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PATHOGENESIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: UNDERSTANDING THE CONTRIBUTIONS OF GENE–ENVIRONMENT INTERACTIONS ACROSS THE LIFESPAN

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SEARCH STRATEGY AND SELECTION CRITERIA

This is a narrative review mostly based on the knowledge and judgment of authors, supported by selected references from a PubMed search that used the terms ("gene-environment" or "early life") AND ("lung function", "FEV1", "FVC" or "COPD"); ("Lifelong") AND ("exposure") AND ("COPD"); ("Genetic") AND ("Environmental" or "environment") AND ("Exposure") AND ("COPD"). We found n=188, n=22 and n=153 studies respectively reporting gene-environment interactions occurring in early life with different lung function indices both in childhood and early adulthood and evidence of lung function trajectory associated risk factors. All PubMed searches were last performed on 27/10/21 with no date limit.

KEY MESSAGES

- COPD has been traditionally understood as a self-inflicted disease caused by tobacco smoking in genetically susceptible individuals; yet, recent research demonstrates that COPD can have roots early in life (pregnancy, infancy and adolescence), and that abnormal lung development (low peak lung function) and/or lung ageing (accelerated decline) can influence the lung function trajectory followed by the individual through life and cause COPD.
- A holistic understanding of COPD pathogenesis requires the integration of a time axis (T) that considers all gene (G) – environment (E) interactions that the individual may encounter through the life span; here we use the term GETomics to refer to this integrated view (GxExT).
- Specifically, this GETomic perspective seeks to integrate basic omics (e.g., genomics, epigenomics, proteomics, lipidomics) with clinical "omics" (e.g., phenomics, physiomics, radiomics) and exposures (e.g. exposome) over time since, both the age of the individual at which a given GxE interaction occurs, as well as the previous, cumulative GxE interactions that the individual may have encountered through life, can influence the final clinical outcome.
- COPD cannot be longer considered a single disease caused only by tobacco smoking, but a clinical syndrome characterized by a recognisable pattern of chronic symptoms (dyspnoea, cough and/or expectoration), structural (bronchitis, bronchiolitis and/or emphysema) and/or functional abnormalities (airflow limitation and/or abnormal gas exchange) due to one or several mechanisms (endotypes) that we propose are the result of different and cumulative GxExT interactions through the lifetime of the individual.

- The proposed GETomic perspective has the potential to identify novel preventive and therapeutic targets earlier in life.

VOCABULARY PANEL (alphabetical order):

- **Biomarker:** Objectively measured indicator of a normal or pathologic biological process (endotype) or response to a therapeutic intervention.
- **Chronic Obstructive Pulmonary Disease (COPD)**: Clinical syndrome characterized by a recognisable pattern of chronic symptoms (dyspnoea, cough and/or expectoration), structural (bronchitis, bronchiolitis and/or emphysema) and/or functional abnormalities (airflow limitation and/or abnormal gas exchange) due to one or several mechanisms (endotypes) that we propose are the result of different and cumulative gene-environment interactions through the lifetime of the individual.
- **Dysanapsis**: Mismatch of airway tree calibre to lung size
- **Endotype**: Biological mechanism underlying a given phenotype
- **Epigenomics:** Study of the chemical changes of the DNA that do not alter its sequence but modify gene expression.
- **Genetics**: Study of the genes (DNA) of individuals. Although several gene variants have been associated with the risk of COPD, the largest contribution arises from the combined effect of many common variants with a small effect size.
- **GETomics**: Proposed holistic strategy that considers all gene (G) – environment (E) interactions that an individual may encounter through the life span (T) to better understand the pathogenesis of COPD. Specifically, it aims to integrate basic omics (e.g., genomics, epigenomics, proteomics, lipidomics) with clinical omics (e.g., phenomics, physiomics, radiomics) and exposures (e.g., exposome) over time since, both the age of the individual at which a given GxE interaction occurs, as well as the previous,

cumulative GxE interactions that the individual may have encountered through life, can influence the final clinical outcome.

- **GxE:** Gene-Environment interaction
- **GxExT:** Gene-Environment-Time interaction
- **Host:** "individual" or "person"
- **Phenotype**: Single or combination of disease attributes that describe differences between patients with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death).
- **Trajectome**: Range of lung function trajectories through the lifetime
- **Treatable trait**: Characteristics of a patient that can be identified by their clinical presentation (phenotype) and/or through validated biomarkers of specific endotypes, that deserve precise treatment.

OPEN QUESTIONS PANEL

- Are the genetic, clinical, epidemiological and biological factors associated to airflow limitation similar across the lifespan?
- What are the differences in the response to the same environmental insult at different ages, and can omics analyses give insights into detrimental responses following exposure?
- Are these differences determined by the regenerative capacity, the aging affectation of different pathways, or by the history of previous exposures?
- Which are the earlier life exposures that determine a lower threshold to develop lung disease later in life?
- Which are the thresholds that determine health and diseases at each age bin, and how are these thresholds affected by insults at different ages?
- How can these thresholds be non-invasively and clinically meaningfully measured?

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) has been traditionally considered a self-inflicted disease caused by tobacco smoking in so-called "susceptible" smokers. Recent research observations question this simple pathogenic model. We propose here that, instead, COPD should be understood as the potential end-result of the accumulation of gene (G)–environment (E) interactions an individual encounter through the life span (T). We use the term GETomics to indicate that this proposal specifically sought to integrate basic omics (i.e. genomics, epigenomics, proteomics, lipidomics) with clinical omics (i.e. phenomics, physiomics, radiomics) and exposures (exposome) over time. Accordingly, we propose that COPD should no longer be considered a single disease, but a clinical syndrome characterized by a recognisable pattern of chronic symptoms (dyspnoea, cough and/or expectoration), structural (bronchiolitis and/or emphysema) and/or functional abnormalities (airflow limitation and/or abnormal gas exchange) due to different and cumulative GxExT interactions through the lifetime that influence normal lung development and/or ageing.

