Risk factors and early origins of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease is mainly a smoking-related disorder and affects millions of people worldwide,with a large effect on individual patients and society as a whole. 慢性閉塞性肺疾患は主としてタバコと関連した疾患であり、世界で数百万人が罹患し、患者、社会に大きな影響を与えている。

Although the disease becomes clinically apparent around the age of 40-50 years, its origins can begin very early in life. この疾患は臨床的には40-50歳で明らかになってくるが、その発生はかなり早期より始まっている。

Different risk factors in very early life-ie, in utero and during early childhood-drive the development of clinically apparent chronic obstructive pulmonary disease in later life. かなり早期（子宮内や幼児期）の異なった危険因子が後生での臨床的に明かなCOPDへと導かれる。

In discussions of which risk factors drive chronic obstructive pulmonary disease, it is important to realize that the disease is very heterogeneous and at present is largely diagnosed by lung function only. COPDの危険因子を議論するためにはこの疾患はかなりheterogeneousであるが、現在は主として肺機能だけで診断されている。

In this Review, we will discuss the evidence for risk factors for the various phenotypes of chronic obstructive pulmonary disease during different stages of life.このReviewでは異なるstageでの各種COPDの危険因子のエビデンスを議論する。

Background 背景

Chronic obstructive pulmonary disease, which is largely a smoking-related disease, affects millions of people worldwide. COPDは主としてタバコと関連していて、世界中で約数百万人が罹患している。

At present, it is the fourth leading cause of death worldwide, and between 1990 and 2010 the proportion of disability-adjusted life-years attributable to the disorder increased by 34% in the USA, where it ranks second in the top 30 contributing diseases.[1,2] 現在世界では4番目の死亡原因であり、米国では1990年から2010年の間に障害調整生存年齢（障害調整生命年（DALY）= 損失生存年数（YLL）+ 障害生存年数（YLD））が34%増加し、30疾患中2位である。

For decades, chronic obstructive pulmonary disease has been characterised by incompletely reversible and usually progressive obstruction of the airways that is associated with inflammation.3 数十年間COPDは完全には回復しない、炎症を伴った気道閉塞であり通常進行性である。

Textbooks generally state that chronic obstructive pulmonary disease becomes clinically apparent around the age of 40-50 years, but this does not imply that the disease cannot have its origins in childhood, since it cannot be recognised at that age. 一般に教科書ではCOPDは40-50歳台で臨床的に明らかになるが、小児期に認識できないので、小児期にその起源を同定できていない。

Rather, premature airflow obstruction can persist from childhood onwards and then is erroneously considered under the umbrella term of smoking-related chronic obstructive pulmonary disease.[4] むしろ時期尚早な気流閉塞が小児期から続くために、タバコ関連COPDの総称の下で

誤って考えられている。

In this Review, we will discuss important new insights into chronic obstructive pulmonary disease, from risk factors to lung development, early origins, and different phenotypes of the disease. このReviewで我々は肺成長に対する危険因子、早期からの起源、疾患の異なったフェノタイプ（表現型）でのCOPDの重要で新しい識見を議論する。

Disease phenotypes and the course of lung function over a lifetime　疾患フェのタイプと生涯における肺機能の経過

Any discussion of the risk factors that drive the development of chronic obstructive pulmonary disease and whether or not the disease has its origins in early life first needs a definition of the disease itself.

GOLD guidelines have defined chronic obstructive pulmonary disease by incompletely reversible airways obstruction- that is, a ratio of the post-bronchodilator forced expiratory volume in 1 s to the forced vital capacity (FEV1:FVC ratio) of less than 70%.5　COPDとなる危険因子のどんな議論も、またCOPDが乳幼小児時期に原因があるか否かについても疾患そのものの定義が必要である。GOLD ガイドラインはCOPD を不完全な可逆性と気道閉塞と定義した、すなわち気管支拡張剤投与後の努力性肺活量に対する一秒量が70%以下であるとしている。

However, the normal range of this ratio changes with age, such that the use of a fixed ratio to diagnose any disorder is not useful in either an individual patient or in larger epidemiological populations in which a lower limit of normal can be better applied.67　しかし年齢とともにこの比率の正常範囲は変化するので、どのような疾患においても固定した比率を用いるのは個々の疾患や大規模の疫学調査では有益ではない。正常下限を適用するのがより良いであろう。

At the age of 30 years, an FEV1:FVC ratio of 75% is very abnormal in women, whereas 30% of healthy people older than 70 years of age will have a ratio below 70%.　30歳代女性がFEV1:FVC比率が75％であってもかなり異常である。一方健康な70歳以上の30％は70％以下である。

Furthermore, the definition based on the FEV1:FVC ratio is so broad that many types of patients with distinct clinical characteristics, prognosis, and treatment response are included. **さらに**FEV1:FVC比率に基づく定義の範囲はかなり広いのではっきりと臨床的な特徴、予後、治療に対する反応の特徴をもった多くのタイプの患者が含まれる。

For example, a subset of patients with asthma develops fixed airflow obstruction in later adult life.8　**例えば喘息を伴う一集団では成人後期に固定した気道閉塞へと進行する。**

The type of inflammation and remodelling in these patients will probably differ from that in smoking-related chronic obstructive pulmonary disease.9　**COPD患者の炎症とリモデルのタイプはおそらく喫煙関連のCOPDとは異なっているであろうと思われる。**

In addition to an overlap with asthma in which a reduced FEV1:FVC ratio can also occur, chronic obstructive pulmonary disease itself is a heterogeneous disorder in terms of its clinical presentation, rate of disease progression, and response to treatment. 喘息を伴いFEV1:FVC比率低下が生じることに加えて、COPD は臨床症状、疾患進行率、治療に対する反応に関してヘテロな疾患である。

Assessment of chronic obstructive pulmonary disease merely by lung function variables like the FEV1:FVC ratio will not do justice to the subphenotypes of the disease that underlie this ratio-ie, the three major phenotypes discussed in the following sections: small airways obstruction, emphysema, and chronic bronchitis. FEV1:FVC比率のような変化する単なる肺機能によるCOPD の評価は疾患のsubphenotypes（亜表現型）を正当化しない。このFEV1:FVC比率の基礎となる――即

ち三つの主なフェノタイプ：末梢気道閉塞、肺気腫、慢性気管支炎を次の項で議論する。
This topic has also been addressed in the new GOLD guidelines.3　これは新しいGOLDガイドラインでも述べられている。

