR2A, CYP2A6, CHRNA3/4/5/7*, and *AGPHD1*, are involved in nicotine addiction and toxicant metabolism. Environmental exposure such as cigarette smoking, biomass smoke, and indoor/outdoor air pollutant during all life stages of an individual has well-documented adverse effects on the lung development, lung function, and COPD susceptibility through cross talking with COPD genes by which environmental exposure pollutants might induce abnormal epigenetic modifications on genome and dysregulated miRNA expression profiles, disturbing the expression and function of COPD genes. Based on the previous findings, we may get an inference that adverse exposure during the different life stages might cause permanent impact on the lung, such as failure to reach the normal spirometric plateau, and the accumulative impairment in the lung that paves the way for COPD development. Lung function apparently reduces with more risk factors (Figure 3).

COPD is common and preventable. Undoubtedly, avoidance of exposure to any adverse environmental factor would be advisable for individuals with/without COPD susceptibility. Preschool age is likely to be the key period for prevention of lung function and respiratory diseases, and measures starting in adulthood may be too late. Early childhood lung function screening,
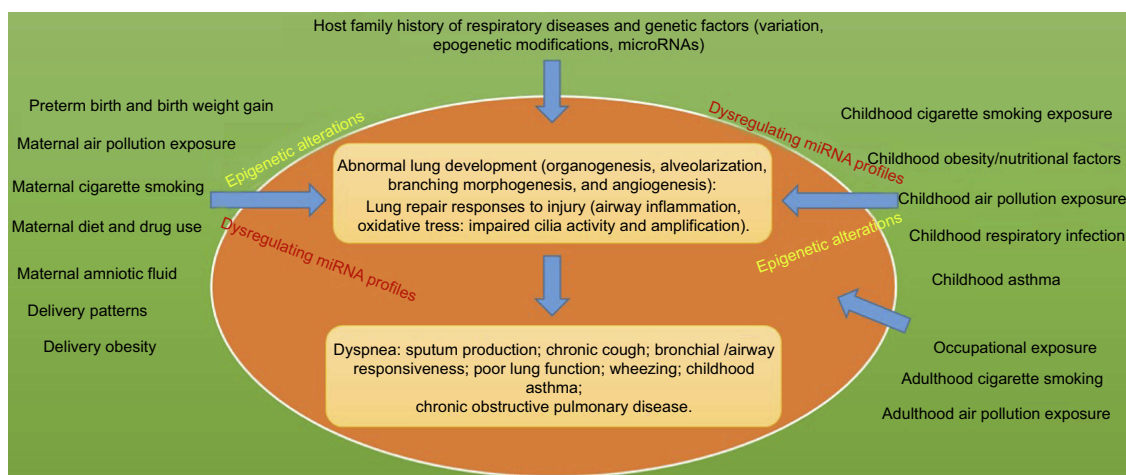

Figure 2 The origins for chronic pulmonary disease resulting from genetic and environmental factors.
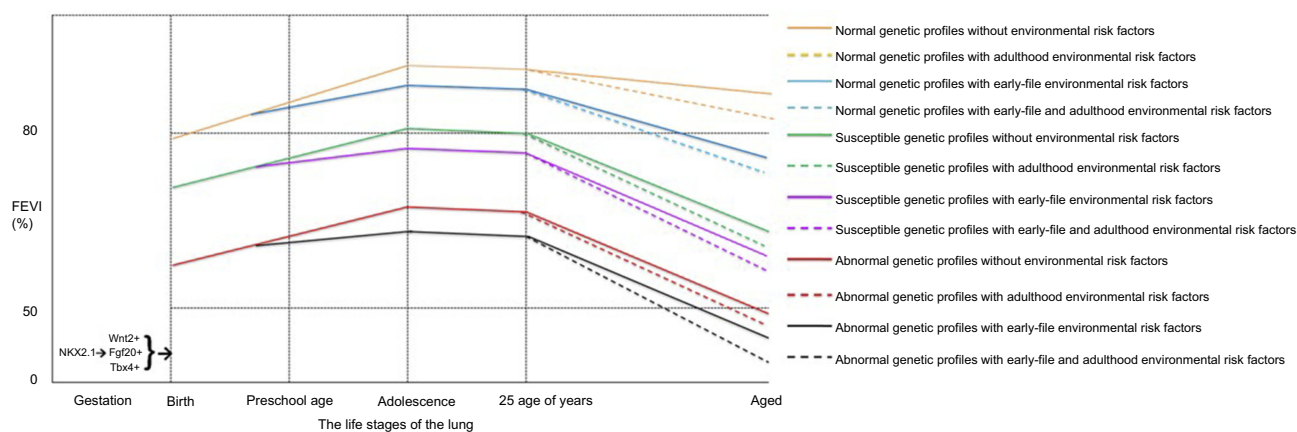
Figure 3 The plausible trajectories to lung function by varied risk factors in different life stages of the lung.

banning cigarette smoking in public places, respiratory infection prevention, searching biomarkers for evaluation of environmental exposure could be the effective protective measures against lung function impairment and COPD development. Interestingly, two oxidative damage-related produce such as 8-Oxo-2′-deoxyguanosine (8-OHdG) and LINE-1 may become epigenetic biomarkers induced by ROS generation resulting from environmental exposure.[167,244,245]

In the future, investigation of genomics, epigenomics and transcriptomics for COPD development will remain urgent. Extensive studies on the diversity of structure and function for miRNAs associated with COPD development will give better insights into the selection of appropriate miRNAs serving as prognostic or therapeutic biomarkers for COPD. Notably, a technique that may safely remove DNA methylation, resulting in the direct re-installation of unmodified deoxycytidine (dC) from 5-formyl-deoxycytidine (fdC) undergoing C-C bond cleavage, has a potential to treat and prevent COPD caused by DNA methylation.[246] Furthermore, gene editing in bronchioalveolar stem cells (BASCs) and basal stem cells (BSCs) that might regenerate both trachea cilia and secrete epithelium and generate alveolar epithelium after extreme injury may contribute to the recovery from both alveolar and bronchiolar injury.[247–251]

Acknowledgments

Authors contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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