Abstract word count: 150 words (max. 150 words)

LIMITATIONS OF THE TRADITIONAL PATHOGENIC UNDERSTANDING OF COPD

Chronic Obstructive Pulmonary Disease (COPD) has been traditionally considered a paradigmatic example of a disease caused by gene (G) – environment (E) interactions (GxE) because it was thought to occur almost exclusively (with the exception of patients with α1 anti-trypsin deficiency)[1] in so-called "susceptible smokers"[2]. However, several recent observations question this model[3]. First, the central dogma of the GxE hypothesis is that a combination of gene(s) and environmental factor(s) determine disease risk[4]. However, few convincing examples of clear GxE interactions that replicate across studies have been identified[5,6], and the genetic effects of identified loci are quite in smokers and never smokers[7,8]. In fact, a very recent and large genome-wide association analysis of 179,689 controls and 21,077 COPD cases of European ancestry from the UK Biobank confirmed the presence of smoking interaction effects at previously reported COPD loci but failed to identify novel susceptibility loci[5]. Two potential, non-mutually exclusive explanations can be considered here. On the one hand, molecular associations can be detected at other "omic" layers such as epigenomics, transcriptomics or proteomics[6]; in fact, as discussed below, the effect of smoking is well captured by epigenetic modifications[9-11]. On the other, the toxic effects caused by the thousands of different compounds and metabolites in cigarette smoke are too complex to be captured by a reductionist approach (i.e. single gene or variant)[12,13], so multi-level integrative approaches are needed[6,14,15]. In fact, polygenic risk scores (PRS) that consider information from all established risk variants from well-powered genome-wide association studies (GWAS) may help identifying subjects with a high genetic risk that are more susceptible to developing COPD when exposed environmental factors[16]. Second, a substantial proportion of patients with COPD are never smokers[17,18]. Of note,

171 in European populations notable sex differences exist among never smokers with COPD (27.2 %
172 females and 7.3 % in males)[19]. Further, recent epidemiological studies have shown that many
173 different environmental exposures and host conditions other than smoking are significantly
174 associated with airflow limitation (the traditional functional defining characteristic of COPD)
175 through the life span (Figure 1)[20]. Finally, several studies have now shown that there is a range
176 of lung function trajectories through life (i.e., a "*trajectome*") (Figure 2), some of which can lead
177 to COPD in late adulthood through two different but non-mutually exclusive mechanisms,
178 abnormal lung development and/or accelerated lung function decline[3,21-23].

179

180 **TOWARDS A NEW UNDERSTANDING OF COPD THAT CONSIDERS THE TIME**
181 **AXIS**

182 We propose here that, to overcome the limitations of the traditional pathogenic model of COPD
183 discussed above, it is necessary to consider (Figure 3): *(1)* the series of dynamic and cumulative
184 GxE interactions beyond tobacco smoking that includes many other environmental (e.g.,
185 infections and air pollutants) and host risk factors (e.g., prematurity, immune
186 fitness/senesence[24,25]); and (2) a time (T) dimension that takes into account *(a)* the age of the
187 individual at which a given GxE interaction occurs, since the biologic response(s) and clinical
188 consequence(s) that may result at different ages are likely to be influenced by a unique set of
189 genes and/or epigenetic mechanisms that modulate the capacity of the system to respond
190 (immune response) and repair[26,27], and *(b)* the cumulative history of previous GxExT encounters
191 (before birth or even before conception[28]) that may render the lungs more fragile and less
192 resilient to confront new GxE hits[29]. We propose the term GETomics to refer to this integrative
193 GxExT understanding of the pathogenesis of COPD, an approach that has also been recently

194 proposed for other medical conditions too[30,31]. Specifically, this term refers to the integration of
195 basic omics (e.g., genomics, epigenomics, proteomics, lipidomics) with clinical omics (e.g.,
196 phenomics, physiomics, radiomics) and exposures (e.g. exposome) over time because, both the
197 age of the individual at which a given GxE interaction occurs, as well as the previous,
198 cumulative GxE interactions that the individual may have encountered through life, this is, the
199 time axis, can influence the final clinical outcome[32]. Below, we review the evidence that
200 supports this proposal in relation to COPD by analysing its three main components, namely
201 environment-host, genetics-epigenetics and time. As discussed below, we think that the
202 integration of the time axis through the life time into our understanding of the pathogenesis of
203 COPD can open novel windows of opportunity for its prevention and early treatment (and
204 perhaps too for the multimorbid conditions that frequently accompany COPD because they share
205 similar risk factors and biologic mechanisms[33]).

206

207 **ENVIRONMENT AND HOST**

208 Tobacco smoking remains a key, preventable environmental COPD risk factor[2] whose impact in
209 lung function can start even before conception, with exposures of future parents during
210 adolescence[28,34]. Its effects during pregnancy are well described, with an estimated lower
211 birthweight of about 19 g for each cigarette smoked by the pregnant mother per day[31]. In fact,
212 stopping smoking during pregancy at any time up to 30 weeks results in increased birthweight,
213 albeit the greatest effects are seen when mother quits before 16 weeks of pregnancy[35]. Needless
214 to say, the effects on lung function of passive smoking, both during childhood and in adulthood,
215 as well as those resulting from active smoking are well established[2]. Yet, smoke exposure is not
216 the only risk factor for low lung function through life. A recent cross-sectional study in 11,423

participants in the LEAD cohort, a general population study in Austria that enrolled subjects spanning an age range from 6-82 years[36], showed that conditions associated with reduced lung function are different in different ages, increase with time and, importantly, interact among them, so the network of interactions becomes much more complex with advancing age (Figure 1). In the younger age bins, an "asthma" signature (including the presence of a doctor`s diagnosis of asthma, wheezing, and elevated eosinophils) emerges as a risk factor for low lung function, in combination with other early life conditions, such as prematurity, no breast feeding, hospitalizations in infancy due to respiratory problems, systemic inflammation, poor nutrition, low fruit and vegetable intake, alcohol consumption in early life, low physical activity, and heavy smoking exposure at an age where lungs are still growing (Figure 1)[20]. In adulthood, the correlation network include respiratory symptoms, allergy, exposure to environmental pollutants other than smoking, low socio-economic status, and multimorbidity. That the complexity (density) of the network increases with age suggests that any preventive or therapeutic intervention may likely be more effective in younger individuals[33]. The relative individual impact of each of this factors is difficult to quantify, but their co-occurrence in the same individual increases significantly the risk of reduced lung function at any age (Figure 4)[20]. Importantly, reduced lung function may not always translate into clinical COPD[3,20].

