

August 29, 2025

RE: Post-publication concern regarding “Longitudinal Data From the KETO-CTA Study: Plaque Predicts Plaque, ApoB Does Not” (Soto-Mota *et al.* JACC: Advances, 2025; doi:10.1016/j.jacadv.2025.101686)

Dear Dr. Silversides and the JACC: Advances editorial team,

I am submitting a post-publication concern regarding the article cited above. An independent re-analysis identifies material issues that could mislead readers. Because the findings may inform lipid-management decisions, I request editorial assessment and correction. Specific concerns are summarized below and documented in detail in the Appendix.

Critical issues

- **Incorrect y-axis tick labels and IQR band (C1–C3):** Fig 1B (Δ PAV) tick labels show 0–10% while data span 0–20% (twofold underestimation); Fig 1A–B IQR bands conflict with the reported sample IQR and data (lower bound of band dips below data); Fig 2E–F y-axis should be –1 to 6 (not –1 to 4). Per-tick, per-panel tick-label misalignment is inconsistent with standard plotting output.
- **Claims exceed reported models (C4):** “No association” is asserted without reporting key models: Δ TPS ~ ApoB; Δ TPS ~ LDL-C; Δ TPS ~ LDL-C exposure.
- **Linear-model assumptions violated (C5):** Change-score regressions fail ≥ 2 diagnostics (Breusch–Pagan $P \leq 0.001$; Shapiro–Wilk $P \leq 0.001$) despite “assumptions...corroborated”.

Major issues

- (i) **Model strategy (M1):** The paper relies on univariable change-score models; field-standard is ANCOVA (follow-up ~ baseline + exposure + covariates).^{1,2} ANCOVA avoids baseline–change artifacts and yields clearer estimates.^{3,4} Omitting age.sex/BP (available in the dataset) leaves associations likely confounded.^{2,5} No reported 95% CIs for β . “Predicts” is used for association models without validated prognostic performance.⁶ High baseline–follow-up correlation; univariable Δ -model R² is not decision-relevant; use partial R².
- (ii) **Bayes factors (M2):** Not prespecified; uses r-scale = 0.8, described as “moderately informative” yet above package’s “ultrawide”; same r-scale applied to all models with justification only for one; no standard sensitivity analysis; treats Bayes factors as posterior probabilities.^{7–9}

Additional items and details are described in the Appendix.

Requested editorial actions

1. **Figure corrections:** Replot Figures 1A, 1B and 2E–2F with correct y-axes and 25th–75th percentile shading; verify all figure captions against the underlying data.
2. **Analyses & reporting:** Align claims with results (include TPS models or remove claims); make ANCOVA the primary analysis; report β , 95% CI, diagnostics; if diagnostics fail, re-specify (e.g., nonlinear terms; HC/sandwich SEs); use association language and reserve “predicts/predictor” for validated prognostic models; either remove Bayes-factor claims or document prespecification and sensitivity.

3. Independent statistical review: Given the scope of figure and modeling issues, I respectfully request that the journal obtain an external statistical review and, depending on the findings, issue the appropriate notice (e.g., Author Correction or stronger).

Materials provided: Appendix (included below); reproducibility GitHub [repository¹⁰](#)

I have no conflicts of interest related to this work and am available to provide any additional information.

Sincerely,

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C1 and C2 reference panels from *Figure 1 Individual Change in Plaque Volume* of the published article (p. 6); left-hand images are published panels, right-hand images are reproductions.

