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·综述·

慢性阻塞性肺疾病前期的研究进展

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【摘要】 慢性阻塞性肺疾病（简称慢阻肺）前期（pre-COPD）是指存在慢性呼吸道症状、肺部结构改变和（或）病理生理学改变，但肺通气功能尚未达到慢阻肺诊断标准（吸入支气管舒张剂后 FEV_1/FVC<0.70），在后续随访中更易进展为慢阻肺的人群。慢阻肺前期发生率高，存在较大的异质性和复杂性。因此，多维度精准辨析慢阻肺前期的发生发展，加强慢阻肺前期的防控与诊治，可能有助于延缓甚至阻断慢阻肺的发生发展，减轻慢阻肺相关的疾病负担，具有重大的公共卫生意义。因此本文对慢阻肺前期的定义、相关队列和临床试验等研究进展进行综述，以提高对慢阻肺前期人群的认识，进一步提升慢阻肺的早期防控水平。

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Progress in pre-chronic obstructive pulmonary disease

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【Abstract】 Pre-chronic obstructive pulmonary disease (Pre-COPD) refers to individuals with chronic respiratory symptoms, structural abnormalities, and/or functional abnormalities, in the absence of airflow limitation, who may develop persistent airflow limitation over time. COPD is characterized by high prevalence and great heterogeneity and complexity. Early multidimensional identification and promotion of early prevention, management and treatment of Pre-COPD can help delay or halt the development of COPD, which has significant public health implications. This review aimed to summarize the definition, relevant cohorts, clinical trials, and other research progress in pre-COPD in order to improve the understanding of individuals with pre-COPD and improve early prevention and management of COPD.

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慢性阻塞性肺疾病（简称慢阻肺）前期（pre-chronic obstructive pulmonary disease，pre-COPD）是指出现慢性呼吸道症状、肺部结构改变和（或）病理生理学改变，但未达到慢阻肺诊断标准［吸入支气管舒张剂后第1秒用力呼气容积（forced expiratory volume in one second，FEV_1）/用力肺活量（forced vital capacity，FVC）<0.70］，在后续随访中更易进展为慢阻肺的人群[1-2]。在既往的慢阻肺全球创议（global initiative for chronic obstructive lung disease，GOLD）中被称为0级，后参照高血压前期和糖尿病前期的概念称为慢阻肺前期[3]。虽然慢阻肺前期的危害是明确的，但尚缺乏确切的定义和标准，对慢阻肺前期患者进行干预能否带来短期和长期获益也尚存争议。因此我们整理近年来慢阻肺前期的相关研究文献，针对其研究进展撰写综述，以期为慢阻肺前期人群的诊治和预防提供参考。

一、慢阻肺前期的定义的演变和由来

2001年GOLD首次发布时将肺通气功能未达慢阻肺诊断标准但出现慢性咳嗽咳痰的人群分类为GOLD 0级：At Risk[4]。然而，2002年发表的哥本哈根城市心脏研究发现，出现慢性咳嗽咳痰的肺通气功能正常受试者相比于无症状肺通气功能正常受试者在15年随访后并没有更易进展为慢阻肺（*OR*：1.2；95%*CI*：0.9~1.6），且在进展为慢阻肺的受试者中91%为基线无症状个体，仅9%为基线出现慢性咳嗽咳痰的个体[5]。基于该项研究证据，2006年GOLD更新时将GOLD 0级剔除出慢阻肺分类标准中[6]。2021年有学者参照高血压前期和糖尿病前期概念将GOLD 0级进一步扩展，其定义为出现慢性呼吸道症状，肺部结构改变，和（或）病理生理学改变、有更高的慢阻肺发生风险的肺通气功能正常个体[1]。而后该名称和定义被广泛接受，也被纳入GOLD 2022和GOLD 2023报告中[2, 7-10]。