Prematurity deserves specific discussion among host risk factors for COPD. Premature birth (birth <37 weeks of gestation) interrupts the normal development of the lungs, especially if it occurs before 32 weeks of gestation, and results in smaller airways, fewer alveoli, and an impaired vascular system[37,38]. As a result, children born prematurely do not often reach maximal lung function in early adulthood and typically follow a low lung function trajectory that can

potentially lead to a COPD-like phenotype later in life (Figure 2)[39,40]. The term "dysanapsis", originally described by Mead in 1980[41], refers to the mismatch of airway tree caliber to lung size. Once believed to be a physiological curiosity[42], it is now considered clinically relevant in several conditions, including prematurity[43], obesity and asthma in children[44], and smoking in older adults[45]. Actually, a recent report used CT to assess dysanapsis in adults and showed that it was indeed associated with more severe airflow limitation[46] (Figure 5) and a differential spirometric response to a standardized dose of inhaled bronchodilator[47]. Further, microCT studies have shown that the number of patent terminal and transitional bronchioles is significantly reduced in adult COPD patients[48,49]. Yet, whether this is due to smoking-induced injury[50] and/or abnormal lung development in early life (dysanapsis[46]) is unclear, but both mechanisms can coexist[3]. In any case, given that the incidence of prematurity has increased, and mortality of babies born prematurely has decreased very significantly over the last decades[51], a marked increase in adult survivors of premature birth with potential lung development limitations is expected in the very near future.

Another potential host factor to consider here is obesity. A very recent Mendelian randomization analysis of the SAPALDIA cohort, a general population study in Switzerland that included 9,651 participants aged 18-60 years at baseline (female 51%) in whom lung function and body mass index (BMI) were measured three times over 20 follow-up years, showed that gene scores associated with childhood BMI relate to lung function later in life, highlighting the importance of a life course perspective in studies on the etiological role of BMI (or other environmental/host factors) in respiratory health[52].

Finally, it is important to highlight that many previous studies have shown that "asthma" can track (in some individuals) into adulthood, so it is often considered that "asthma" is an important host risk factor for "COPD" later in life[53]. For instance, early life predictors of COPD in adulthood in the Tasmanian Longitudinal Health Study (TAHS) included childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma, and maternal smoking. However, what is often missed is that "asthma" is a clinical diagnosis based upon a pattern of respiratory symptoms such as wheezing, dyspnoea, chest tightness or cough, and variable expiratory airflow limitation[54]. This same pattern of symptoms can occur in children who, for whatever reason, do not develop their lungs properly and who, most likely will be "diagnosed" with (and treated for) "asthma". So, a careful interpretation of available evidence indicates that what really tracks with poor lung function in adulthood (and perhaps with clinical COPD) is "a diagnosis" of asthma in childhood, which may correspond to the disease we call now "asthma" or, alternatively, to a deficient lung development that may resemble "asthma" clinically and lead to COPD later in life[55]. Of note, a very recent report from the European Community Respiratory Health Survey indicated that the "asthma-COPD overlap" in adults aged 40-68 seems to have its origins earlier in life than in those with "COPD" alone[56].

GENETICS AND EPIGENETICS

The genetic basis of COPD is reviewed in a companion paper in this Series[6] and will not be discussed in detail here. Suffice to say that there are now many gene variants associated with the risk of COPD, lung function, and other pulmonary and non-pulmonary traits of the disease (thus, contributing to explain the clinical heterogeneity of the disease), albeit the largest contribution to the phenotype arises from the combined effect of many common variants of small effect size and

not from rare variants with large effect sizes[6]. Of particular relevance for the current discussion, large-scale genome-wide association studies (GWAS) have found a clear and consistent overlap between lung function related genes in children and adults[57-59], and some of the genes associated to COPD relate to lung development[6]. Recently, the use of polygenic risk scores (PRS) support findings that the genetics between adult and childhood lung function traits indeed overlap[60].

On the other hand, environmental exposures may interact with the genome via epigenetic modifications, which primarily refer to chemical changes of the DNA that do not alter its sequence[26,61,62]. DNA methylation, the addition of a methyl group to cytosines next to guanines (a CpG site), is the most widely studied epigenetic modification in humans, but other epigenetic mechanisms such as histone modifications (acetylation or methylation) and miRNA also modify gene expression. Epigenetic changes may be inherited across cell generations, and recent data indicate that changes may be transmitted across human generations (i.e. transgenerational changes)[63]. Of note, even in the absence of disease, age-associated epigenetic changes also occur so chronological age is one of the strongest determinants of DNA methylation levels[64].

