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政策纵观：大麻、大麻二酚、大麻素滥用的危害

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1. 引言

虽然经典的实验室和动物数据早已证实了大麻素的遗传毒性，但直到最近，随着现代分析技术的应用，才揭示出大麻素暴露可能导致疾病流行的具体规模。随着许多地方大麻使用立法的放宽、全球大麻合法化运动的广泛开展以及大麻使用量的增加和现有品种大麻素效力的普遍提高，这项工作的重要性和紧迫性更加突出。基于美国夏威夷一个先天性畸形的溯源流行病学调查结果[1]得到了美国科罗拉多、加拿大和澳大利亚类似研究结果的证实[2–4]。美国和欧洲的最近研究已经发现分别有46/62例和90/95例先天性畸形[5–6]与大麻素暴露的各种指标存在因果关系。美国和欧洲对癌症的类似研究发现，分别有25/28例和33/40例的癌症可能与大麻素暴露指数有关[7]。重要的是，只要数据有可比性，研究结论几乎完全相似。最近的研究采用了稳健的混合面板时空回归模型，逆概率加权和期望值（*E*值）作为因果推断的主要工具[5–7]。*E*值是衡量一种可归因于其他未被控制的混杂因素影响效应的统计量[8]。它有95%置信区间（CI）。其值大于9被认为是未被控制的混杂因素影响效应较高[9]。

最近，关于急性和慢性病的临床流行病学研究[10]和基于DNA甲基化年龄的新型表观遗传生物年龄研究[11]证实，30岁时接触大麻后衰老速度加快约30%。在这项研究中，过去四年中的大麻使用情况被量化为平均每月仅3.39天，而一生中使用大麻的平均天数仅为每月2.68天[11]。此外，对患者的生理研究表明，这种效应随着年龄的增长而增加，并与实际年龄的平方成正比[12]。事实上，已经有研究报道了大麻素暴露后的整体DNA高甲基化[13]。这种基因启动子甲基化的变化是衰老的典型特征，也是功能逐渐丧失的明显原因。下文对这些发现进行了详细总结，这些发现数量众多，而且具有明显的多样性，涉及许多身体系统和过程。

2. 证据背景

以下情况都与大麻素有因果关系。

2.1. 癌

在美国和欧洲的研究中，这些癌症与大麻素有因果关系：

• 美国（25/28种癌症）：泛癌、急性淋巴性白血病、急性髓性白血病、膀胱癌、脑癌、乳腺癌、慢性髓性白血

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病、慢性淋巴性白血病、结直肠癌、卡波西肉瘤、肾癌、肝癌、肺癌、黑色素瘤、骨髓瘤、霍奇金淋巴瘤和非霍奇金淋巴瘤、食管癌、口咽癌、卵巢癌、胰腺癌、前列腺癌、胃癌、睾丸癌和甲状腺癌[7]。

• 欧洲（33/40种癌症）：急性淋巴性白血病、急性髓性白血病、膀胱癌、乳腺癌、慢性髓性白血病、慢性淋巴性白血病、结直肠癌、肝细胞癌、卡波西肉瘤、肾癌、肝癌、肺癌、骨髓瘤、黑色素瘤、霍奇金淋巴瘤和非霍奇金淋巴瘤、食管癌、口咽癌、卵巢异常生殖细胞瘤、胰腺癌、前列腺癌、胃癌、睾丸癌、睾丸非精原细胞瘤和甲状腺癌。除了在美国发现的肿瘤外，还有肛门癌、阴茎癌、子宫癌、胆囊癌、喉癌、间皮肉瘤、睾丸精原细胞瘤和外阴癌。

2.2. 先天畸形

这些受影响的系统和先天畸形与大麻素有因果关系：

• 在美国和欧洲发现的特别受影响的系统：中枢神经系统、心血管、染色体、口面部、四肢、胃肠道、泌尿系统、皮肤和全身一般系统；

• 在美国发现的特别受影响的先天畸形：62种畸形中的46种[6]；

• 在欧洲发现的特别受影响的先天畸形和系统：95种畸形和系统中的90种[5]；

• 40种共同畸形：无耳畸形/小耳畸形、主动脉弓中断、主动脉瓣狭窄、房间隔缺损、房室间隔缺损、双肾发育不全、膀胱萎缩、后鼻孔闭锁、染色体异常、唇腭裂、单纯性腭裂、畸形足、主动脉缩窄、先天性白内障、膈疝、右心室双出口、唐氏综合征（21三体综合征）、爱德华氏综合征（18三体综合征）、脑膨出、22q11.2缺失、先天性髋关节脱位、先天性巨结肠、前脑无裂畸形、左心发育不全、尿道下裂、大肠/直肠/肛肠闭锁/狭窄、肢体复位异常、小眼球/无眼球、食管闭锁/狭窄（+气管食管瘘）、脐膨出、Patau综合征（13三体综合征）、先天性后尿道瓣膜、肺瓣膜闭锁、单心室、小肠狭窄或闭锁、脊柱裂（无脑畸形）、法洛四联症、全肺静脉回流异常、Turner综合征（女性X0）和室间隔缺损[5–6]。

