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儿童哮喘控制水平相关影响因素的研究进展

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摘　要

支气管哮喘(简称哮喘)是一种以慢性气道炎症和气道高反应性为特征的异质性疾病，目前，该疾病是全球慢性疾病发病、死亡的主要原因，其患病率仍在逐年攀升，且临床控制率并不理想，影响着患儿的生活质量和身心发育，加重家庭负担。由于哮喘控制水平的影响因素复杂，有多种因素共同作用，给临床医生也加大了负担。本文综述了影响儿童哮喘控制水平的相关因素的最新研究进展，为哮喘的防治提供依据。

关键词

儿童，哮喘，控制水平，影响因素，综述

Research Progress on Factors Influencing the Level of Asthma Control in Children

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Abstract

Bronchial asthma (hereinafter referred to as asthma) is a heterogeneous disease characterized by chronic airway inflammation and airway hyperresponsiveness. At present, the disease is the main cause of morbidity and mortality of chronic diseases worldwide. Its prevalence is still rising year by year, and the clinical control rate is not ideal, which affects the quality of life and psychosomatic development of children, and increases the burden on families. Because of the complex factors affecting the level of asthma control, there are many factors working together, which also increase the burden on clinicians. This article reviews the latest research progress of related factors af-

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fecting the control level of childhood asthma, which provides basis for the prevention and treatment of asthma.

Keywords

Children, Asthma, Control Level, Influencing Factors, Overview

1. 引言

支气管哮喘(简称哮喘)是一种复杂的、异质性呼吸道疾病，是全世界儿童和成人均受累的最常见呼吸系统疾病之一，对儿童生活与学习造成了严重困扰，在现有的研究中，已经确定了某些导致加重哮喘的风险，包括遗传学、免疫学和环境等因素[1]，都影响哮喘相关的发病率、流行率和死亡率等。在我国，14 岁及以下儿童哮喘总患病率为 3.3% [2]，且其临床控制现状亦不佳，达到良好控制的患儿仅占 16.4% [3]。尽管全世界患有哮喘的人数之多，但哮喘的机制和病因尚未完全清楚，通过了解影响哮喘控制情况的相关因素，对哮喘进行有针对性预防，可更加有效地控制哮喘的发作。这篇综述的目的是将哮喘的相关影响因素进行广泛概述。

2. 个体因素

2.1. 性别、年龄与性激素

随着年龄的变化，哮喘在性别中所占比例有所不同。在学龄期前中，男孩哮喘的患病率比女孩更高；而在青春期前后，哮喘的患病率开始从男性的较高变为女性的较高；直到成人后，女性哮喘的患病率高于男性；怀孕期间哮喘的严重程度增加[4] [5] [6]。

青春期前后的这种变化，表明了性激素及社会、心理精神等因素对哮喘发作的重要影响。雌激素主要通过雌激素受体(ER)ERα 和 ERβ 起作用，雌激素受体(ER)激活转录过程和信号传导过程，从而控制基因表达[7] [8]。在一项动物实验中，与 ERα 小鼠相比，在基线时，ERβ 小鼠在两性中都表现出肺功能恶化，其中雌性小鼠比雄性变化更明显，此项研究还发现 ERβ 的保护作用或 ERα 在气道中的侵害作用[9]。Shah SA 等[10]完成的队列研究表明，激素替代疗法可使绝经期女性降低哮喘发作的风险。最近，有研究表明，可能由于雌激素改变了糖皮质激素的作用，增强了 Th2 细胞的存活率和 2 型细胞因子的产生，导致患有严重哮喘的女性的循环 Th2 细胞水平高于男性[11]。目前，关于性激素与哮喘的具体机制尚未研究清楚，但根据目前研究可明确推测两者的紧密关系。