Central to the concept of epigenetics is that gene expression activity is affected. If exposure and associated epigenetic changes occur early in life, perhaps starting already *in utero* (e.g., maternal smoking), life-long cellular trajectories may be affected, which may then be followed by tissue and organ effects that may translate into physiologic and pathophysiologic consequences. For instance, maternal smoking during pregnancy is associated with widespread changes in offspring DNA methylation across the genome at birth, and importantly, these changes appear to persist at

least up to adolescence[65]. Further, differential methylation of genes related to maternal smoking are relevant to diseases such as childhood "asthma", but differential methylation as a causal mechanism between maternal smoking and "asthma" is not proven[13]. Likewise, epigenetic marks identified in *foetal* lung tissue may portend risk for COPD in later life[66]. Finally, the epigenetic effects of smoking relate to both the intensity and duration of the exposure and can have long lasting effects from years to decades, further emphasizing the relevance of the time axis in this GxE interaction[11].

Similar to maternal smoking during pregnancy, gestational age is associated with DNA methylation levels in thousands of genes in newborns, and a substantial proportion of changes persist across childhood[67]. The same magnitude of effect on methylation profiles is observed for birth weight[68]. During the *foetal* period, epigenetic processes are important for controlling development and growth. The examples of maternal smoking during pregnancy and gestational age at birth associated with persistent epigenetic changes in newborns provide compelling evidence of early long-term effects of certain environmental exposures, and highlight crucial roles for early-life events and related mechanisms for later health and disease.

Extending the consideration that trajectories of the epigenome can be set *in utero*, network-based approaches have been applied to capture the complexity of GxE interactions at a genome-wide scale. For example, a co-methylation analysis revealed network features highly preserved for foetal *in-utero* smoke exposure, COPD and lower adult lung function, with enrichment in developmental and inflammatory pathways, including Hippo, Wnt, TGFB and PI3K/AKT

pathways [66]. Likewise, a recent study has shown that lung methylation profiles relate to smoking more in mild-moderate COPD than in patients with severe disease[69]. In this study, however, severe patients were significantly younger, suggesting that different epigenetic patterns are associated with different lung function trajectories some of which can lead to severe COPD at younger ages[69].

Finally, studies of DNA methylation in lung tissue have shown differences in males and females[70]. In fact, a recent study demonstrated that sex-specific methylation patterns are associated with trajectories of lung function measured at ages 10, 18 and 26, and that enriched pathways were associated with poorer lung function trajectories[71]. Sex-specific age-associations of COPD symptoms observed later in life may start with the setting of an individual tracking along the early life methylation-lung function axes. Indeed, sex-specific associations with COPD have been observed for different "omic" levels, including genetic, epigenetic, transcriptomic, metabolomic and proteomic network layers[72], and what has emerged is that sex and gender are important endogenous (hormones, sex chromosome) and exogenous (smoking behaviours, occupation roles) determinants of the final outcome of similar GxExT interactions across the life-course, with varying and complex impact on health and disease.

THE TIME AXIS

Normal lung development starts *in utero* during the embryonic phase (gestational weeks 4-7) with lung bud differentiation and trachea and bronchi formation[73]. It continues throughout the *foetal* period and postnatally with lung growth and cellular proliferation until maximally attained

lung function peaks at around 20-25 years of age, earlier in females[74,75]. This is followed by a relatively short *plateau* phase of about a decade, and mild lung function decline thereafter (~20 ml/year, more in male[74]) due to physiological lung ageing[22] (Figure 2).

Any insult to the airways or lung parenchyma during the very long (>20 years) lung developmental period may have long-term consequences for health and disease[27]. This is now recognized as the developmental origins of health and disease (DOHaD)[76,77]. Indeed, as discussed above, several asthma, COPD and lung function genes identified in adult studies point towards relevant functions for *foetal* developmental processes[6,78]. On the other hand, adult lung diseases may be the consequence of an acceleration of physiological age-associated changes[50]. Interestingly, aging related DNA methylation pathways have been linked to lung development pathways too[79], so chronological age, starting in early life, may capture linear and non-linear cumulative environmental pressure on the epigenome that may increase the risk of COPD later in life. Given that lung aging seems to recapitulate key developmental epigenetic signatures in transcription factors, and that differential methylation of transcription factors has been associated with COPD[80], looking closely at the molecular endotypes that emerge from GxExT investigations may reveal novel opportunities for the early prevention of COPD through targeting gene regulation among other potential molecular strategies.

As a result of all of the above, there is a range of lung function trajectories through life[3,22] (i.e., a *trajectome*), both above and below the normal one (Figure 2). Lung function trajectories below the expected normal range can be due to suboptimal growth and development in

childhood/adolescence leading to reduced peak lung function, shortened *plateau* and/or accelerated lung function decline due to accelerated lung ageing and/or other factors damaging the lungs[81], and are known to be associated with increased risk of developing COPD in adulthood[21,82,83]. Recent observations in the population-based CARDIA study showed that both lower peak and accelerated decline in FEV1 are risk factors for future emphysema identified on computed tomographic scans, independently of smoking status[84]. Besides, low peak lung function in early adulthood is associated with increased prevalence and earlier incidence of cardiovascular and metabolic conditions, as well as with premature death (Figure 6)[85], suggesting that abnormal lung development may be associated with altered development of other organ systems. If this is the case, reduced lung function in infancy, adolescence or early adulthood may well be a marker of a more systemic deficit[3,22]. On the other hand, recent research has shown that supranormal trajectories (Figure 2) are associated with healthier ageing [86] and reduced risk of developing COPD [87]. Therefore, understanding the GxExT interactions that underlie these different lung function trajectories is of paramount importance to prevent and treat the disease associated conditions as early and efficiently as possible, as well as to promote healthier ageing[33].

