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Letter to the Editor

Beyond linear assumptions: Advancing lipidomic analysis in localized provoked vulvodynia

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Letter to the Editor

Chrysilla et al. provided valuable insights into the pathophysiology of localized provoked vulvodynia (LPV) through their integrated analysis of inflammatory mediators and lipidomic profiles.[1] A major strength of their study is its integrated design, combining in vitro fibroblast and in vivo behavioral assays. The lipidomic approach, detecting 122 mediators, represents an important step toward elucidating LPV's biochemical complexity. Moreover, simultaneous evaluation of pro-inflammatory and pro-resolving lipids under non-steroidal anti-inflammatory drug (NSAID) exposure offers a holistic perspective on disease mechanisms; for example, ibuprofen completely ablated prostaglandin E2 (PGE2) in fibroblast cultures (Fig. 2A) yet reduced pro-resolving mediators such as 11(12)-epoxyeicosatrienoic acid (EET) and resolvin E2 (RvE2) by over 50% (Fig. 4B, 4G), highlighting therapeutic trade-offs that could inform clinical strategies. This dual effect underscores the clinical challenge of balancing inflammation suppression with resolution, a critical consideration for chronic pain management. However, the interpretation of lipidomic clustering warrants more cautious consideration, as it relies heavily on the principal component analysis (PCA).

PCA—a linear dimensionality reduction technique—may not fully capture non-linear relationships inherent in lipid metabolism and inflammatory signaling.[2–4] These pathways involve dynamic, multi-level interactions among cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) networks, unlikely to conform to PCA's linear assumptions. Their PCA plots (Figs. 3A and 3B) illustrate separation between treatment groups but do not report the proportion of variance explained, a key metric for assessing robustness. Furthermore, lipidomic datasets often exhibit compositional constraints and correlated features, making linear projections prone to distortion and potentially masking biologically relevant clusters.[5,6]

This reliance introduces two analytical limitations: first, PCA assumes linearity and orthogonality of components, problematic for lipidomic datasets characterized by non-linear dependencies; second, subsequent interpretations may implicitly depend on parametric assumptions in statistical tests applied to high-dimensional, noisy data—conditions under which these assumptions rarely hold. Such oversimplification risks misdirecting therapeutic insights, especially when lipid mediators influence both nociceptive signaling and inflammation resolution.

To address these limitations, future studies should prioritize biologically meaningful feature selection and adopt analytical frameworks that better reflect lipidomic complexity. High predictive accuracy alone does not guarantee reliable identification of disease-relevant features, and interpretability remains a challenge. Robust unsupervised approaches such as Feature Agglomeration and Highly Variable Gene Selection offer principled strategies for identifying lipidomic signals without imposing linear constraints.[7,8] Additionally, non-parametric correlation measures (e.g., Spearman's rho, Kendall's tau) are well-suited for detecting monotonic relationships in lipid-lipid interactions, offering resilience to outliers and distributional assumptions.[9,10] Incorporating these strategies will not only enhance statistical rigor but also uncover mechanistic patterns that inform precision medicine approaches for LPV and related chronic pain disorders, ultimately improving translational relevance.

In conclusion, while Chrysilla et al.'s study provides critical insights into NSAID effects in LPV, adopting frameworks beyond linear assumptions is essential for capturing lipid signaling complexity. Advanced analytical strategies will enhance interpretation, support reproducible research, and accelerate targeted therapy development for chronic vulvar pain, with direct clinical implications. Ultimately, integrating computational tools with lipidomics can bridge molecular insights and actionable interventions, improving outcomes and guiding future therapeutic innovation.

CRediT authorship contribution statement

Souichi Oka: Writing – original draft, Conceptualization. **Kiyo Yoshida:** Investigation. **Yoshiyasu Takefuji:** Writing – review & editing, Supervision, Project administration.

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Data availability statement

No new data were created or analyzed in this study.

References

1. Chrysilla E., Fischer S., Jang J.-M., et al. A cautionary tale: non-steroidal anti-inflammatory drug use and localized provoked vulvodynia. *J Pain*. 2025;36:105559. https://doi.org/10.1016/j.jpain.2025.105559.
2. Elhaik E. Principal component analyses (PCA)-based findings in population genetic studies are highly biased and must be reevaluated. *Sci Rep*. 2022;12(1):14683. https://doi.org/10.1038/s41598-022-18634-2.
3. Yao Y., Ochoa A. Limitations of principal components in quantitative genetic association models for human studies. *eLife*. 2023;12:e79238. https://doi.org/10.7554/eLife.79238.
4. Mohseni N., Elhaik E. Biases of principal component analysis (PCA) in physical anthropology studies require a reevaluation of evolutionary insights. *eLife*. 2024;13:RP94685. https://doi.org/10.7554/eLife.94685.
5. Lenz M., Müller F.J., Zenke M., Schuppert A. Principal components analysis and the reported low intrinsic dimensionality of gene expression microarray data. *Sci Rep*. 2016;6:25696. https://doi.org/10.1038/srep25696.
6. Dey R., Lee S. Asymptotic properties of principal component analysis and shrinkage-bias adjustment under the generalized spiked population model. *J Multivar Anal*. 2019;173:145–164. https://doi.org/10.1016/j.jmva.2019.02.007.
7. Zhang J., Wu X., Hoi S.C.H., Zhu J. Feature agglomeration networks for single stage face detection. *Neurocomputing*. 2020;380:180–189. https://doi.org/10.1016/j.neucom.2019.10.093.
8. Xie Y., Jing Z., Pan H., Xu X., Fang Q. Redefining the high variable genes by optimized LOESS regression with positive ratio. *BMC Bioinform*. 2025;26(1):104. https://doi.org/10.1186/s12859-025-05678-9.
9. Okoye K., Hosseini S. Correlation Tests in R: Pearson Cor, Kendall's Tau, and Spearman's Rho. In: Okoye K., Hosseini S., eds. *R Programming: Statistical Data Analysis in Research*. Springer Nature; 2024:247–277. https://doi.org/10.1007/978-981-97-3385-9_12.
10. Yu H., Hutson A.D. A robust Spearman correlation coefficient permutation test. *Commun Stat Theory Methods*. 2024;53:2141–2153. https://doi.org/10.1080/03610926.2022.2121144.

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