Small airways obstruction　末梢気道閉塞
FEV1, FVC, and their ratio explain only a small percentage of the variation in symptoms and quality of life in chronic obstructive pulmonary disease.10,11　FEV1、FVCとその比率はCOPDにおける症状やQOLの小さな変化だけを説明する。
Importantly, these parameters mainly indicate obstruction of the large airways, whereas the small airways and lung parenchyma are the main sites of disease activity in chronic obstructive pulmonary disease. 重要なことは末梢気道と肺実質がCOPD における病勢の主な場所であるにもかかわらず、これらのパラメータは中枢気道の閉塞を主に示している。
Indeed, Hogg and colleagues12 showed that a higher percentage of small airways containing inflammatory cells is associated with more severe air flow obstruction in chronic obstructive pulmonary disease.　実際Hoggとその同僚たちはより高度に炎症細胞が末梢気道にあればあるほどCOPDではより高度な気流閉塞を伴っていることを示した。
Furthermore, detailed radiological assessments showed narrowing and loss of airways in patients with chronic obstructive pulmonary disease compared with healthy people.10 さらに詳細なレントゲン学的な評価では健康人に比してCOPD患者では気道の狭窄と破壊が見られる。
Such changes are already present in mild chronic obstructive pulmonary disease, even in lung regions without signs of emphysematous destruction. このような変化は軽症のCOPDでもすでに見られ、肺気腫様の組織破壊の見られない部分の肺でさえも見られる。
These findings are in agreement with parametric response mapping findings on CT made by Galban and colleagues,13 which show that the severity of airflow obstruction is mainly determined by changes in the small airways, and emphysema only contributes if severe emphysema is present. これらの所見はGalban等によってCTにおけるパラメトリック（母集団　(population)　の特性を示す定数）応答マッピングと一致している。それは気道閉塞の強さが主として末梢気道の変化によって規定され、重症の肺気腫がある場合のみ肺気腫が関与する。
However, emphysema and airways obstruction are not independent.　しかし肺気腫と気道閉塞とは別々のものではない。
Therefore, emphysematous alveolar destruction leading to loss of alveolar tethering points will contribute to airway obstruction through the loss of interdependence.　よって肺胞同士をつなぐポイントを破壊する肺気腫様肺胞破壊が気道破壊へと関連している。
However, the contribution of this mechanism to airway obstruction is difficult to measure in life in view of the challenges involved in reaching the small airways and lung tissue with noninvasive techniques. しかしながら、気道閉塞へのこのメカニズムが非侵襲的な方法での末梢気道や肺組織の検査からでは生涯の予測をするのは困難である。
Taken together, these findings suggest that small airways disease in mild chronic obstructive pulmonary disease probably precedes the development of emphysema leading to more severe illness. まとめると、これらの所見はおそらく軽度のCOPD での末梢気道疾患がより重症な疾患に繋がる肺気腫へと進展する過程であることを示唆している。
More work is needed in this area, with the use of sensitive markers of distal airway disease such as multiple breath washout.　この分野でMultiple Breath Washoutのような末梢疾患の感受性の高いマーカーを使用するようなさらなる研究が要求されている。

Emphysema　肺気腫

The aforementioned findings corroborate earlier studies that the association between emphysema and airflow obstruction is quite weak,14,15 and emphysema can already be present in patients with chronic obstructive pulmonary disease with mild airfl ow obstruction only.14　前述の所見は肺気腫と気流閉塞との関連が極めて弱いという早期の研究と一致する。肺気腫は、軽度の気流閉塞のみを伴う慢性閉塞性肺疾患患者に既に存在し得る。

This situation might have important implications for the clinical expression of the disease, since more severe emphysema is an independent predictor of a worse health status, higher BODE index,16 a marker of disease prognosis, a higher number of chronic obstructive pulmonary disease exacerbations, and more rapid disease progression. この状態は疾患の臨床的発現のために重要であるかもしれない、なぜならより重症な肺気腫はより悪化した状態、より高いBODE指数、疾患予後のマーカ、そしてより早い疾患の進行の独立した予測因子であるからである。

The type of emphysema might also be important in this respect,17,18 which adds further complexity. 肺気腫の型もまたこの方面では重要であり、さらに複雑にしている。

Patients with centrilobular emphysema have a higher degree of inflammation in their small airways than do those with panlobular emphysema,17 a finding that is associated with thickening of the small airway walls and more severe bronchial hyper-responsiveness.18　小葉中心性肺気腫患者は汎小葉性肺気腫での末梢気道炎症よりも重症である。汎肺気腫では末梢気道壁の肥厚とより過敏な気道過敏性を伴っている。

Chronic bronchitis　慢性気管支炎

Chronic bronchitis is usually defined as symptoms of cough and phlegm (or sputum production) on most days for more than 3 months in 2 consecutive years. 慢性気管支炎は2年連続して3ヶ月以上ほとんどの日に咳と痰（または痰の産生）症状として定義される。

It is present more frequently in smokers and patients with chronic obstructive pulmonary disease with more severe airflow obstruction. 喫煙者やより高度な気道閉塞を伴ったCOPD 患者に高頻度に見られる。

Several studies have suggested that chronic bronchitis contributes to dyspnoea and wheeze, worse health status, increased numbers of exacerbations, and more rapid disease progression in chronic obstructive pulmonary disease.[19-23]　慢性気管支炎はCOPDでの呼吸困難と喘鳴、健康状態の悪化、増悪回数の増加、急速な悪化の進行を幾つかの研究が示唆している。

Increased mucus hypersecretion, cough, or both can be associated with respiratory infections or increased airway inflammation, both of which contribute to more frequent chronic obstructive pulmonary disease exacerbations. 増加した粘液過分泌、咳、もしくは両方が呼吸器感染や気道炎症の悪化もしくは両方がより頻回にCOPD増悪に寄与している。

In turn, these exacerbations can induce symptoms of cough and sputum production that can persist for weeks after their onset.[24]　次に、これらの増悪は咳や痰のような症状を誘発し、発症後数週間続く。

The latter might introduce bias, leading to over-reporting of chronic bronchitis in patients with chronic obstructive pulmonary disease who have frequent exacerbations. 後者はバイアスを生じ、頻回に増悪するCOPD患者について過剰な慢性気管支炎の報告を誘導している。

Controversy remains around this subject since the ECLIPSE study did not find chronic bronchitis to be a risk factor for chronic obstructive pulmonary disease exacerbations, after adjustment for disease severity.[14,25]　このことに関して、ECLIPSE study　が、補正すると慢性気管支炎はCOPD増悪の危険因子ではないとする報告以来論争が続いている。

The differential results in studies investigating the role of chronic bronchitis in chronic obstructive pulmonary disease could be because of the use of varying definitions or different populations under study.[19,26] COPDにおける慢性気管支炎の役割の研究結果がそれぞれ異なるのは研究での定義や異なる対象のためである可能性がある。
Furthermore, chronic bronchitis is not an objective measure and can be affected by factors such as sex and sociocultural behaviour.[14,27] さらに慢性気管支炎は客観的な基準ではなく、性や社会文化的な因子によって影響される。
The three domains of chronic obstructive pulmonary disease-small airways obstruction, emphysema, and chronic bronchitis-can be captured by similar lung function abnormalities.
COPD、肺気腫、慢性気管支炎の三つの領域は類似した肺機能異常によって捕らえられている。
Only in the last decade has much attention been given to the differential relevance of these subphenotypes. 過去わずか十年間だけこれらの亜phenotypeとの異なる関係に多くの注意が払われた。
Thus, most studies that have attempted to address the issue of early origins of chronic obstructive pulmonary disease have not been designed to do so successfully. それで、多くの研究がCOPDでの早期の発生の問題に取り組むよう試みたがそれほど上手くいくようなデザインがなかった。
This is an unavoidable weakness of our existing knowledge. これは我々の今ある知識の避けられない弱点である。

The roots of chronic obstructive pulmonary disease: importance of normal lung development COPD
COPDのルーツ：正常な肺生育の重要性
Normal airway development 正常な気道の発育
The lung bud initially develops as an outpouching of the fetal foregut at 6 weeks' gestation. 肺芽は最初に在胎6週で胎児の前腸の外反（嚢）として成長する。
By the end of the first trimester of pregnancy, airway generations down to the bronchiolar level and their accompanying vessels have been formed. 妊娠第1期の終わりまでに気道は気管支レベルまで成長し、血管も一緒に発育している。
Type 2 cell differentiation and the first appearance of surfactant occurs at around 23 weeks' gestation. 2型細胞の分化やサーファクタントの発現は在胎23週ごろに見られる。
Pre-acinar vessels follow airway development, whereas intra-acinar vessels follow the development of alveoli. 前腺房血管は気道の生育と共に発育し、腺房内血管は肺胞発育と共に生育する。
Recent transcriptomic approaches have identified different molecular phases of lung development,[28] but so far this has not led to clinical applications. 近年の遺伝子発現研究では肺発育の異なる分子時期を同定したが現在の所、臨床応用には至っていない。
The most recent work on postnatal airway functional changes using spirometry has been undertaken by the Global Lung Initiative and has collated and refined much previous work.[29-31]
Global Lung Initiativeによるスパイロを使用して生後の肺機能の変化を見た最近の研究が以前の研究を照合してより明瞭にした。
Airway development has three key stages: the start point for lung growth, namely airway function at birth, with reduced lung function at birth being a risk factor for asthma at 10 years of age;[32] childhood and young adult airway growth to the plateau at 20-25 years of age;33 and lung function decline, the rate of which can vary even in patients with established chronic obstructive pulmonary disease.[34,35] 肺の発育には3つの重要なステージがある：肺発育の出発点即ち生下時の気道の機能低下している場合は10歳時点で喘息の危険因子となる。小児期と青年期の気道発育は20-25歳でピークとなる。その後下降するが、その下降率はCOPD患者でもかなり変動がある。
All risk factors for reduced lung function can be present in an individual. 肺機能低下させる全