2.2. 肥胖

肥胖是哮喘发生和加重的确切相关危险因素。超重或肥胖性哮喘是由于全身炎症和代谢失调影响肺部的机械特性和气道重塑引起的[12]，其特征是 Th1 型炎症[13]。大量研究表明，哮喘发作风险的增加与体重增长加速、肺大小和气道生长不成比例有关[14] [15]。在一项病例对照研究中，肥胖哮喘患儿的白介素(IL)-33 和转化生长因子(TGF)β1 显著升高[16]，它们是参与气道重塑和与适应性 T 辅助细胞相互作用的最重要的细胞因子之一[17]。在最近的遗传学研究中，确定了儿童体重指数(BMI)和哮喘之间的一个共

同因果基因组区域，研究显示白介素(IL)-6 和脂联素(adiponectin)可能是儿童肥胖和哮喘之间的潜在生物介质[18]。尽管肥胖驱动哮喘发作和改变现有哮喘的机制尚不清楚，但通过先前研究可以看出，肥胖在儿童期哮喘发作中的起着重要作用[16] [18]。国外一项 Meta 分析发现，通过完成代谢和减肥手术(MBS)，超过 50%的患者完全停用哮喘药物[19]。Sikorska-Szaflik H 等人提出，可采用饮食干预和减肥对肥胖哮喘患者实现预防和控制[20]。

2.3. 母乳喂养

众所周知，母乳是婴儿的最佳营养来源，含有许多重要的营养素、抗炎剂和免疫调节剂。母乳喂养对婴幼儿的健康有许多益处，比如可明显降低过敏性疾病[21]、婴幼儿营养不良[22]、上呼吸道感染以及糖尿病等的发生[23] [24]，此外，其也可哮喘的也是重要的保护因素。世界卫生组织和美国儿科学会(AAP)建议，婴儿应纯母乳喂养 6 个月[25]。大量研究表明，纯母乳喂养与儿童哮喘之间存在持续的时间依赖性、保护性的关联[24] [26]。在 NHANES 研究中，3~4 岁的儿童从 4 至 6 个月开始纯母乳喂养的保护作用受益最大[27]。在一项队列研究中表示，母乳喂养持续时间与肺容量有关[28]。但在最近的观察性研究中，纳入 110 名青春期前儿童，发现母乳喂养时间较长的儿童 FEV1 更高，同时发现母乳喂养对气道有保护作用，并不是对肺实质(肺容量和肺泡毛细血管膜)或过敏性气道炎症的保护作用[29]。

2.4. 肠道微生态

最近，许多学者发现，微生态环境与哮喘之间的关系，包括细菌、病毒、真菌甚至古细菌等，可以显著影响气道炎症[30]。婴幼儿早期肠道微生态的变化的主要受饮食(母乳或配方奶粉)、抗生素使用和出生模式(顺产或剖宫产)等因素的影响[31] [32] [33]。母乳喂养是婴幼儿早期肠道微生物群落种植的重要来源，如 Heisel T 及其同事发现，母乳喂养与 1 个月和 6 个月婴儿的粪便中的细菌－真菌的相关性[33]。且已在人类和动物研究中反复证明了肺和肠道之间的联系是双向的，微生物群是负责哮喘中这两个部位之间相互作用的重要因素[34] [35] [36]。已有很多研究证据证明了不同肠道菌群对哮喘的影响，例如，双歧杆菌与生命早期的全身炎症和免疫失调有关[37]。最近，在动物实验中，新生儿肺炎链球菌感染在婴儿期和成年期的肺部切片显示炎性细胞浸润增加和肺泡隔增厚等组织病理学病变，其感染也可诱导气道高反应性以及逐渐形成的肠道微生物群落的长期破坏[38]。最新研究发现，L-丙氨酰－谷氨酰胺可能通过调节微生物群及其衍生代谢物来降低呼吸系统的炎症浸润，改善哮喘症状[39]，可能与改变 NF-κB，mTOR 和 STAT3 等信号通路来有关[40]。综上所述，或可通过调整饮食结构、补充益生菌等方法，改善肠道微生态，从而提高免疫机制、改善肺部炎症浸润，减轻哮喘症状。