二、慢阻肺前期的可能具体定义

1. 慢性呼吸道症状和急性呼吸道事件：慢性支气管炎是指每年出现咳嗽咳痰症状3个月以上且持续时间达到2年或以上，为慢阻肺患者的常见症状，同时部分肺通气功能正常人群也会出现慢性支气管炎症状，既往流行病学调查发现40岁以上肺通气功能正常人群中2.2%~17%出现慢性支气管炎症状[5, 11-14]，2002至2005年中国慢阻肺流行病学抽样调查显示，40岁以上人群中16.1%（男性20.0%，女性13.2%）出现慢性支气管炎且肺通气功能正常[14]。有多项大型队列研究探讨肺通气功能正常有慢性支气管炎人群的长期预后，研究结论并不一致，可能同纳入不同种族、年龄、吸烟状态的受试者有关[5, 15-21]，本团队汇总14篇相关研究开展的一项荟萃分析显示，肺通气功能正常有慢性支气管炎人群更易进展为慢阻肺、有更高的全因死亡风险、更高的呼吸疾病死亡风险和更快的肺功能下降速率，进一步亚组分析显示，在年龄小于50岁和吸过烟的个体中预后不良更加显著[22]。提示肺通气功能正常有慢性支气管炎可作为慢阻肺前期的具体定义之一。

呼吸困难也是慢阻肺患者的常见症状，在肺通气功能正常人群中也有部分个体会出现呼吸困难。由于呼吸困难影响因素众多，包括心肺功能、神经肌肉功能、代谢因素等，目前较少流行病学研究探讨肺通气功能正常出现呼吸困难人群的患病率情况，其相对肺通气功能正常无呼吸困难人群有更高全因死亡风险较为明确[23-25]，但对于其是否更易进展为慢阻肺研究相对较少且研究结论不一[19-20, 26]，是否可作为慢阻肺前期具体定义之一仍有待探讨。

慢阻肺患者出现呼吸困难和（或）咳嗽和咳痰增加为特征的事件称之为慢阻肺急性加重[2]，肺通气功能正常人群也会出现呼吸困难和（或）咳嗽和咳痰增加称之为急性呼吸道事件[27-31]。肺通气功能正常人群的急性呼吸道事件年发生率在0.13~0.27次·人$^{-1}$·年$^{-1}$左右[28-30]。COPDGene队列研究显示肺通气功能正常受试者中出现急性呼吸道事件者相比于未出现急性呼吸道事件者肺功能下降速度更快且有更高的全因死亡风险[28, 31]，尚无出现急性呼吸道事件的肺通气功能正常人群的慢阻肺发生风险的研究，其是否可作为慢阻肺前期具体定义之一仍有待探讨。

2. 胸部影像改变：人群中存在着相当比例的胸部影像出现肺气肿的肺通气功能正常个体[32-34]，由于不同的诊断标准和定量或视觉评估方式，其出现比例不尽相同，难以进行荟萃分析汇总结果。多项队列研究显示出现肺气肿的肺通气功能正常受试者与未出现肺气肿者比较更易进展为慢阻肺[35-36]、肺功能下降速率更快[37-39]和全因死亡风险更高[40]，但少数小样本量队列研究显示肺通气功能正常出现肺气肿的受试者并没有更易进展为慢阻肺[38]且肺功能下降速率并没有更快[41-42]。关于胸部CT显示的气体陷闭同慢阻肺发生和肺功能下降速率的研究较少但相对较为明确。SPIROMICS队列研究显示气体陷闭指标RV_{CT}/TLC_{CT}高的受试者相比于RV_{CT}/TLC_{CT}低的受试者更易进展为慢阻肺且肺功能下降速率更快[43]。SPIROMICS队列的另一项研究显示气体陷闭指标参数响应图（PRM^{fSAD}）越高则肺功能FEV_1下降速率越快[41]。气道壁增厚是慢阻肺的重要病理改变之一，部分肺通气功能正常个体也出现气道壁增厚。MESA队列和NELSON队列均证实肺通气功能正常受试者出现气道壁厚度指标Pi 10增高同随访中慢阻肺的发生和肺功能快速下降相关[44-45]。

考虑到胸部CT指标如肺气肿程度等存在显著的种族特异性[46]，欧美人群的相关研究结论并不一定适用于中国人群，仍然有待进一步多国多中心标准化研究以明确胸部CT出现慢阻肺样改变的肺通气功能正常人群是否可作为

慢阻肺前期的具体定义之一。

3. 呼吸生理改变：组织病理学观察到小气道病变（小气道狭窄或消失和小气道炎症）是慢阻肺发生发展的核心环节[47-48]，目前临床上常用肺通气功能来检测小气道病变程度。肺通气功能诊断小气道功能障碍的方法有多种多样，尚无明确共识，导致相关研究中小气道功能障碍的定义也多种多样。既往研究发现出现小气道功能障碍的无气流受限的受试者（MMEF<80% 预计值、FEV_1/Slow Vital Capacity<0.70、FEV_3/FEV_6<正常值下限）相较于无小气道功能障碍者更易进展为慢阻肺[49-52]，尚无目前临床常用的 MMEF、FEF50 和 FEF75 三者中至少两者<65% 预计值的小气道功能障碍诊断标准的预后研究[53]，仍有待进一步的探索。