C1 — Figure 1B: y-axis ticks labeled 0–10% while data span 0–20%

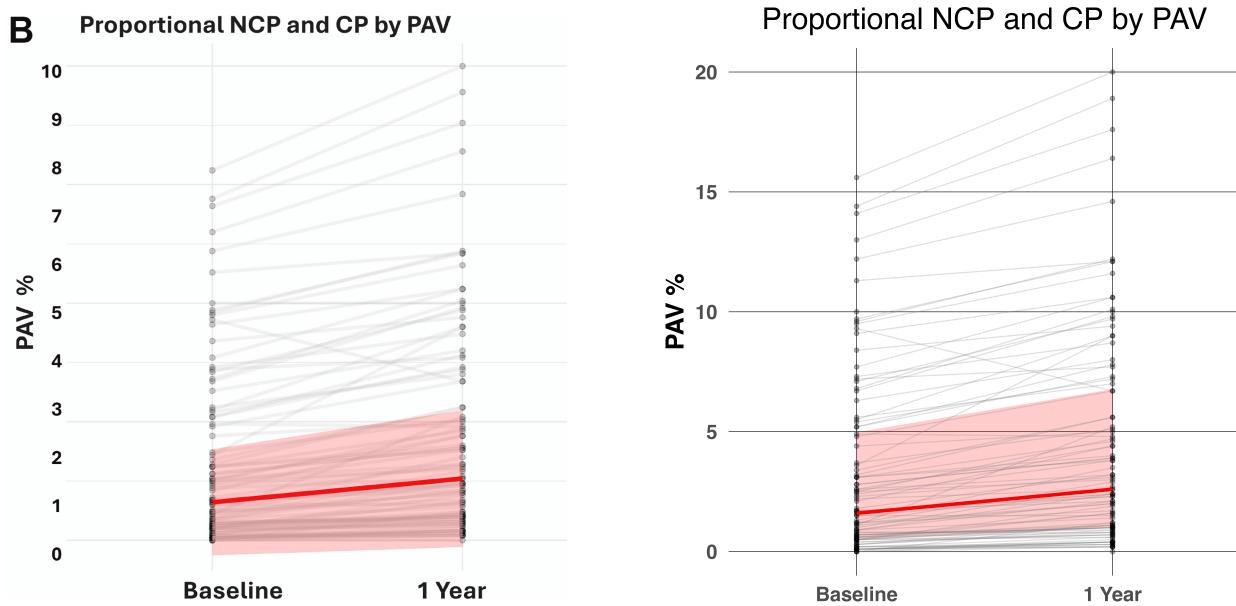


Figure 1: Left: published (axis 0–10%). Right: reproduced (axis 0–20%).

Issue (error). The published panel's y-axis tick labels show 0–10% although the values span 0–20%, causing a twofold underestimation of both absolute PAV and Δ PAV when read from the axis.

The reproduction uses the correct 0–20% range. The underlying data are unchanged.

Requested correction. Update the Figure 1B y-axis label to **0–20%**.

1. Compute Q1–Q3 across subjects at baseline and at 1 year, and plot those ranges as the shaded band(s).
2. Revise the caption to: “The red line shows the median paired change from baseline to 1 year. The shaded band shows the interquartile range (25th–75th percentiles) across subjects at each timepoint (baseline and 1 year).”
3. Regenerate the panels fully from code/data so the shaded band matches the computed quartiles.