2.5. 维生素 D

维生素 D 除在机体生长骨骼发育中的发挥作用外，其缺乏还与多种不良健康影响有关，如肺炎、1 型糖尿病、自闭症等[41] [42] [43]。也有研究报道了维生素 D 在哮喘的发生和恶化中的影响[44] [45]。维生素 D 可能通过影响肺部的发育、调节免疫应答和气道重塑等在哮喘发作中发挥作用[46]。但在 VDKA 随机临床试验中，在持续性哮喘和维生素 D 缺乏的儿童中，与对照组相比，补充维生素 D3 并没有显着改善严重哮喘恶化的时间[47]，这与先前的研究结果是不同的。由 Li Q 等人完成的队列研究中表明，充足的维生素 D 水平会降低 3 年内哮喘发作的风险以及医疗保健利用率，并在 1 年内改善肺功能[48]。我们需要进一步研究来评估维生素 D 对哮喘发生和发展的影响。

2.6. 精神心理因素

患有哮喘的儿童可能面临更高的精神心理问题(如抑郁和焦虑)，加重家庭负担和医疗负担(如急诊科

就诊次数)，降低用药依从性等[49] [50] [51]。哮喘与精神障碍之间存在着双向关联[52] [53]，并且可能有某种共同的病因或病理生理过程[54]。焦虑、抑郁等心理因素也可引发机体的应激反应，通过下丘脑－垂体－肾上腺(HPA)轴和自主神经系统(交感神经/副交感神经)，使皮质醇释放增加，皮质醇则负反馈抑制免疫反应，同时诱导 Th1/Th2 细胞因子失调，从而增强气道反应性、增加气道炎症[55] [56] [57]。有专家指出，长期慢性的应激源会刺激内源性糖皮质激素的释放，导致外源性糖皮质激素的抵抗，干扰抗炎作用，影响哮喘恶化和治疗效果[58]。最近，有研究发现，脾酪氨酸激酶(Syk)抑制剂 R406 通过调节糖皮质激素受体来提高对地塞米松的敏感性，恢复糖皮质激素的抗炎作用[59]。综上所述，我们在对哮喘患儿诊断及调整治疗时，同时应关注患儿心理的调节与疏导。

2.7. 合并症

2.7.1. 呼吸道感染

大量研究证明，由细菌、病毒等引起的呼吸系统感染与哮喘发作或恶化密切相关[60] [61]，尤其是鼻病毒和呼吸道合胞病毒导致的严重细支气管炎与复发性喘息和哮喘的发生、恶化有关，并且 2 岁以下儿童的病毒性下呼吸道感染会增加哮喘的患病风险[62]。鼻病毒和呼吸道合胞病毒的主要侵袭的部位是气道上皮纤毛细胞，刺激大量干扰素(IFN)-λ、白细胞介素(IL)-6、白细胞介素(IL)-8 等细胞因子分泌，降低肺部黏液清除率，引发反复发作的喘息或哮喘恶化[63] [64]。新生儿的气道和胃肠道中的细菌可以促进免疫系统的成熟，防止哮喘。随着年龄的增长，细菌感染则可导致哮喘的发生、发展和恶化。Thorsen J 等证明了，在儿童口咽微生物群中，最常见的细菌是肺炎链球菌、流感嗜血杆菌等[65]。在纵向研究与横断面研究的比较发现，乙型流感嗜血杆菌联合疫苗接种是防止儿童喘息的保护因素。除此之外，真菌和非典型病原体(如肺炎支原体、衣原体等)也与哮喘存在着正相关[66] [67] [68]。