ての危険因子は各個人にある。
A failure to reach the normal plateau and accelerated loss of function in adulthood mean that the threshold for respiratory symptoms and disability is reached earlier than normal (figure 1). 正常に最高の値に肺機能が達しないと成人期に肺機能低下を加速し、呼吸器症状の閾値を低下させ、正常よりも早期に肺機能不全になる。
Importantly, the first 4 years of life are a crucial time window; for the most part, there is no catch-up in airway function after the age of 4-6 years.[36-39] 重要なことは生後4年は非常に重要な時期であり、多くの場合4-6歳を過ぎて肺機能のキャッチアップは見られない。
The sole exception might be some survivors of chronic lung disease of prematurity, since one study showed that spirometry was clearly abnormal at age 7-9 years,40 but had normalised by 20-22 years of age.[41]　例外は未熟児で数人の慢性肺疾患での生存者で7－9歳で明らかにスパイロで異常であったが20-22歳でまでに正常となった例が報告されている。

Normal alveolar development　肺胞の正常発育
The timing of alveolar development is more uncertain than that of airway development. 肺胞発育の時期は気道の発育よりもはっきりしない。
Conventional wisdom suggests that there are around 5×10^5 alveoli at birth, that there is a rapid phase of secondary septation and alveolar development in the first 2 years of life, and that thereafter few, if any, new alveoli develop. 通常の概念では生下時$5x10^5$あり、２歳までに二次的な隔壁形成と肺胞の発育がみられ、その後はたとえあってもほとんどない。
Recent histological studies in monkeys42 and hyperpolarised helium studies in 5 human beings43,44 suggest that in fact alveoli continue to develop throughout the period of soatic growth. Little is known about normal alveolar ageing.　最近のサルでの組織学的研究や5人の人間での過分極ヘリウムの研究では実際の肺胞では身体の発育している間中発育し続けている。

Epidemiology of risk factors for chronic obstructive pulmonary disease, and relation with its early origins COPDの危険因子の疫学と早期発症との関連
The main risk factor for the development of chronic obstructive pulmonary disease is smoking.45 COPDの主な危険因子はタバコである。
However, it is not the only risk factor, since recent studies have shown that many people develop the disease without ever having smoked.[46] しかしタバコだけが危険因子ではない。なぜなら最近の研究ではタバコを吸ったことがないのにCOPD になる多くの症例が報告されている。
Therefore, other factors besides personal smoking, such as indoor and outdoor air pollution and other environmental triggers, such as second-hand smoke during pregnancy or early childhood, might also be important, as are dietary factors.[45,47-49] Indeed, one study showed that early childhood disadvantage (defi ned as at least one of: maternal, paternal, or childhood asthma; maternal smoking; and childhood respiratory infections) conveys as much risk for chronic obstructive pulmonary disease as does smoking in adult life.[49] そのためタバコ以外の戸外大気汚染や他の環境因子、妊娠中や小児期の受動喫煙が重要である。また食事の因子も重要である。実際、母・父・小児期の喘息、母親の喫煙、小児期の呼吸感染のうち少なくとも一つが、大人になってからのタバコと同様にCOPD の危険因子としてと定義された。
An important new insight is that chronic obstructive pulmonary disease can also have its origins in childhood or even in utero. 重要な新しい知見は小児期あるいは子宮内でさえもCOPDが発症するということである。
Lung function can be compromised during lung development in utero-eg, low birthweight babies

or children whose mothers smoked in pregnancy have reduced lung function soon after birth.[50] 肺機能は子宮での発育中に障害される。母親が妊娠中に喫煙していた低出生体重児や小児は生後間もなく肺機能が低下する。

This reduced function then continues throughout life, resulting in a lower plateau at around 20-25 years of age (figure 1). この低下した肺機能は一生続き、20-25歳時の最高値がより低くなる。

The question remains as to whether different factors contribute to different types of chronic obstructive pulmonary disease.　異なった因子がCOPDの異なった型に関係しているかはまだ疑問のままである。

It might well be the case that several genetic factors, environmental factors (smoking, air pollution, occupational hazards, and infections) and lifestyle issues (diet and exercise), encountered at different stages of life, can lead to different types of the airflow obstruction that are referred to as the single disease entity chronic obstructive pulmonary disease (figure 2), depending on when they are encountered and in what combinations. いくつかの遺伝因子、環境因子（喫煙、大気汚染、職業的な危険、感染）、ライフスタイル（食事、運動）これらは人生の異なった時期に遭遇するが、これらがCOPDの単一疾患としての異なった型の気道閉塞と関連する。それはいつこれらの因子にであったか、そして何と関係していたかによる。

The panel summarises the different environmental risk factors for chronic obstructive pulmonary disease, which will be discussed in more detail in the following sections.　パネルはCOPDの異なった環境での危険因子をまとめている。それは次のセクションで議論する。

Low lung function at an early age 乳幼児期の肺機能

The most informative birth cohort studies have come from Tucson (AZ, USA) and show that in healthy people without wheezing illness, lung function centile shortly after birth affects lung function centile in the third decade of life.[38,51,52]　最も優れた出生コホートはTuscon（ツーソン：米国　アリゾナ）での研究である。その中で、喘鳴のない健康人では出生直後の肺機能が30年間影響があることを示した。

Prospective data in this population to the age that chronic obstructive pulmonary disease becomes clinically apparent are eagerly awaited. COPDが臨床的に明瞭になる年齢でのこのコホートでの人々での前向きコホートの調査結果を首を長くして待たれていた。

Cohort studies following participants into middle age, most notably the Melbourne asthma cohort, have shown the effectiveness of tracking of lung function-ie, the spirometry centile in mid-childhood determines the spirometry centile in middle age.[53]　中年まで追跡したコホート研究で最も有名なメルボルン喘息コホート研究がある。それは肺機能を追跡調査したもので、小児期中期の肺機能が中年時の肺機能を決定することを示した。

Notably, the Melbourne cohort howed that severe asthma was an important risk factor for the development of chronic obstructive pulmonary disease, and was a more prominent indicator than was smoking. さらにこのメルボルンコホート研究では重症喘息がCOPD の重要な危険因子であること、そしてそれは喫煙よりも著明であった。

Furthermore, patients with chronic obstructive pulmonary disease had the lowest lung function compared with healthy people and asthmatics at 10 years of age, which continued through to 50 years of age.[54] Taken together, these cohorts show that spirometry at 4-6 years of age affects the height of the spirometry plateau achieved at 20-25 years, and hence the start point for spirometry decline.　さらにCOPD患者は10歳の時点で健康人や喘息よりも肺機能が最も低かった。それは50歳まで続いている。同時にこのコホート研究では4-6歳の肺機能（スパイロ）が20-25歳の肺機能が最

も最高になるときの値に影響し、そこから肺機能が下がる。
Although clearly cigarette smoking is a highly important determinant of the rate of decline of spirometry in adult life, early life events are also important. 喫煙は成人肺機能低下の重要な決定因子であり、幼少児期の出来事もまた重要である。