在 40 岁以上社区人群中存在 4.7%~25.2% 的个体肺功能 $FEV_1/FVC \geq 0.70$ 但 FEV_1<80% 预计值，既往研究称之为 GOLD U 级或者限制性通气功能障碍，而今多改称为保留比值受损肺功能（preserved ratio impaired spirometry，PRISm）[54]。多项大样本量队列研究显示 PRISm 相比于健康对照更易进展为慢阻肺、有更高的全因死亡风险和呼吸疾病相关死亡风险[55-59]，符合慢阻肺前期人群的定义，因此推测 PRISm 可能是未成年时肺发育不良的个体成年后进展为慢阻肺的过程状态[60-61]，但 PRISm 存在诊断方法的可靠性和诊断不稳定性的情况值得注意[62]，仍然需要进一步深入的研究以明确。

肺弥散功能用于评价肺泡毛细血管内膜进行气体交换的效率。既往多用于评估间质性肺疾病，近年来研究发现肺通气功能正常人群中有 6.7%~24.0% 存在弥散功能障碍[63-64]，且肺通气功能正常受试者中弥散功能降低者较弥散功能正常者更易进展为慢阻肺和肺功能下降速率更快[65]，弥散功能降低可作为慢阻肺前期的具体定义之一。

除此之外，还存在一些呼吸生理改变，例如可逆性气流受限（吸入支气管舒张剂前 FEV_1/FVC<0.70 且吸入支气管舒张剂后 $FEV_1/FVC \geq 0.70$）[66]、支气管舒张实验阳性[67]、FEV_1 快速下降等[67-69]均可能为慢阻肺前期的具体定义之一。

三、慢阻肺前期队列研究

慢阻肺前期近年来受到学界的广泛关注[3]，以下简要列举 3 项国内外慢阻肺前期相关队列研究。

1. COPDGene 队列研究：COPDGene 队列由美国心肺血液研究所和慢阻肺基金会资助，于 2008 年在美国 21 家医学中心开展[70]，基线招募肺通气功能正常的吸烟者 4 387 例、PRISm 受试者 1 323 例和吸烟的慢阻肺患者 4 483 例[71]。收集慢阻肺流行病学问卷、肺功能、胸部双相 CT、6 min 步行试验和生物标志物等数据，每 5 年进行一次全面随访，目前正进行第二次也就是 10 年随访。基于 COPDGene 队列产生大量慢阻肺临床研究和基础研究成果，有力地推动了慢阻肺研究进步[71-72]。同时基于队列中招募的肺通气功能正常个体数据，发表了大量慢阻肺前期相关研究[28, 34, 39, 55, 61-62, 71, 73]。目前该队列仍在随访，更长随访时间的数据将为慢阻肺前期的相关研究提供有力支撑。

2. SPIROMICS 队列研究[74]：SPIROMICS 队列研究由美国心肺血液研究所资助，在美国 6 家医学中心开展，该研究入组 900 例肺通气功能正常吸烟者、200 例肺通气功能正常非吸烟者、1 500 例轻中度慢阻肺患者和 600 例重度极重度慢阻肺患者，收集包括慢阻肺流行病学问卷、肺功能、胸部双相 CT、6 min 步行试验和生物标志物（血清、血浆、DNA、尿样及诱导痰）等资料和数据，共随访 3 年。类似于 COPDGene 队列，SPIROMICS 队列研究者近年来加强了对队列中慢阻肺前期人群的预后分析，在慢阻肺前期领域发表大量的研究成果[41, 43, 51-52, 66-67]。

3. ECOPD 队列研究：ECOPD 队列是一项基于中国广东人群开展的多中心、前瞻性、观察性、以社区人群为基础的队列研究，该研究基线共入组 1 040 例肺通气功能正常受试者和 772 例轻中度慢阻肺患者和 131 例重度极重度慢阻肺患者[75]。收集包括慢阻肺流行病学问卷、舒张前后肺通气功能、脉冲震荡肺功能、胸部双相 CT、6 min 步行试验、运动心肺功能、生物标志物（血清、血浆、尿样及诱导痰）和空气污染等资料和数据，目前正在随访中。其主要目标是从高危因素、慢性呼吸道症状、呼吸生理、胸部影像和血尿痰生物标志物等多角度探索社区人群中肺通气功能正常个体的哪些特征或标志物同预后不良（慢阻肺发生和肺功能快速下降）相关，进一步采用机器学习算法构建慢阻肺前期人群预后不良的个体化精准化预测模型。相比于 COPDGene 队列和 SPIROMICS 队列从医疗中心招募受试者，ECOPD 队列从社区人群中筛选受试者，其受试者的情况更能代表疾病初始状态，相关研究成果将指导中国慢阻肺前期人群的临床实践[60, 76-77]。