2.7.2. 胃食管反流病

胃食管反流病(GERD)是由胃内容物逆行流入食道引起的疾病，可分为反流性食管炎(RE)和非糜烂性胃食管反流病(NERD)，其临床表现不仅限于食管，也侵及咽喉、呼吸道等食管邻近器官[69] [70]。如果治疗不及时，每天有超过 1/4 的婴儿和>10%的儿童出现胃食管反流病症状[71]。研究表明，胃食管反流病通常与哮喘恶化共存，早期胃食管反流病与随后的儿童哮喘有关，但两者相关性较弱[72] [73] [74]。胃食管反流病可能会增大气道上皮的通透性，增加黏膜下层与过敏原和病原体暴露，白细胞介素(IL)-33 的释放增多，导致炎症和恶化的风险增加[75]。之前的研究报告了使用抑酸药物(如质子泵抑制剂)治疗与胃食管反流病的哮喘之间没有显著影响[73]，然而在儿童早期使用质子泵抑制剂治疗会使哮喘的风险增加 1.4 至 1.6 倍[76] [77]。

2.7.3. 阻塞性睡眠呼吸暂停低通气综合征

阻塞性睡眠呼吸暂停低通气综合征(OSAHS)是长时间的上气道部分梗阻或间歇性、完全性梗阻，从而影响睡眠时正常通气和正常的睡眠模式[78] [79]。OSAHS 在儿童期的发病高峰是 2~6 岁[79]，小儿患者的症状通常包括打鼾、喘气、呼吸暂停以及呼吸急促等，可能是由于上气道梗阻，刺激气道迷走神经导致支气管收缩，同时激发炎症反应，释放炎症因子(如淋巴细胞、C 反应蛋白等)，进而影响哮喘[80]。已有大量研究证明了哮喘和 OSAHS 之间的双向联系[81]。同时，在一项表型分析中，98%的 OSAHS 哮喘患者属于肥胖哮喘组[82]。哮喘与两者之间的具体病理生理机制尚未清楚。最近，由 Mahboub B 等完成的病例对照研究，在患有 OSAHS 的哮喘患者中，与对照组相比，持续气道正压通气可改善对糖皮质激素耐药情况，并发现血液中 IL-4、IL-8、IL-17 和 IFN-γ 的显著降低[83]，这可改善患者的肺通气，改善缺氧。

3. 家庭因素

3.1. 家族史

正如多项研究所表明的，人们普遍认为哮喘易感性具有很强的遗传成分。父母哮喘病史是儿童哮喘的最主要的危险因素之一，Mirzakhani H 等[84]进行了一项针对 806 名妇女、其伴侣(婴儿的亲生父亲)及其子女的维生素 D 产前哮喘减少试验(NCT00920621)，发现与非哮喘父母相比，父母双方都患有哮喘的儿童风险最高，且哮喘不受控制的母亲所生的孩子患哮喘的风险更高。有专家提出，哮喘基因影响的关联，单卵双胞胎比同性异卵双胞胎与哮喘的相关性高，此外，还发现儿童哮喘与呼出的一氧化氮之间的关联可能通过过敏原特异性 IgE 水平，而不是血液嗜酸性粒细胞的遗传学来解释的[85]。除此之外，DNA 甲基化、组蛋白修饰和 microRNA 表达等表观遗传学被广泛研究，这可能有助于更好地了解哮喘的发病机制[86]。

3.2. 烟草烟雾暴露史

父母吸烟是儿童接触烟草烟雾的常见原因。烟草烟雾暴露于气道，引起氧化应激与慢性炎症，加重小气道阻塞，降低肺功能[87] [88]。最近，有研究表明，烟草烟雾暴露可能通过阻止转化生长因子(TGF)-β1 诱导上皮－间充质转化(EMT)过程的正常激活，同时干扰 Notch-1 信号传导，影响支气管上皮的修复机制[89]。在母亲妊娠或早期儿童生活中被动接触烟草烟雾(如二手烟)，会对儿童的呼吸系统的产生终生的不利影响。具体来说，母亲吸烟或母亲妊娠接触二手烟都会增加后代患喘息和哮喘的风险[90]。在一项间隔 3 年的纵向研究中发现，父母长期吸烟加重了患儿的呼吸道症状，增加了药物的使用率，用力肺活量(FVC)、第一秒用力肺活量(FEV1)、呼气流量峰值(PEF)等肺功能指标降低[91]。所以，减少烟草烟雾的接触可能有助于儿童期哮喘的良好控制。