Bronchial hyper-responsiveness 気管支の過敏性
Bronchial hyper-responsiveness is often thought to be a hallmark of asthma, but it has also been shown to be present in chronic obstructive pulmonary disease.[55-57] 気管支過敏性は喘息の特徴であると一般に考えられているが、COPDにおいてもみられる。
Bronchial hyper-responsiveness precedes the development of chronic obstructive pulmonary disease-like symptoms in the general population[58] and more severe bronchial hyper-responsiveness is associated with subsequent accelerated lung function decline.[8,59,60] 気管支過敏性は一般人のCOPD様の症状が出てくるのに先立ってみられ、より重症の気管支過敏性が続いて起こる肺機能低下と関連している。
What drives the relation between bronchial hyper-responsiveness and chronic obstructive pulmonary disease has not yet been elucidated. 気管支過敏性とCOPDとの関係を結びつけるものが何であるかについてはまだ解明されていない。
It has been that bronchial hyper-responsiveness consists of variable and fixed components.[61] 変化する、変化しないコンポーネントからなる気管支過敏性である。
The variable components largely derive from the acute release of pro-inflammatory mediators as a result of ongoing airway inflammation.[55,62-64] 変化する因子は主として進行している気道炎症の結果として炎症を促進するメディエーターの急性放出に由来する。
The persistent components result from structural changes in the airways such as epithelial desquamation, goblet cell metaplasia, fibrosis, increased smooth muscle mass, angiogenesis, and extracellular matrix changes. 持続的な因子は上皮の剥脱、腺細胞過形成、繊維化、平滑筋肥厚、血管新生、細胞外物質の変化のような気道における構造的変化の結果である。
These changes can occur in both the large and small airways and are associated with a reduced number of airways, especially the smaller airways, in chronic obstructive pulmonary disease.11 これらの変化は 中枢・抹消気道の両方でおこり、気道の減少を伴い、特にCOPDでは抹消気道に著明である。
An interesting idea is that small airway abnormalities might be associated with the severity of bronchial hyper-responsiveness in chronic obstructive pulmonary disease, just as in asthma, but at a more acinar level, which links bronchial hyper-responsiveness to chronic obstructive pulmonary disease development in association with small airway disease.[65] 抹消気道異常が喘息と同様にCOPDにおける気管支の過敏性の重症度と関連するが、より細葉レベルでは抹消気道疾患に伴ってCOPDの進行と気道過敏性とが関連しているという興味ある考え方がある。
Moreover, bronchial hyper-responsiveness at 1 month of age is a risk factor for reduced lung function in childhood.[66-68] さらに生後一か月時の気道過敏性が小児期の肺機能低下の危険因子である。
This association might be compatible with the hypothesis that abnormal lung development underlies the presence of bronchial hyper-responsiveness, which might be partly due to maldevelopment of the airways in utero.[69] この関連は異常な肺の成育が気道過敏性の存在下にあり、それは部分的には子宮内での気道の異常な発育によるものかもしれないという仮説と両立する。
Taken together, the presence and severity of bronchial hyper-responsiveness is an independent risk factor for the development of chronic obstructive pulmonary disease. 纏めると気管支の過敏性の存在と重症度はCOPD進行の独立した危険因子である。

In-utero and early childhood exposures

Adverse events in the mother can have direct effects on the fetus or child, or prime the body of a child to develop an abnormal response to an event later in life.子宮内と幼小児期の暴露は胎児や小児に直接影響がああるか、もしくは人生の後年での事象に対する異常な反応を起こす。

According to the developmental origins of health and disease (DOHAD) hypothesis,[70] in-utero events can reprogramme an individual for immediate adaptation to gestational disturbances, which can have consequences for the risk of the development of metabolic diseases later in life. 健康と病気の発達上の起源DOHAD仮説によると子宮内の事象は妊娠中の障害に対する即応のために各個人で再プログラムできる。それは後生での代謝疾患へと進展するリスクとなる。

A changed gestational environment has been linked to adult metabolic disease by both in-utero caloric deficiency (from famine or uteroplacental insufficiency) and in-utero caloric abundance (from a maternal high-fat, calorie-dense diet). 変化した妊娠中の環境は子宮内でのカロリー不足（飢餓から子宮胎盤不全）や子宮内カロリー過剰（母の高脂肪、高カロリー食）による成人代謝疾患と関連する。

Other chronic diseases have followed a pattern of prenatal environmental effects on adult life, and chronic obstructive pulmonary disease might also have links with the DOHAD hypothesis. 他の慢性疾患では成人期において出生前の環境が影響していた。そしてCOPDは健康と病気の発達上の起源DOHAD仮説と関連していた。

Indeed, Barker's hypothesis emerged almost 25 years ago from epidemiological studies of birth and death records that showed a high geographical correlation between rates of infant mortality and particular classes of later adult deaths (eg, respiratory disease) and an association between birthweight and rates of adult death from ischaemic heart disease.[71,72] 実際Barkerの仮説は約25年前の出生と死亡の疫学的な研究から来ている。それは乳児死亡と後の成人死（例えば、呼吸器疾患）の特定の種類との高い地政学的関係、そして出生体重と成人の虚血性心疾患による死亡率との関係があった。

These theories stimulated interest in the fetal origins of adult disorders. これらの理論は成人病の起源が胎児期であるということに対する関心を刺激することになった。

The DOHAD hypothesis has been studied little in respiratory diseases, but examples include the effect of in-utero smoke exposure leading to enhanced responses to postnatal allergen and fungal exposure,73 and neonatal hyperoxia in mice leading to changed inflammatory and fibrotic responses to influenza A infection when the mice reached adulthood.[74]健康と病気の発達上の起源DOHAD仮説では呼吸器疾患に関してはほとんど研究されてなかった。しかし例えばマウス子宮内でのタバコの煙への暴露が生後のアレルゲンや真菌暴露に対する反応を助長すること、またマウスでの新生児期の低酸素症はマウスが成人したときのインフルエンザA感染に対して炎症や繊維化への変化へと導くことが報告されている。

If such effects also have a role in human beings, it will become important to obtain a more detailed antenatal and perinatal history from adult patients, which is not often done at present.75 そのような影響が人間にもあるならば、現在あまり行われていない成人患者の出生前、周産期の病歴を得るのが重要となってくるであろう。

The following issues have been described and will be discussed in more detail below: transgenerational effects, antenatal effects, perinatal effects, and early childhood exposures. 次の問題が下記により詳細に記述され議論される。：世代間の影響、出生前の影響、周産期の影響、幼児期暴露

Worryingly, transgenerational epigenetic effects on asthma risk have been shown to exist. 厄介

なことに、喘息危険に関する世代間の後生的な影響が存在することが示された。（訳注：epigenetic (DNA配列には変化がないがメチル化等により細胞分裂を経て伝達される遺伝子機能の変化とそれを扱う学問領域)) エピジェネティクス,エピジェネティックス

Thus, a grandmother who smoked increases the risk of her daughter's children having asthma, even if the daughter herself does not smoke.[76] こうして祖母の喫煙が祖母の娘が喫煙していなくても、その娘のこどもの喘息へのリスクを上げる。

The mechanism of this eff ect is thought to function through gene methylation.[77] このメカニズムは遺伝子のメチル化の機能によるものと考えられている。

The possibility that diet, pollution, and other known epigenetic eff ects might also have epigenetic transgenerational eff ects on the fetus cannot be excluded. 食事、公害、他の知られている後生的な影響もまた胎児への後生的な世代間の影響があるかもしれない可能性が除外できない。

Preventive strategies are mandatory, but will probably only deliver results in the very long term. 予防的な戦略が必須であるが、恐らく長い期間かかってから結果が出るであろう。