Finally, like any other organ, the immune system also develops, matures and ages[88]. As a result, there are marked differences in immune function and immune phenotypes between children and adults[88], so the immune responses elicited by GxE interactions may differ depending on age of occurrence, this is, T[25,89]. Studies on the chromosome 17q12-21 asthma locus have taught us important lessons on GxExT effects since associations with SNPs at this major locus have been repeatedly associated with childhood asthma[90]. In fact, recent data suggest that this locus

primarily reflect early life susceptibility to respiratory viruses[91], which may have long-term lung health consequences[92]. Interestingly, functional interactions between one of the key 17q12-21 genes, *GSDMB,* and COPD-associated genes, such as *IL-27* and *HHIP,* have now been identified, which links this asthma locus to COPD[93]. On the other hand, in experimental models, neutrophilic inflammation during development disrupts the cellular matrix and predisposes to COPD[94], whereas aged T cells in young mice (with mitochondrial dysfunction) induce premature aging and multimorbidity[95]. Further, as shown in Figure 7, infection with γ-herpesvirus in aged mice cause a much more intense inflammatory response than that elicited in young animals, illustrating that the same environmental insult can have very different consequences depending on the age at which it occurs[32]. Finally, cell senescence, a hallmark of cellular aging[96], also plays a key role in organ development and disease, when senescence cells accumulate and secrete a specific set of immune mediators collectively known as Senescence-Associated Secretory Phenotype (SASP)[97]. Thus, an excessively aged immune system for a given chronological age may also increase the risk of COPD.

CLINICAL IMPLICATIONS OF INTEGRATING A TIME AXIS IN THE PATHOBIOLOGY OF COPD

Integrating the time axis in the pathobiology of COPD has implications for disease understanding, prevention and management. In terms of *disease understanding*, we propose that COPD should not be longer considered a single "disease" caused only by tobacco smoking but a complex clinical *syndrome*[98]. A syndrome is a recognisable pattern of symptoms and clinical signs that can be caused by different mechanisms (e.g., febrile syndrome) [99,100]. According to this definition, we propose that COPD should be considered a syndrome because it is characterized

by a recognisable pattern of chronic symptoms (dyspnoea, cough and/or expectoration), structural (bronchitis, bronchiolitis and/or emphysema) and/or functional abnormalities (airflow limitation and/or abnormal gas exchange) due to one or more mechanisms (endotypes[101]) that are the end result of different and cumulative GxExT interactions through the lifetime of the individual. Currently, the presence of non-fully reversible airflow limitation is a mandatory requirement for the diagnosis of COPD[102], but there is increasing recognition that a pre-COPD stage, with symptoms, structural abnormalities and functional abnormalities other than airflow limitation do indeed exist[103], albeit its natural history and response to treatment is still unclear[104].

In relation to *prevention* of COPD, there is no question that avoiding smoke/inhaled exposures at all times (*in utero*, infancy-adolescence) and favouring early quitting of personal smoking[74] are key preventive measures that must continue to be fully endorsed. However, a GxExT approach to COPD opens opportunities for its prevention that go well beyond smoking[27]. For instance, in a chronically undernourished population in Nepal, maternal supplementation of diet with vitamin A before, during, and after pregnancy improved lung function in offspring in preadolescent years[105]. Likewise, supplemental vitamin C taken by pregnant American smokers improved new-born lung function and decreased wheezing through 1 year in the offspring[106]. Whether other preventive strategies can contribute to improve lung health in other populations require research[107]. In fact, the transition from infancy to adulthood is often a “black box” which may be, however, full of opportunities for prevention and early intervention[108]. For instance, recent studies have shown that the presence of chronic bronchitis in children[109] and young adults[110] predicts the development of airflow limitation later in life. In this setting, spirometry should be viewed as a global health-marker that, if used routinely for screening in young populations

(during school, university, army, driving licence testing, other) may help to identify individuals at risk of respiratory and non-respiratory multimorbidity and premature death (Figure 6) in whom to intervene[33,85,111].

Finally, in relation to the *management* of COPD, a GxExT understanding of COPD requires to translate the lifelong lung function concept (trajectome) to clinical practice. Unfortunately, lung function is not currently measured routinely in infancy, adolescence or early adulthood, so identifying in the clinic what lung function trajectory a given patient has followed so far (or will follow in the future) is difficult. It clearly requires that the attending physician specifically interrogates the patient on potentially relevant early-life factors and the validation of biomarkers associated to different lung function trajectories such as the following: *(1)* serum levels of the pneumo-protein Clara Cell secretory protein (CC16) appear consistently associated with low lung function at different age bins[112], have been associated with accelerated lung function decline[113,114] and are influenced by smoking[115-117]. Interestingly, CC16 levels are related too with "asthma" persistence as well as with persistence of reduced lung function both in childhood and adulthood. Finally, several genetic variants have been related with serum CC16 levels[118]; *(2)* YKL-40 is a secreted human glycoprotein involved in airway remodelling that has been associated with early-life inflammation in children with a history of prematurity, and is now considered a biomarker of altered lung development[119]; *(3)* miR-145-5p plasma levels in children with "asthma" appear associated with abnormal lung growth leading to COPD[120]; *(4)* there is an association between eosinophil levels and the development of persistent airflow limitation in children with a diagnosis of "asthma"[121]. More recent research confirmed that higher circulating eosinophil levels were associated with increased risk of developing COPD[122] and that FEV_1

decline was faster in patients with mild to moderate COPD and higher blood eosinophil counts[123]; and, finally, *(5)* some 'aging' biomarkers, like telomere shortening, have also been associated with structural remodelling of the lung in children with bronchopulmonary dysplasia, and in young patients with COPD [124], supporting still another potential link between altered lung development and aging[119]. In any case, current and future therapeutic interventions need to be tested in younger individuals[104], when they may be more effective for primary prevention due to the reduced complexity of the network of interacting risk factors (Figure 1)[125]. For instance, treatment with tiotropium in the UPLIFT study reduced the decline of lung function in young (≤50 years)[126] but not in older COPD patients[127]**.**