2.3. 衰老

有14条证据显示衰老加速与大麻有关：心血管年龄加速、肝硬化和肝炎、染色体损伤、晚期DNA甲基化生物年龄使表观遗传生物年龄提前30% [11]、卵母细胞和精子变化、内分泌紊乱、遗传毒性和致癌、先天畸形的遗传毒性、组蛋白减少50%、线粒体抑制、神经炎症性精神疾病、衰老和死亡率升高、急性和慢性疾病的综合征模式以及端粒酶抑制。这些不仅是定义衰老的疾病，也是衰老产生的疾病[14]。

3. 讨论

在其他值得注意的发现中，实验室中发现的大麻素指数剂量反应效应已得到充分证明，在先天异常和癌症数据集中也有类似的流行病学发现[5–7]。这一发现在现代背景下变得很重要，因为许多地方同时发现大麻的使用率、使用强度和大麻素的效力都在增加——这些趋将共同导致社区的高暴露遗传毒性[15–16]。此外，对癌症和先天畸形的研究表明，大麻素的遗传毒性比烟草和酒精的总和要大得多[5–7]——这一发现适用于许多大麻素[6–7,17–24]。

大麻素遗传毒性的许多机制已经被确定，包括染色体断裂和易位[21,25]、DNA碱基氧化[21]、精子和卵母细胞形态异常[26–27]和线粒体抑制[28]，以及继发性抑制在底物和能量供应水平上对表观遗传机制进行下游抑制[29]。最近，一系列研究证实了大麻素对表观基因组扰动的核心作用。大麻素对衰老、癌症和先天畸形有着重要的表观遗传学影响。Schrott等[30]的一篇关于大麻依赖和大麻戒断的表观突变的论文将这一研究推向高潮。表1总结了该论文补充数据中359页证据的重要发现[30]。有25个表观遗传变异位点涉及细胞的基本表观遗传机制，包括DNA甲基转移酶和启动CpG去甲基化的10–11易位1–3（TET1–3）甲基胞嘧啶氧合酶。此外，有382个表观遗传变异位点涉及组蛋白甲基转移酶、去甲基化酶、乙酰转移酶和去乙酰化酶，它们控制了基因组对转录机制的可及性。Takahashi和Yamanaka [31]、Yu等[32]和Ocampo等[33]，发现干细胞因子有47个表观遗传变异位点，将无丝分裂期染色体结合到有丝分裂纺锤体上的中心体机制有127个表观遗传变异位点，在纺锤体检查点释放后控制纺锤体两极和染色体分离的马达蛋白有225个表观遗传变异位点。最后，对关键的胚胎形态音猬因子（Sonic hedgehog）、Notch、血管内皮生长因子（VEGF）、骨形态发生蛋白（BMP）和Eph受体酪氨酸激酶家族一个成员（EphB2）有242个表观遗传变异位点。

重要的是，有许多特定系统的结果表明了对大脑、心血管系统、四肢和其他身体系统的影响。例如，通过副交感神经节细胞从神经嵴迁移失败来预测先天性巨结肠病及心房和心室间隔形态发生缺陷。欧洲的数据显示，先天性椎体、肛门、心脏、气管、食管、肾脏和肢体（VACTERL）多系统综合征的强信号，与主要的Sonic Hedge-

表1 大麻对表观基因组学影响的关键研究结果

Structure/function	Epigenetic hits
Key cell function	
Fundamental epigenomic machinery	25
Histone post-translational machinery	382
Stem cell factors	47
Tubulin	110
Centrosomes and kinetochores	127
Motor proteins: dynein-dynactin and kinesins	225
Embryonic morphogenesis	
Morphogens: Sonic hedgehog, Notch, VEGF, EphB2, BMP	242
System	
Brain	166
Limbs	131
Uro-nephrological	73
General	60
Gastrointestinal	37
Cardiovascular	29
Face	22
Body wall	15
Chromosomes	4
Cancer	810

Reproduced from Ref. [30] with permission.
VEGF: vascular endothelial growth factor; EphB2: a member of the Eph receptor tyrosine kinase family; BMP: bone morphogenetic protein.

hog形态发生途径受到抑制及其多系统影响相一致[5]。有趣的是，随着大麻含量的增加，这种严重的综合征已经变得很常见。在本研究中，VACTERL患病率与每日大麻使用率之间的相关性的P值为6.16×10^{-6}，E值为1.70×10^{20}，其CI的下限为8.94×10^{11} [5]。