The most important and most studied adverse antenatal event is maternal smoking, which, together with maternal atopy and maternal hypertension, leads to impaired lung function soon after birth.[78,79] 最も重要で、最も研究されてた出生前の不利な出来事は母親のアトピーや高血圧と同様に生後間もなくの肺機能を傷害する。

Studies in animals have shown that maternal nicotine exposure leads to a reduction in airway alveolar points, increased lung collagen deposition, longer airways with smaller diameters, and mucus hypersecretion.[69,80-82] 母親のニコチン暴露が気道の肺胞領域を減少させ、コラーゲンの肺沈着を増加させ、より長い気道で気道径を小さくさせ、粘液の過分泌を誘導することが動物実験で示された。

These factors probably all contribute to airway obstruction and increased bronchial hyper-responsiveness in mice postnatally, even if they were not exposed to allergen.[69] これら因子のおそらく全てがマウスの生後気道過敏性を増加させる。たとえ抗原に暴露されることがなくても。

Exposure to smoke also leads to changes in cord blood immunological responses.[83,84] 煙への暴露もまた臍帯血の免疫学的反応の変化へと誘導する。

Other antenatal eff ects that can aff ect fetal lung development, immune responses in cord blood, or both include maternal diabetes, maternal medication use (eg, paracetamol and antibiotics),[79] maternal exposure to air pollution,[85] and previous pregnancy (including miscarriage).[84] 他の出生前の問題（母親の糖尿病または母親の薬の使用（アセトアミノフェンや抗生物質）もしくは両方、母親の大気汚染への暴露、以前の妊娠（流産を含む））が胎児肺発達、臍帯血の免疫反応に影響する。

Maternal diet in mice has been shown to exert epigenetic eff ects on the pups,[86] but this has not yet been shown in human beings. Even if reductions in lung function are small, they can still be of relevance. マウスにおいて母親の食事が子どもに後生的な影響を与えることが示された。

In a recent study, Guerra and colleagues[87] showed that early childhood reductions in lung function caused by parental smoking are important and aff ect rates of development of chronic airflow obstruction when these children smoke themselves. 最近の研究では、Guerra等が乳幼児期の肺機能低下は両親の喫煙によるものが重要であり、この子ども達が喫煙すると慢性気道閉塞の発症率に影響するを示した。

Therefore, they showed that parental and active smoking act synergistically to aff ect early lung function deficits in young adulthood.[87] 彼等は両親と本人の喫煙が相乗効果的に幼少児期の早期の肺機能障害に影響を及ぼすことを示した。

Thus, even if early life exposures do not directly produce major lung function deficits, they

can also play a part in increasing susceptibility to active smoking and predisposing people to the progressive nature of chronic obstructive pulmonary disease, as has been recorded in at least some patients. こうして、たとえ早期の暴露が大きな肺機能障害とならなくても、早期の暴露が少なくとも一部の患者で報告されているように、COPDの進行する自然経過に対して喫煙している人や罹患しやすい人の感受性を高める。

Perinatal effects comprise the timing of delivery (prematurity), the mode of delivery (caesarean section versus vaginal), and the place of delivery (home or hospital).88-90 周産期の影響は出産の時期（未熟児）、出産の形態（帝王切開と経膣分娩）、分娩の場所（自宅か病院）によって異なる。

The effects of prematurity are well documented. 未熟児の影響はよく報告されている。

Premature birth, even if the baby does not require ventilatory support, is associated with decrements in lung function in the perinatal period, and these effects are more pronounced with the need for more intensive and prolonged treatment. たとえ新生児が人工換気を受けていなくても、未熟児であることが周産期に肺障害を伴い、より強力で長期の治療を受ける必要が明らかにある。

Interestingly, so-called late preterms (week 33 up to week 40 gestation) also have impaired childhood spirometry,[91] and late preterm birth is much more frequent than is extremely preterm delivery. 興味あることに、いわゆる晩期早産（在胎週数３３から40週）もまた小児期の肺機能（スパイロ）を傷害する。晩期早産は極端な早産よりもずっと頻度が高い。

The evolution of lung function after preterm birth is controversial: some early life studies have shown catch up in lung function,[41] whereas others have reported an even further decline in lung function in early life.[92,93] 早産後の肺機能発達は異論が多い：いくつかの若年期の研究では肺機能はキャッチアップするとの研究報告があるが、他の研究では後年さらに肺機能が低下すると報告されている。

Wheeze is common in childhood, but importantly is not associated with evidence of airway inflammation, as indicated by the concentration of exhaled nitric oxide94 and exhaled breath temperature,95 although evidence of increased oxidative stress might be present.[96] 喘鳴は小児期にはよく見られる。しかし重要なことは呼気NO濃度や呼気温度で示されるように気道炎症を伴っていない。しかしながら酸化ストレスが増加しているというエビデンスがある。

This finding is important because these children might develop irreversible airflow obstruction, similar to chronic obstructive pulmonary disease, later in life. これは喘鳴児が後年COPDと同様な非可逆性気道閉塞へと進行するかもしれない重要な所見である。

However, this disorder does not necessarily have a similar pathophysiology to the airfl ow obstruction in lifelong smokers. しかし、この疾患では生涯喫煙者の気道閉塞と同様の病理生理学である必要はない。

A further degree of complexity is the changing nature of preterm survivors; “old” bronchopulmonary dysplasia babies were bigger, were ventilated at higher pressures, and had a mainly airway disease disease, whereas “new” babies with the disorder, who are smaller and more preterm, receive surfactant and are ventilated with faster rates at lower pressures, and have pulmonary hypoplasia and alveolar maturation arrest, albeit possibly with some recovery of alveolar numbers.[44] さらに複雑なことは早産児生存者の変化する自然経過である：昔の気管支肺形成不全児はもっと大きく、高圧で換気されていた。そして主に気道疾患であった。しかしこの疾患の最近の児は小さく、より早産で、サーファクタント治療を受け、低い圧で換気され、いくらかの肺胞数の回復の可能性があるにもかかわらず、肺の低形成や肺胞の成熟停止が見られる。

The mode of delivery is believed to exert long-term consequences by affecting the nature of early bacterial colonisation of the baby-vaginal delivery leads to maternal vaginal and bowel

flora predominating, whereas caesarean section favours environmental bacteria.[97] 出産の方法は早期の新生児の細菌コロニーの形成に影響を与え長期にわたってそれが続くと信じられている。経膣分娩は母親の膣と腸細菌叢へと導くが、帝王切開は環境細菌へと導く。

The importance of the microbiome is discussed in the next section. 細菌叢の重要性は次の項で議論する。

What is clear is that caesarean delivery is associated with an increased subsequent risk of atopy and food allergy, and changed fecal flora at 7 years of age.[88,89] 帝王切開で明らかなことは7歳の時点でアトピー、食物アレルギー、腸内細菌の変化である。

Place of delivery has been the least studied factor. 分娩の場所はあまり研究されていない。

Babies of atopic parents who were delivered at home had a reduced prevalence of atopic disease (asthma, eczema, and food allergy) at 6-7 years of age, and faecal Clostridium difficile isolation at 1 month was positively associated with atopic disease at the same age.[90] 家庭での分娩は6-7歳時ではアトピー疾患（喘息、湿疹、食物アレルギー）の有病率を下げる。一ヶ月時の便のClostridium difficile分離は6-7歳時でのアトピー疾患有病率増加と関連していた。

Early childhood exposures 幼少児期の暴露

The adverse effects of parental cigarette smoking are well documented. 両親による喫煙の影響はよく報告されている。

However, a key controversial question is whether or not early viral infections cause asthma and thus long-term susceptibility to chronic obstructive pulmonary disease. しかし重要な議論は早期のウイルス感染が喘息やCOPDに対して長期の影響があるかどうかである。