CONCLUSIONS AND FUTURE DIRECTIONS

Life is a *tabula rasa* that begins to be written (and filled up) from conception (and even before[34,128]). As discussed above, integrating the time axis through the life span in our understanding of COPD has the potential to prevent and manage more efficiently patients with COPD and, perhaps too, other chronic non-communicable diseases of the elderly which often share genetic and environmental risk factors among them and with COPD[108]. Further, considering a GxExT approach to COPD in research can provide relevant information not only on lung function determinants but also on the time-point of COPD diagnosis/development, severity of disease and heterogeneity of clinical presentation including exacerbation, chronic bronchitis *vs.* emphysema, systemic manifestations, and response to therapy. To achieve this potential, however, we need to improve our understanding of the paradigm proposed here. The ideal study would involve a birth-cohort followed prospectively until death with repeated and detailed pheno-endotypic characterization (including biomarkers), ample biological profiling

assessement and comprehensive monitoring of the exposome (perhaps through the blood exposome that includes all biologically active chemicals[129]), as well as tissue probes if at all possible. As this ideal study is not currently a realistic option, a potential alternative is to use different available cohorts that span different age bins to understand the biologic determinant and clinical impact of the trajectome and its GxExT determinants. This is precisely the goal of a Clinical Research Collaboration currently ongoing under the auspices of the European Respiratory Society (www.cadset.org)[130]. In this setting, investigations of the GxExT basis of the trajectome will have to consider not only the the specific nature of a given GxE interaction but also: *(1)* in which phase of the lung function trajectory (T) does this specific GxE interaction occurs (developmental vs. ageing); *(2)* what specific lung function trajectory was the individual already following when that GxE interaction took place; *(3)* how long, intense and/or repetitive the exposure is; and, *(4)* what is the the previous, cumulative, exposome history of the individual (Figure 3). Likewise, comprehensive analytical non-reductionistic and agnostic approaches (network analysis, systems biology) that integrate different omic levels, environmental and clinical data will be required to provide a more integrated view of the GxExT interactions by illustrating not only their relationship with the outcome of interest but also among the components of the network[131-134]. Of note, this research strategy has already been applied to COPD[135].

Finally, we also need to deploy this GxExT perspective to daily clinical practice. This requires a significant educational effort directed to health care professionals. For instance, asking for early life events and exposures should become routine in clinics attending adult patients with chronic

511 airway diseases. It is about time to implement a “Looking back to look forward” concept in
512 COPD in particular, and probably more importantly, in respiratory and human health in general.

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DECLARATION OF INTERESTS

AA declares having received research funds and honoraria as speaker and consultant from AZ, GSK, Chiesi and Menarini for COPD related initiatives, outside the submitted paper.

EM has received advisory board reimbursements and speakers' fees from AstraZeneca, Chiesi, Novartis and Sanofi outside the submitted work.

DLD has received research funds from NIH and the Alpha-1 Foundation and funds from Bayer and Novartis.

RBK declares having received honoraria as a speaker from AZ, GSK, Menarini and Novartis Pharma.

RF declares having received research funds from ISC-III, AZ, GSK, Menarini, honoraria as speaker from Chiesi, and consultancy fees from GSK, for COPD related initiatives outside the submitted work.

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878 **FIGURE LEGENDS**

879 **Figure 1.** First-neighbour networks of FEV1<lower limit of normal (centre yellow node) in
880 different age bins. Each node represents one variable, node size is proportional to the prevalence
881 of that variable in that specific age bin, and node colour indicates variable category. Links
882 between nodes indicate the existence of a significant ($p<0.05$) relationship between them, thicker
883 edges indicate lower P values, and the line type indicates whether the odds ratio is >1
884 (continuous) or <1 (dashed). Reproduced with permission from reference[20]. For further
885 explanations, see text.

886

887 **Figure 2**. Lung function trajectories through the lifespan (trajectome). The y-axis (% predicted
888 peak) represents lung function expressed as a proportion of the peak value expected in a healthy
889 subject who develop the lungs properly (100%). Reproduced with permission from reference[22].
890 For further explanations, see text.

891

892 **Figure 3.** From conception to death (bottom arrow), any individual encounters many
893 environmental (E) factors (exposome[132,136-138]) represented here as a pink cloud (importantly the
894 position of different exposures included in the cloud are not necessarily related to the time axis at
895 the bottom of the figure (arrow) and may occur several times during the life span). At different
896 time points (ages), these E factors interact with the genomic (G) background of the individual
897 through epigenetic mechanisms (and others) and induce a biologic response (endotype [101]), such
898 as innate-acquired immune responses, that modulate organ structure (development/maintenance-
899 repair/ageing) and function, and eventually determines health or disease (in this schema

900 represented by different developing and/or ageing lung function trajectories). The biological and
901 clinical effects of different GxE interactions depend not only on their specific characteristics but
902 also on the T at which this occurs (age) and previous cumulative history of other GxExT
903 interactions (GETomics). For further explanations, see text.

904

905 **Figure 4.** Prevalence of low lung function (FEV1<LLN) in different age bins by the number of
906 associated factors coexisting in the same individual. Reproduced with permission from
907 reference[20]. For further explanations, see text.