C3 — Figures 2D–2F: y-axis ticks labeled –1 to 4 while data span –1 to 6

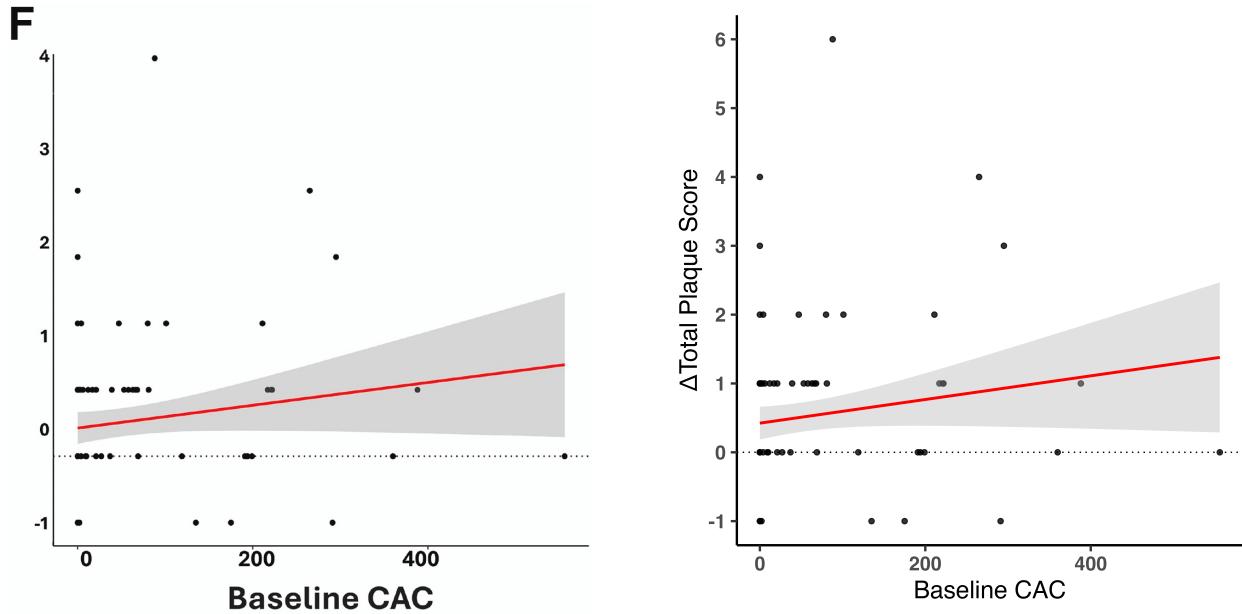


Figure 3: Left: published (y-axis labeled -1 to 4). Right: reproduced (axis –1 to 6); OLS $lm(y \sim x)$ line with SE band.

Issue (error). Axis shown as –1 to 4; underlying data require –1 to 6. Similar to Figure 1B, Panel 2F published panel’s y-axis label is inconsistent with the plotted scale. The label indicates –1 to 4, but the range should be –1 to 6. The same mislabeling of y-axis ticks is visible in panels **2D** and **2E** (not shown). This can mislead readers about the plotted domain and relative spread.

Requested correction.

Correct the y-axis tick labels to reflect the actual plotted range in each panel.

Panels 2D and 2E exhibit the same y-axis label–range mismatch; 2F is shown as the example.

C4 — Conclusions exceed support from reported models

Quoted claims (paper):

“In lean metabolically healthy people on KD, neither total exposure nor changes in baseline levels of ApoB and LDL-C were associated with changes in plaque.” (p. 1)

“... no association between NCPV vs LDL-C or ApoB and **TPS** vs LDL-C or ApoB.” (p. 6)

“changes in and baseline levels of ApoB were not associated with changes in NCPV or TPS as measured by CCTA.” (p. 8)

Issue (inconsistency). These statements bundle multiple non-equivalent associations. Several of those models are not reported. The audit table below maps each claim to the model it implies and whether it was reported.

Claim → model → reported? (audit checklist):

Abstract/Results component	Required model (example)	Reported in paper?
Δplaque vs $\Delta\text{LDL-C}$	$\Delta\text{NCPV} \sim \Delta\text{LDL-C}$	Not reported
Δplaque vs LDL-C exposure	$\Delta\text{NCPV} \sim \text{LDL-C exposure}$	Not reported
Δplaque vs LDL-C baseline	$\Delta\text{NCPV} \sim \text{LDL-C baseline}$	Not reported
Δplaque vs ΔApoB	$\Delta\text{NCPV} \sim \Delta\text{ApoB}$	Reported
Δplaque vs ApoB exposure	$\Delta\text{NCPV} \sim \text{ApoB exposure}$	Not reported
Δplaque vs ApoB baseline	$\Delta\text{NCPV} \sim \text{ApoB baseline}$	Reported
ΔTPS vs $\text{LDL-C / ApoB / exposure}$	$\Delta\text{TPS} \sim (\text{LDL-C or ApoB or exposure})$	Not reported

A review of Table 3 Model Results from the study confirms these omissions: it reports selected ΔNCPV regressions but includes no models with ΔTPS as the outcome and no models using LDL-C baseline or ApoB exposure as independent variables. These models are also absent from the supplementary material.