Infection with respiratory syncytial virus, and especially rhinovirus, is unquestionably associated with the later development of asthma;[98] however, the most convincing evidence suggests that the association is not causative. RSV、特にライノウイルス感染は疑問の余地なく後の喘息発症と関連している；しかし最も確定的なエヴィデンスではその関係は原因的なものではない。

Immunological abnormalities are detectable in the cord blood of babies who subsequently develop wheezing lower respiratory tract illness,[99] and impaired lung function precedes the first wheezing episode.[100] 喘鳴下気道疾患に進行したり、肺機能障害が最初の喘鳴に先行して見られる児の臍帯血で免疫学的な異常が見られる。

Furthermore, the 17q21 locus is associated with rhinovirus-induced wheezing.[101] さらに17q21遺伝子はライノウイルスによる喘鳴と関連がある。

Therefore, viral infections are a marker of pre-existing impaired structure and function that lead to asthma, rather than being directly causal. よってウイルス感染は直接的な原因というよりは喘息になる元々ある障害された構造や機能のマーカである。

Other important factors also impinge on lung health. 他の重要な因子もまた肺の健康に悪影響を与える。

The role of early bacterial colonisation is an active research topic. 早期の細菌コロニー形成の役割はさかんに研究されている課題である。

We now know that the lower airway, far from being sterile, contains a rich bacterial flora, as shown by molecular microbiology techniques.[102] 下気道は分子細菌学によって示されたように、無菌とはほど遠く、細菌コロニーに富んでいることが知られている。

Furthermore, normal immunological development and response to allergens is critically dependent on a healthy lower airway flora.[102,103] さらに正常な免疫学的な発達とアレルゲンに対する反応は健康な下気道細菌叢に大きく依存している。

The relevance of the flora to the development of chronic obstructive pulmonary disease remains

to be established. COPDの進行と腸内細菌との関連はまだ確率されていない。
However, childhood respiratory infections are known to affect later risk of chronic obstructive pulmonary disease.[49] しかし小児期の呼吸器感染が後年にCOPDのリスクであることが知られている。
Therefore, changes in the airway microbiome and the consequent risk of chronic obstructive pulmonary disease are probably worth investigating. よって、気道細菌叢の変化とそれに伴うCOPDのリスクはおそらく研究する価値がある。
The effects of the microbiome on airway immune responses and thus risk of atopic disease is another mechanism whereby the risk of chronic obstructive pulmonary disease might be modulated. 気道免疫反応における影響とそれによるアトピー疾患のリスクはCOPDのリスクの別の別のメカニズムである。
The protective effects of the farming environment on atopic disease have long been known, and have recently been related to greater environmental bacterial and fungal diversity.[104] アトピー疾患における農業をしている環境の予防効果はかなり以前より知られているが、最近より多くの環境細菌と真菌の多様性と関連してることが解ってきた。
However, the COPSAC study showed that early upper airway colonisation with Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae, alone or in combination, is associated with worse wheeze outcomes,[105] and, more recently, with raised amounts of Th1, Th2, and Th17 cytokines in nasal samples.[106] しかし、COPSAC研究ではHaemophilus influenzae, Moraxella catarrhalis, あるいは Streptococcus pneumonia の単独または組み合わせによる上気道での早期のコロニー化さらなる喘鳴の悪化と関連していることを示した。
The precise interactions between bacteria and viruses, the host immune system, and long-term outcomes have yet to be established, but clearly anything that can modulate the host airway flora, such as antibiotic therapy, could potentially have profound effects. 細菌とウイルス間の正確な相合作用、宿主免疫系統、そして長期の影響はまだ確率されていないが、抗生物質のような宿主の気道細菌叢を乱すものは全て潜在的に大きな影響がある。
Excessive weight gain in the first year of life is associated with failure of normal lung development.[107] 生後一年以内の過剰な体重増加は正常な肺の生育を妨げる。
Postnatal exposure to air pollution is another major cause of failure of normal lung growth.[108,109] 出生後の大気汚染暴露 はまた正常な肺の生育を妨げる大きな原因である。
In the CAMP study, 25% of participants with mild asthma showed impairment of lung growth over a 4-year period, irrespective of treatment (budesonide, nedocromil, or placebo).[110] CAMP研究では治療に関係なく（ブデソナイド、ネドクロミル、プラセボ）軽症喘息の25%で4年間以上肺成長障害が見られた。
The basis of this intriguing finding is not known. この複雑な原因はよく分かっていない。
An important aspect of the development of the lung in childhood is that a disconnect exists between lung structure (growth) and lung function. 小児期の肺成長の重要な点は肺構造（成長）と肺機能との間に乖離があることである。
Longtitudinal cohort studies into the course of lung function and growth have invariably used spirometry as a surrogate for both structure and function. 肺機能と成長の経過をみる長期のコホート研究では構造と機能を代理するものとしてスパイロが例外なく使用されている。
This approach is not ideal-spirometry is only indirectly related to lung size and respiratory mechanics, and gives no indication of the size of the pulmonary capillary bed. このアプローチは理想的ではないースパイロは非間接的に肺の大きさと呼吸器の構造と関連しているだけであり、肺毛細血管床の大きさを示しているわけではない。
Furthermore, spirometry is insensitive to distal airway function. さらにスパイロは末梢気道の機

能には役立たない。
Therefore, caution is needed when drawing inferences about lung growth and aspects even of airway function in the studies published so far. よって過去の論文において肺成長や肺（気道）機能での推論を引用するときは注意が必要である。
Genetics Chronic obstructive pulmonary disease is a multifactorial disease in which genes and the environment interact to drive the development of the disease.[111] COPDは遺伝と環境が疾患の進行に相合作用する多因子疾患である。
Several genome-wide association studies have discovered genes that are associated with both the presence of the disorder and the severity of airflow obstruction-namely, CHRNA3, CHRNB3/4, HHIP, and FAM13A. いくつかのゲノム全領域関連解析（GWAS）で疾患と気道閉塞重症度と関連があることが示されたーCHRNA3, CHRNB3/4, HHIP, FAM13A
Furthermore, several genes have been associated with low lung function in the general population, including AGER, GPR126, GSTCD, HTR4, THSD4, and TSN1. さらに幾つかの遺伝子は一般集団での肺機能低下と関連があった（AGER, GPR126, GSTCD, HTR4, THSD4, TSN1）
However, low lung function in the general population could be due to asthma, chronic obstructive pulmonary disease, or both, especially in older people. しかし一般集団での肺機能低下は喘息、COPDまたは両方（特に老人では）による可能性がある。
This situation greatly hampers the study of the genetics of chronic obstructive pulmonary disease and indeed these published genes might not be specific for either asthma or chronic obstructive pulmonary disease. このことがCOPDの遺伝研究を大いに妨げており、事実この関連の遺伝子の論文では喘息、COPDいずれにも特異的ではない。
They might also indicate abnormal lung development in utero, different environmental drivers of disease, or both. このことがまた子宮内での肺発育、または疾患の異なった環境要因、あるいは両方を示すものかもしれない。
In addition to active cigarette smoking, passive environmental tobacco smoke exposure also induces lung inflammation and oxidative stress.[112] さらに喫煙や受動喫煙もまた肺の炎症や酸化ストレスを誘導する。
Environmental tobacco smoke exposure has been associated with compromised lung function at birth78,113 and in adulthood,[114,115] and with respiratory symptoms[116,117] and increased risk of chronic obstructive pulmonary disease.[118,119] タバコ煙暴露は生下時、成人期に肺機能障害と呼吸器症状を伴い、COPDのリスクを上げる。
Environmental tobacco smoke exposure can therefore affect lung development in utero, lung growth during childhood, and lung function loss during adulthood. タバコ煙暴露は子宮内、小児期の肺発育、成人期の肺機能障害に影響する。
A gene-environment interaction exists since it has been shown that infants from mothers carrying GST-null polymorphisms are most susceptible to the adverse effects of smoking.[120,121] GSTの無い遺伝的多型を持つ母親からうまれた乳児はタバコの影響を受けやすいことが示されているので遺伝-環境相合作用は存在する。
A recent study showed that polymorphisms in GSTO genes interact with environmental tobacco smoke exposure both in utero and in adulthood and significantly affect FEV1 in adulthood, thus supporting the notion that genes and environmental stimuli interact at different stages of life (figure 2).[122] 最近の研究ではGSTO遺伝子の遺伝的多型は子宮内と成人期においてタバコ煙と相合作用して 成人期のFEV1に有意に影響し、遺伝子と環境刺激が人生の異なる時期に相合作用することを支持している。
However, the authors acknowledged that they did not record consistent significant interaction