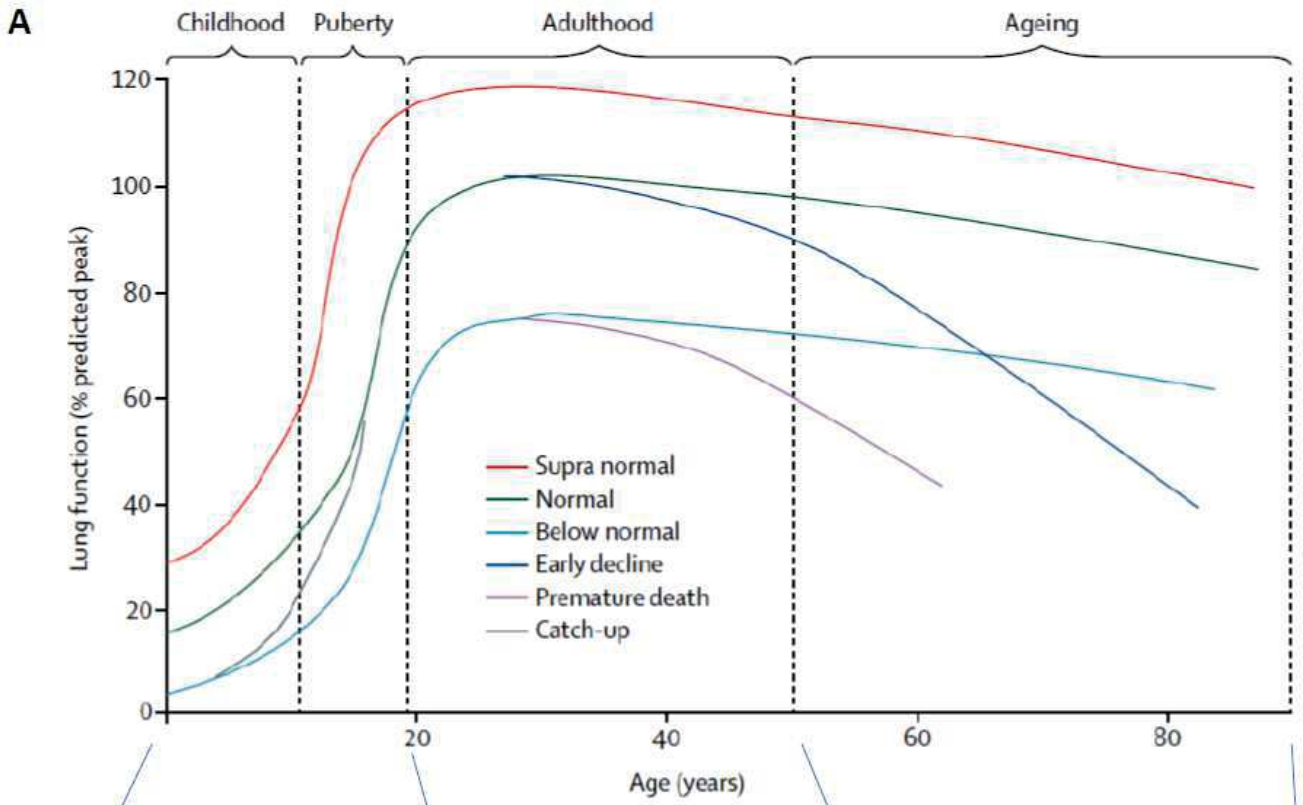
908

909 **Figure 5.** Representative coronal CT images with segmented central airway trees (coloured
910 pink), and corresponding airway to lung ratio measures of dysanapsis (expressed as % of
911 predicted airway tree size) and the forced expired volume in the first second to forced vital
912 capacity (FEV1/FVC) ratio. Reproduced with permission from reference[46]. For further
913 explanations, see text

914

915 **Figure 6**. From left to right, prevalence of participants in the Framingham Offspring Cohort with
916 at least one respiratory, cardiovascular, or metabolic abnormality by lung function level in early
917 adulthood (FEV1 below or above 80% of reference), cumulative incidence of respiratory,
918 cardiovascular, and metabolic abnormalities during follow-up (dotted lines indicate the age at
919 which half of the population reports the first comorbidity) and Kaplan-Meier survival curves and
920 Cox model Hazard Ratios (HR). Reproduced with permission from reference[85]. For further
921 explanations, see text.

Figure 7. Haematoxylin and eosin staining showing increased disruption of lung architecture, inflammation, and fibrosis in aged mice infected with γ HV-68 compared with infected young mice and aged and young saline controls. Reproduced with permission from reference[32]. For further explanations, see text.



B

Childhood and puberty	Adulthood	Ageing
• Spirometry check-up • Avoid smoking exposure • Avoiding infections (i.e. RSV vaccination) • Understanding and treating catchup (i.e. vitamin supplementation)	• Spirometry check-up • Avoid active smoking • Reduce detrimental exposures • Regular exercise • Adequate nutrition	• Spirometry check-up • Avoid active smoking • Reduce detrimental exposures • Regular exercise • Adequate nutrition

Which are the earlier life triggers that determine to develop lung and multimorbid diseases later in life?

What are the differences in the response to the same environmental insult at different ages?

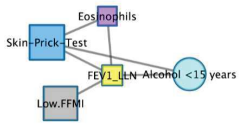
Are these differences determined by the regenerative capacity, the aging affectation of different pathways, or by the history of previous expositions?

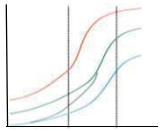
Phenomics, physiomics, radiomics, Diseasome

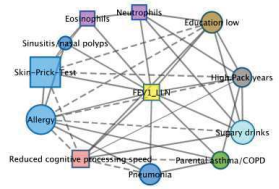
Health and disease
Phenotypes and treatable traits

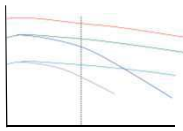
Health and disease
Phenotypes and treatable traits

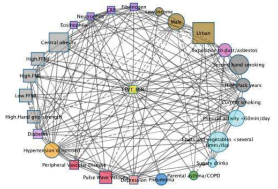
Health and disease
Phenotypes and treatable traits