人类新皮层的旺盛生长被不同程度地归因于Slit-Robo信号传递、视黄酸梯度以及新皮层中与小脑蛋白相关的大量突触。大麻素直接抑制这些关键的形态发生素信号系统[13,34]和表观基因组[30]。因此，毫不奇怪，大麻接触与一系列先天性神经系统疾病严重程度有关，从神经发育迟缓和神经行为障碍[35–36]到小头畸形[1]、严重的小头畸形[5]、无脑畸形[1,5–6]和大量的严重精神疾病[37]，并被认为正在指数级推动美国自闭症的流行[38–40]。此外，Schrott表观基因组关联研究（EWAS）数据库公布了不同癌症的810个表观遗传变异位点，这些结果共同预测了20种流行病学上常见的癌症[30]。

综上所述，这些数据有力地证明了大麻素的遗传毒性与多种不良结果有因果关系，而且呈指数关系，这些不良后果包括精神疾病、包括自闭症谱系障碍在内的发育性神经综合征、多种癌症和先天畸形，以及临床上显著的衰老加速。这些不良后果超过了烟草和酒精造成的不良后果，这强烈表明大麻素应受到与所有其他强效基因毒性药物类似的管制。

目前，大麻二酚被广泛吹捧，但尚未被充分了解。《南华早报》最近的一篇社论错误地指出，大麻二酚没有已知的副作用[41]。事实上，大麻二酚已被证明即使在低剂量下也具有遗传毒性，并与DNA断裂、单链和双链断裂、微核形成和DNA碱基氧化有关[21]。早在1999年，大麻二酚就被证明与毒性抗癌药物一样具有遗传毒性[26]。此外，大麻二酚已被证明可以直接或间接地与音猬因子信号调控途径相互作用。大麻二酚直接与平滑的受体相互作用，该受体是Sonic hedgehog信号通路头部的7个跨膜受体之一[42]。大麻素也与音猬因子信号通路的成员发生表观遗传学上的相互作用，包括斑块受体（PTCH1）、其负调控因子[斑块结构域包含4（PTCHD4）和融合同源物抑制因子（SUFU）的hedgehog信号负调控因子]、多个内皮生长因子结构域8（MEGF8）、跨膜蛋白107（TMEM107）、BMP4和染色质结构域解旋酶DNA结合蛋白7（CHD7）。此外，在音猬因子通路GLI家族锌指3（Gli3）核端的关键转录因子上有185个表观遗传变异[30]。音猬因子是一种主要的组织形态发生因子，参与了大多数身体组织的形态发生，这意味着大麻素与胚胎学中许多人体组织的无序结构必然有关。

在美国，对大麻二酚暴露的数据估计与9种先天畸形（总共62种畸形）有显著的相关性，而烟草和每月饮酒分别与11种和5种畸形相关[7]。与大麻二酚有关的先天畸形E值的CI下限值之和为39，而与烟草和每月饮酒有关的CI下限值分别为8和0，这使大麻二酚比目前的合法药物具有更强的致畸作用[7]。

众所周知，历史上，许多中国人被海外殖民列强强迫吸食鸦片。大麻作为通往其他成瘾药物的一条已明确的途径，引发了非常严重的潜在担忧，即未来可能重演过去的恐怖，就像在旧金山等现代城市所发生的事情一样。在这个城市中，无家可归和患有精神疾病的人普遍存在，且迅速增加，许多患有精神疾病的流浪者在街上徘徊，成为恶性循环的受害者，这种恶性循环往往开始于大麻的使用[43–46]。由于这些原因，限制人们接触毒性大麻素是公共卫生部门的首要责任——不仅是对他们自己的人群，而且至少对未来四代人负责。目前，大麻素所声称的好处很大程度上是假设的和（或）理论上的，并且它们极其严重的风险日益明确，而且在跨代遗传毒性上越来越明显，因此这一责任就更加重大。明确迹象表明，精子和卵母细胞的主要遗传毒性及与年龄相关的形态变化不仅

意味着配子的衰老，而且还为受精卵受孕前预先衰老的假定提供了证据，其深远的跨代遗传毒性影响目前尚未得到充分探索。

Authors’ contribution

Conceptualization was done by Albert Stuart Reece, Gary Kenneth Hulse, and Wei Wang; methodology and investigation by Albert Stuart Reece; and funding acquisition, project administration, and supervision by Gary Kenneth Hulse and Wei Wang. Albert Stuart Reece wrote the original draft, which was reviewed and edited by Gary Kenneth Hulse and Wei Wang.

Compliance with ethics guidelines

Albert Stuart Reece, Gary Kenneth Hulse, and Wei Wang declare that they have no conflict of interest or financial conflicts to disclose.

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