effects of the GSTO single nucleotide polymorphisms and environmental tobacco smoke exposure on the FEV1:FVC ratio. しかし著者等はFEV1:FVC比におけるGSTO単一ニュクレオチド遺伝的多型と環境タバコ煙暴露との一貫した有意の相互作用を認めなかった。

Further analyses showed that the effects were restrictive in origin, rather than obstructive, which draws attention to the problems that exist with the use of just a reduction in FEV1 as a sign of chronic obstructive pulmonary disease. さらなる解析ではその影響は閉塞と言うよりはむしろ元々拘束性であった。そのことがCOPDの兆候として単にFEV1低下を用いることが問題があると言われるようになった。

A factor that limits research into the early origins of chronic obstructive pulmonary disease is the logistical difficulty of combining studies of early life events and the presence of the disease about 50-60 years later in the same people. COPDの早期の原因が幼少児期（人生早期）の出来事と同じ集団で5-60年後の疾病と関連づけるのは困難である。

Therefore, research has to rely on indirect evidence. そのために研究は間接的なエビデンスに頼ってきた。

Population-based studies have connected genes important for lung growth, such as ADAM33, with susceptibility to chronic obstructive pulmonary disease,123 and patient studies have confirmed this finding by recording different prevalences of single nucleotide polymorphisms between healthy controls and patients with chronic obstructive pulmonary disease in most studies and by linking gene polymorphisms with chronic obstructive pulmonary disease pathophysiology.[124-126] 集団研究ではCOPDと関連するADAM33のような肺成長に重要な遺伝子と関連付けられてきた。患者研究ではこの所見は健康人（コントロール）とCOPD患者とのでは単一ニュクレオチド遺伝的多型が異なることやCOPDと遺伝的多型との関連について多くの研究において確認されてきている。、

Additionally, reduced lung function in childhood has been shown to be associated with ADAM33 single nucleotide polymorphisms, specifi cally in children of mothers who smoked during pregnancy—another example suggesting that in-utero effects might have imprinting effects on lung function after birth.[127] さらに小児期に低下した肺機能はADAM33単一ニュクレオチド遺伝的多型を伴っており、特に妊娠中に喫煙していた母の子どもにおいて特にみられる。例えば、子宮内の影響として生後の肺機能にimprinting effects（刷り込み効果）があることが示唆されている。

Another study showed that SOX5, a gene necessary for lung development, is associated with chronic obstructive pulmonary disease,[128] which again suggests that the development of the disease might have its origins in utero. 肺の生育に必要な遺伝子であるSOX5はCOPDと関連しており、それが子宮内から始まる疾患の進行を示唆している。

This finding is corroborated by a recent study addressing the genetics of chronic obstructive pulmonary disease through an investigation of genes that were previously associated in genome-wide association studies with chronic obstructive pulmonary disease, low lung function, or both.[129] この所見は以前のCOPD、低肺機能、もしくは両方の全ゲノム関連研究の遺伝子研究によるCOPDの遺伝子を調べた最近の研究によって確証された。

These genes were then associated with transient early wheeze, a phenotype in early childhood that is associated with low lung function early in childhood and with low lung function in later childhood.[129] これらの遺伝子は幼児期のフェノタイプである一過性喘鳴を伴っており、乳児の肺機能低下と後の小児期の肺機能低下と関連している。

Of note, children with wheezy bronchitis (or episodic viral wheeze as it is now known) had an accelerated rate of decline in spirometry at age 45-50 years, a known risk factor for chronic obstructive pulmonary disease.[130] 特に重要なことは、喘鳴を伴う気管支炎（ウイルス性喘鳴）の小児は45-50歳でスパイロの低下が加速され、COPDの危険因子として知られている。

AGER, a gene previously associated with chronic obstructive pulmonary disease, showed replicated association with the FEV1:FVC ratio in childhood. COPDと関連していることが知られている遺伝子AGERは小児においてもFEV1:FVC比がCOPDと同様であることが示されている。
Furthermore, some genes known to be associated with chronic obstructive pulmonary disease in general population studies interacted with environmental tobacco smoke, showing lower FEV1 in exposed children. さらに一般集団においてCOPDと関連する幾つかの遺伝子は受動喫煙と相合作用あることが解っており、タバコ煙に暴露されている小児ではFEV1が低下している。
Some genes showed an interaction only with in-utero tobacco smoke exposure, whereas others had an interaction with adult smoke exposure only. 幾つかの遺伝子は子宮内でタバコ煙暴露とだけ相合作用があるが、他の遺伝子では成人でのタバコ煙のみ相合作用がある。
Hence, these findings might indirectly provide evidence for the genetic contribution to lung developmental genes, early life lung function, and chronic obstructive pulmonary disease in later life. 従ってこれらの所見は肺の生育、若年期の肺機能、後年のCOPDに対して遺伝子の関与がある間接的な証拠を示している。
Finally, chronic obstructive pulmonary disease encompasses chronic bronchitis, airways obstruction, and emphysema. 最終的にCOPDは慢性気管支炎、気道閉塞、肺気腫へとなる。
Therefore, without formal testing, one cannot simply tell which genes are associated with which phenotype of chronic obstructive pulmonary disease. 正式なテストをしないでどの遺伝子がCOPDのフェノタイプと関連しているかを簡単に述べることはできない。
New studies are needed to formally test emphysema as assessed by CT scan, small airways disease and chronic obstructive pulmonary disease as defi ned by lung function, and to compare which genes are important in which component. これからの研究では肺気腫はルーチンにCTスキャンで、末梢気道疾患、COPDは肺機能によって定義されることが必要である。また遺伝子のどの部分が重要であるかを比較することも必要である。
However, a recent study showed that the estimated heritabilities of FEV1 and FEV1:FVC were both about 37%,[131] and heritabilities for chest CT scan phenotypes close to 25%. しかし最近の研究ではFEV1とFEV1:FVCの推定遺伝率は両方ともに37％であり、胸部CTスキャンフェノタイプでの遺伝率は25％近くである。
The investigators reported similar estimates of coheritability (genetic covariance) for pairs of the phenotypes.[131] 研究者は対のフェノタイプに対する共通遺伝性（遺伝子の共分散）の同様な推測をしている。
The latter finding suggests that substantial overlap of causal genetic loci exists. 後年の研究では原因遺伝子座の相当なオーバーラップ示唆している。

Conclusions 結論
Chronic obstructive pulmonary disease is a heterogeneous disease in its clinical expression, and so far epidemiological and genetic studies have mainly focused on the determinants of low lung function in the disease. COPDは臨床的なはヘテロ（一個体中に、対立遺伝子の両方を有する）な疾患であり、今までの疫学的、遺伝子的な研究は主にCOPDの肺機能の決定因子に焦点を当ててきた。
Only a few studies have investigated measurements of small airways function, chronic bronchitis, and emphysema with respect to their endogenous, genetic, and environmental risk factors. 数少ない研究のみが内因的、遺伝的、環境危険因子に関する末梢気道機能測定、慢性気管支炎、肺気腫について研究をしてきた。
Strong circumstantial evidence suggests that both genetic factors and environmental factors in utero and during early childhood are important for lung development and the outcome of

clinically apparent chronic obstructive pulmonary disease in adulthood. 子宮内と小児期ににおける遺伝因子と環境因子の両方が肺の生育と臨床的に明瞭な成人期COPDにとって重要であることを強く示唆している。