Genomics, epigenomics, proteomics, metabolomics

Endotypes and biomarkers
Epigenetics
Immune response
Development and repair

Endotypes and biomarkers
Epigenetics
Immune response
Repair and ageing

Endotypes and biomarkers
Epigenetics
Immune response
Repair and ageing

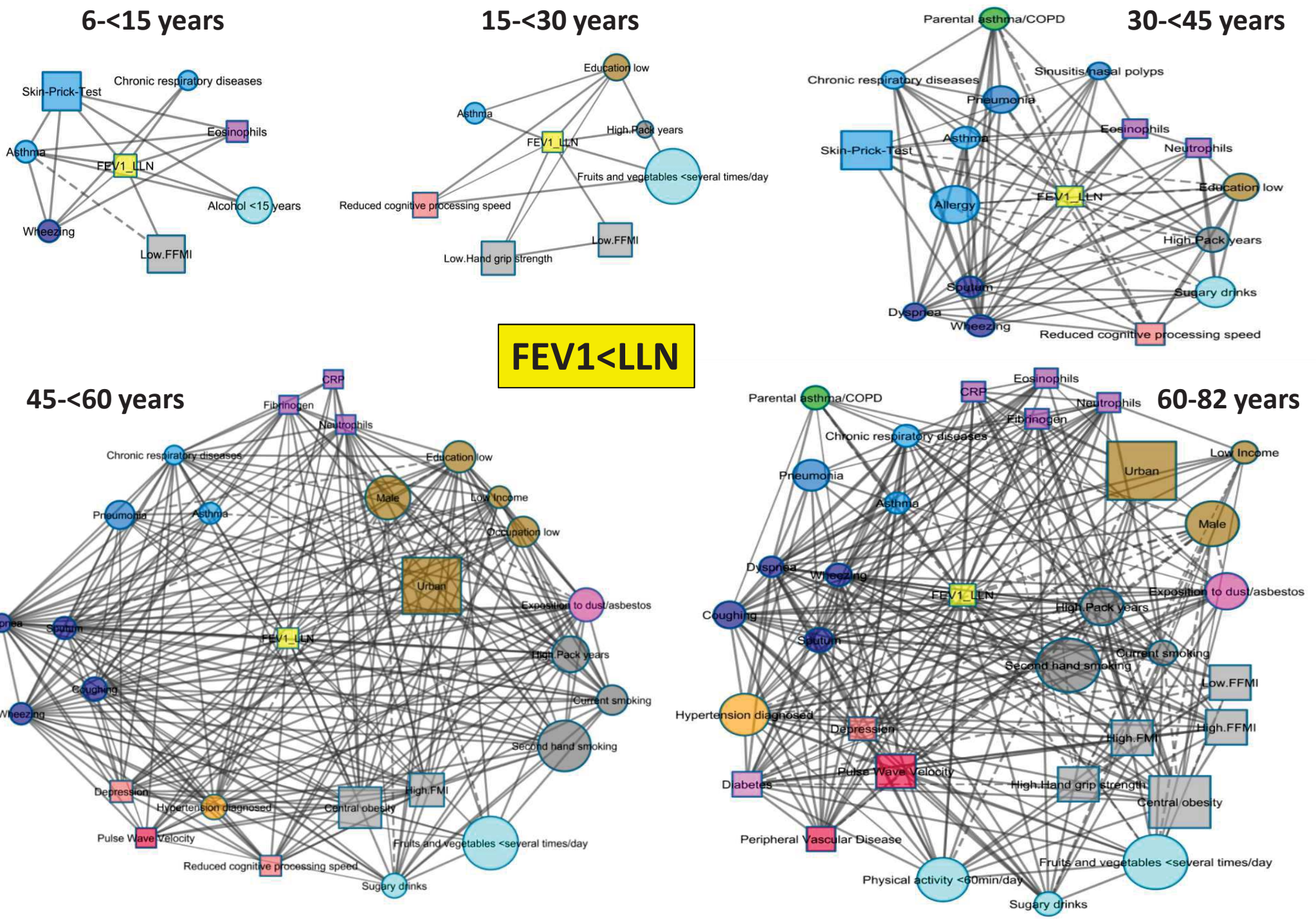
Exposome

Low birthweight
Infections
Vaccinations
Lifestyle
Alcohol
Smoking
Pollution
Accidents

Genome

Prematurity
Breastfeeding
Maternal smoking
Diet
Microbiome
Allergens
Exercise
Socioeconomic status
Sunlight
Occupational exposure

Conception — **Time (age)** — **Death**


6-<15 years
Skin-Prick-Test
Chronic respiratory diseases
Eosinophils
Asthma
FEV1_LLN
Alcohol <15 years
Wheezing
Low.FFMI
15-<30 years
Education low
Asthma
High.Pack years
FEV1_LLN
Fruits and vegetables <several times/day
Reduced cognitive processing speed
Low.FFMI
Low.Hand grip strength
30-<45 years
Parental asthma/COPD
Chronic respiratory diseases
Sinusitis/nasal polyps
Pneumonia
Eosinophils
Asthma
Neutrophils
Skin-Prick-Test
Education low
Allergy
FEV1_LLN
High.Pack years
Sputum
Sugary drinks
Dyspnea
Wheezing
Reduced cognitive processing speed
FEV1<LLN
45-<60 years
CRP
Fibrinogen
Neutrophils
Chronic respiratory diseases
Education low
Male
Low Income
Pneumonia
Asthma
Occupation low
Urban
Exposition to dust/asbestos
Dyspnea
Sputum
FEV1_LLN
High.Pack years
Coughing
Current smoking
Wheezing
Second hand smoking
Depression
High.FMI
Hypertension diagnosed
Central obesity
Pulse Wave Velocity
Fruits and vegetables <several times/day
Reduced cognitive processing speed
Sugary drinks
60-82 years
Eosinophils
Parental asthma/COPD
CRP
Neutrophils
Fibrinogen
Chronic respiratory diseases
Low Income
Urban
Pneumonia
Asthma
Male
Dyspnea
Wheezing
FEV1_LLN
Exposition to dust/asbestos
Coughing
High.Pack years
Sputum
Current smoking
Second hand smoking
Low.FFMI
Hypertension diagnosed
High.FFMI
Depression
High.FMI
Pulse Wave Velocity
Diabetes
High.Hand grip strength
Central obesity
Peripheral Vascular Disease
Fruits and vegetables <several times/day
Physical activity <60min/day
Sugary drinks