四、慢阻肺前期的防控和治疗

1. 减少危险因素暴露：减少危险因素暴露以延缓或阻断慢阻肺前期的发生发展是目前确认的最重要的手段。包括：戒烟[78]、减少二手烟暴露[79]、减少生物燃料暴露（换用清洁燃气或改造厨房通风设备）[80]、减少职业粉尘暴露[81]、减少空气污染暴露[82-83]和尽量避免出生时儿时肺生长发育不良因素[84-85]等。

2. 药物治疗：关于慢阻肺前期人群的药物临床试验较少[3]，主要有以下两项双支扩剂治疗慢阻肺前期的药物临床试验。双支扩剂可显著改善慢阻肺患者呼吸道症状和肺功能[86]，因此 Han 等[87]于 2017 年组织开展 RETHINC 研究，纳入肺通气功能正常出现慢性呼吸道症状（CAT≥10 分）的受试者 1∶1 接受吸入双支扩剂茚达特罗/格隆溴铵或安慰剂治疗 12 周，研究结果显示双支扩剂治疗有慢性呼吸道症状的肺通气功能正常受试者相比于安慰剂治疗并不能显著改善呼吸道症状评分，但可一定程度上改善肺功能和延缓肺功能下降速率。Thamrin 等[88]纳入出现小气道病变的肺通气功能正常受试者和 GOLD 1 级慢阻肺患者，1∶1 随机安排吸入双支扩剂治疗或安慰剂治疗 12 个月，研究结果显示双支扩剂治疗相比于安慰剂未能显著改善肺通气功能，但可

一定程度上改善肺弥散功能和小气道功能。

虽然上述两项临床试验主要研究终点均为阴性结果，但对于后续设计慢阻肺前期人群的药物临床试验带来重要启发。首先，对于慢阻肺前期人群的药物治疗试验应进一步针对其相应的临床亚型选用针对性药物。双支扩剂主要舒张支气管平滑肌进而缓解呼吸困难症状，对于以慢性咳嗽和慢性咳痰为主的肺通气功能正常人群可能并不适用，后续应选用针对慢性气道炎症的药物进行相关临床试验[89]。其次，对于慢阻肺前期人群，最重要的研究终点是慢阻肺的发生，但慢阻肺前期人群发生慢阻肺需要较长的时间，因此，相应的药物临床试验应参照糖尿病前期设计更长时间的治疗期以验证长期维持治疗疗效[3, 90-91]。最后，虽然上述两项研究为阴性结果，考虑到在临床上有大量慢性呼吸道症状或小气道病变的肺通气功能正常个体正在接受双支扩剂治疗[30]，其结果仍然有力的指导了该类人群的临床实践，对节约医疗资源有较强的现实意义。

五、未来和展望

慢阻肺前期尚缺乏统一的且受到广泛认可的具体定义和标准，药物干预慢阻肺前期能否带来短期和长期获益也尚存争议，然而慢阻肺前期所产生的危害是明确的。未来仍然需要加强对慢阻肺前期人群的队列研究和干预性临床试验，期望通过更全面的筛选和管理发现慢阻肺前期人群，通过危险因素干预、中西医结合干预和（或）药物干预预防或延缓慢阻肺前期人群发展成为慢阻肺。

利益冲突　所有作者声明无利益冲突

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本刊对论文中有关实验动物描述的要求

在医学论文的描述中，凡涉及实验动物应符合以下要求：(1)品种、品系描述清楚；(2)强调来源；(3)遗传背景；(4)微生物学质量；(5)明确体重；(6)明确等级；(7)明确饲养环境和实验环境；(8)明确性别；(9)有无质量合格证明；(10)有对饲养的描述(如饲料类型、营养水平、照明方式、温度、湿度要求)；(11)所有动物数量准确；(12)详细描述动物的健康状况；(13)对动物实验的处理方式有单独清楚的交代；(14)全部有对照，部分可采用双因素方差分析。