Letter to the editor

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Association between cannabis use and risk of gynecomastia: commentary on "Gynecomastia in adolescent males: current understanding of its etiology, pathophysiology, diagnosis, and treatment"

Jia-Lin Wu[1,*], Jun-Yang Luo[1,*], Xin-Yi Deng[2], Zai-Bo Jiang[1]

[1]Department of Interventional Radiology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
[2]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China

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Address for correspondence:
Zai-Bo Jiang
Department of Interventional Radiology, The Third Affiliated Hospital, Sun Yat-sen University, 600 Tianhe Road, Guangzhou 510630, China
Email: jiangzbo@mail.sysu.edu.cn
https://orcid.org/0000-0003-0523-6488
*These authors contributed equally to this study as co-first authors.

Cannabis, also known as marijuana, is one of the most widely used substances in high-income countries for over three decades [1]. In recent years, with the increasing legalization of cannabis in various regions, it has been reported that over 200 million individuals have used cannabis [2]. As a result, the detrimental consequences linked to cannabis use have emerged as a significant global concern. In the *Annals of Pediatric Endocrinology & Metabolism*, Metwalley and Farghaly [3] conducted a retrospective review focusing on the current understanding of gynecomastia, encompassing its etiology, pathophysiology, diagnosis, and treatment. The authors explored various potential etiologies of gynecomastia, such as obesity, aromatase excess syndrome, primary or secondary hypogonadism, congenital adrenal hyperplasia, among others. Notably, smoking was not addressed in their study, despite being an important factor that may influence the development of gynecomastia. Previous studies revealed a significantly higher incidence of gynecomastia among individuals who were marijuana smokers compared to both control patients and tobacco-only smokers [4,5].

However, the mechanisms underlying cannabis use and gynecomastia, especially the potential causal interactions between altered breast hypertrophy and smoking behavior, remain elusive. Although the biologically plausible scenario where phytoestrogens present in marijuana smoke could potentially interact with the estrogen receptor, its challenge to demonstrate the causal association between marijuana or tobacco use and gynecomastia due to selective bias and nature of observation study. Here, we attempt to clarify the causal associations between cannabis use or tobacco and the risk of gynecomastia using a 2-sample Mendelian randomization (MR) approach.

MR is a research methodology employed to investigate the causal relationship between risk factors and outcomes by utilizing genetic variants single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs). Genetic instruments of exposure for tobacco smoking behaviors, including age of smoking initiation (N=341,427), smoking initiation (N=1,232,091), cigarettes per day (N=337,334), and smoking cessation (N=547,219) obtained from a large published genome-wide association study (GWAS) [6]. Summary statistics for lifetime smoking (N=462,690) were acquired from UK Biobank samples [6]. Data for lifetime cannabis use (N=184,765) were derived from International Cannabis Consortium, 23andme, and UK Biobank [7]. Summary statistics for cannabis use disorder (N=374,177) was derived from a GWAS meta-analysis [8]. The summary statistics as the outcomes data for male hypertrophy of breast (N=167,020) were acquired from UK Biobank. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline and all participants included were of European ancestry. Details regarding ethical approval can be found in the original research. We selected independent genome-wide significant ($P<5\times10^{-8}$) SNPs for each exposure phenotype as IVs. Inverse-variance weighted (IVW) was used as the main MR analysis method. $P<0.05$ (2-sided) was considered statistically significant. All statistical analyses were performed in R ver. 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

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After conducting a series quality control and sensitivity analysis, we found that there were no significantly causal effects of age of smoking initiation, smoking initiation, cigarettes per day, smoking cessation, lifetime smoking, lifetime cannabis use and cannabis use disorder on the risk of gynecomastia, the odds ratio (OR) and its 95% confidence interval (CI) of using IVW method were 1.002 (95% CI, 0.997–1.007; *P*=0.403), 1.000 (95% CI,, 0.999–1.001; *P*=0.691), 1.000 (95% CI, 0.999–1.000; *P*=0.311), 1.000 (95% CI, 0.999–1.002; *P*=0.591), 1.000 (95% CI, 0.998–1.002; *P*=0.877), 1.000 (95% CI, 0.998–1.001; *P*=0.715), and 1.000 (95% CI, 0.997–1.002; *P*=0.834), respectively. The F statistics of IVs significantly associated with above exposure traits were all larger than 10, eliminating the bias of weak IVs. Neither heterogeneity nor pleiotropy was found in MR estimates (all *P*>0.05).

Gynecomastia is the benign proliferation of men glandular breast tissue [9]. Previous findings about the link of cannabis use or tobacco smoking with gynecomastia might be affected by various factors attributed to the inherent constraints and selective bias of observational studies [5]. MR analysis capitalizes on the fortuitous distribution of these genetic variants to simulate the randomization employed in clinical trials, thereby effectively alleviating confounding, and reverse causation biases. In summary, our MR results indicating that there is no causal association between marijuana or tobacco smoking and the occurrence of gynecomastia, suggesting that the previously observed associations of smoking behaviors with gynecomastia may be biased. Thus, further large population-based longitudinal studies are needed to validate our results.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

ORCID
Jia-Lin Wu: 0000-0002-8877-8348
Jun-Yang Luo: 0000-0002-2665-1608
Xin-Yi Deng: 0009-0002-6460-9985
Zai-Bo Jiang: 0000-0003-0523-6488

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