Whether and how these different risk factors lead to the different phenotypes of the disease remains to be elucidated in future studies. これら異なった危険因子がCOPDの異なったフェノタイプへとへ同様にして導くかについては今後のさらなる研究に待たなければならない。

However, efforts to prevent chronic obstructive pulmonary disease will clearly need to encompass more than just targeting of smoking (as important as this risk factor is) and should also focus on optimisation of lung health in the early years of life, before birth, and possibly even before conception. しかし COPDを予防するための努力は単に喫煙（同様に重要な危険因子）のみではなく、乳幼児期、生前、恐らく妊娠以前から肺の最適な健康に焦点を合わせるべきであろう。

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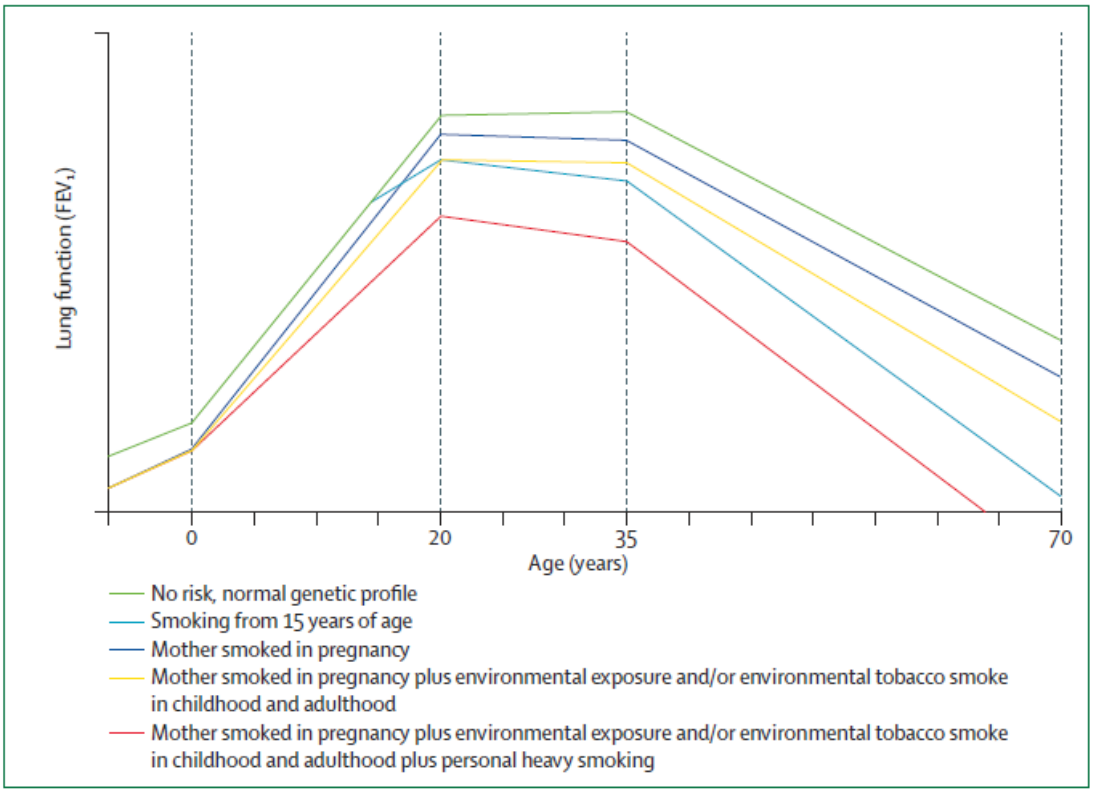

Figure 1: **Risk factors for chronic obstructive pulmonary disease during the different stages of life and how they can affect the risk for the development of clinically apparent disease**

FEV_1=forced expiratory volume in 1 s. Any or all of a reduced starting point at birth, a failure to reach the normal plateau, and accelerated loss of function in adulthood mean that the threshold for respiratory symptoms and disability is reached earlier than normal. The extent of the effects of smoking varies between individuals and has been reported differently; therefore, the figure is a scheme to show the effects of smoking during the different stages in life.

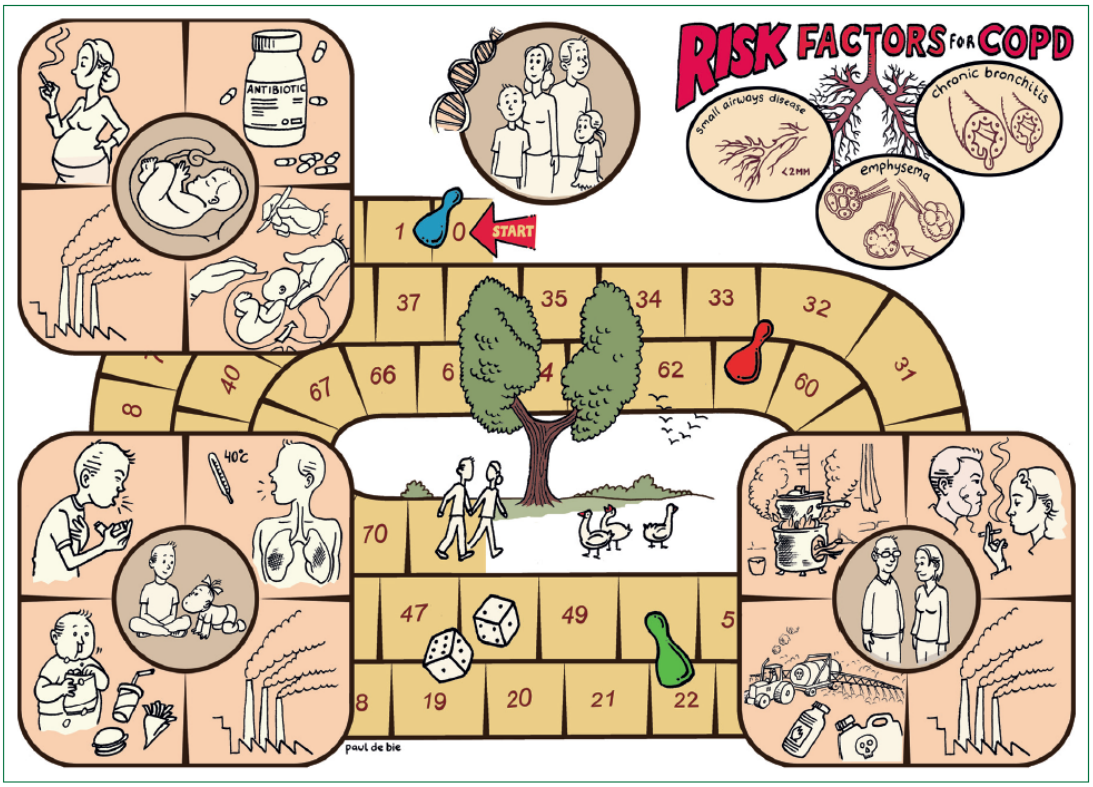

Figure 2: **Graphic representation of the risk factors for chronic obstructive pulmonary disease during the different stages of life**
Risk factors are shown for in utero and perinatal life (upper left corner), early childhood (lower left corner), and adulthood (lower right corner). General risk factors are also shown (upper right corner). COPD=chronic obstructive pulmonary disease.