3.3. 经济水平与文化程度

父母的经济水平和文化程度也会影响哮喘的有效控制，尤其是对发展中国家造成了较大的经济负担[92]。一般来说，较高的父母教育和收入会有更有利于患儿控制病情的住房环境[93]。Bukstein DA 等[94]完成的一项调查表示，与高收入患者相比，低收入患者更频繁地出现湿疹症状，且不太可能与医护人员制定哮喘治疗方案，这种差距可能与高医疗负担、心理压力大、对哮喘的认知不足等有关。但一项前瞻性队列研究发现，在调整母亲产前和产后因素后，母亲受教育程度较高，儿童患喘息的风险增加，考虑可能的原因是患儿和母亲的心理压力过大有关[95]。

4. 规范化教育与管理

首先，进行规范化教育与管理的前提是要正确诊断哮喘，许多疾病可与哮喘的症状非常类似，如声带功能障碍、囊性纤维化等[96]。其次，要提高家长对哮喘的认知度和参与度，加强患儿的用药依从性。在一项关于哮喘小组教育的研究表明，通过对家长或照顾者进行教育管理，可以提高他们对哮喘的该疾病知识，有利于患儿的病情控制[97]。但在我国家长对哮喘的普遍认识、重视度不够，且依从性差，哮喘发作或加重时误以为是“感冒”发作，这不仅延误了病情还错过了最佳用药时间。最后，若患儿可以对吸入控制治疗的依从性好和正确使用吸入器是哮喘控制良好的关键。目前，有新技术及方法来解决此类问题，但可信度仍待进一步确定。Hesso I 等[98]完成的观察性队列研究显示，患者使用装有电子监测设备(EMD)的干粉吸入器(DPI)1 个月后观察到，EMD 提供的客观数据显示实际依从率并没有升高，反而显着降低。除此之外，远程医疗也成为新型医疗服务方法，但较少实践于临床。新型医疗技术应用于临床，或受到不同的限制，时间不定，所以我们需要对吸入器设计和使用以及患者的持久教育进行持续的干预，

以确保吸入的药物的达到最佳效果。

5. 社会因素：气候与环境因素

气候变化影响着哮喘的控制水平。当前，气候变化是因为大量温室气体(主要是二氧化碳)的排放，大气中二氧化碳增多会增加植物的光合作用，授粉期延长，产生更多地花粉，可诱发哮喘患者的 IgE 介导的超敏反应[99]。哮喘患者在春夏、秋冬季节交替时最为敏感。此外，寒冷天气或寒潮也会诱发加重哮喘，冷空气刺激支气管收缩，分泌炎症细胞(中性粒细胞等)及气道阻塞，加重症状[100]。洪水易引发霉菌繁殖，诱发哮喘的发生。空气污染的问题也亟待解决。空气污染物主要包括气态(如臭氧、二氧化氮、二氧化硫等)和细颗粒物(PM)，可以增强气道的通透性，促进过敏原渗透到黏膜中，同时引起 Th2 和 Th17 产生适应性免疫反应，诱发哮喘[99] [101]。家庭和学校环境中也有许多患儿可持续接触的过敏原，如尘螨、霉菌、宠物、老鼠、二手烟或其他污染物等[102]。所以，减少接触过敏原、改善环境会有助于预防和管理哮喘。

6. 小结

哮喘的病因复杂，其发生与发展往往不是一蹴而就，多是因为受到多种危险因素相互作用的结果。但目前尚不清楚这些危险因素的具体诱发机制，但临床医生可以帮助患儿及其家长通过减少暴露过敏原等危险因素，调节患儿的生活习惯和情绪，加强对家长或照顾者的教育与管理，从而改善用药依从率，提高哮喘的控制水平，减少重症、不受控制的哮喘的发生，尽量减轻哮喘对患儿及家庭带来的影响，使儿童哮喘实现更精准、有效的个体化治疗。

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