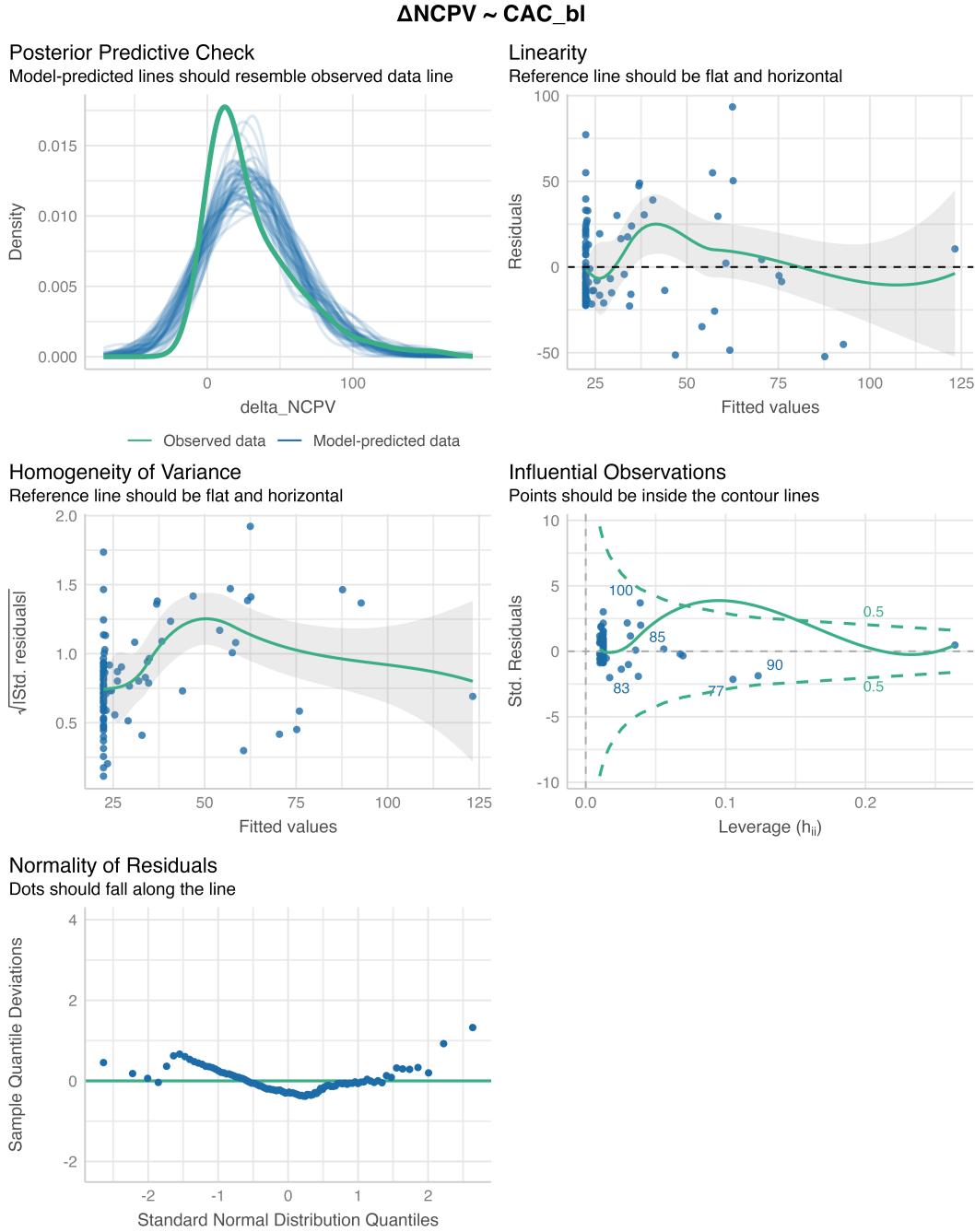


Figure 6: C5b. `performance::check_model(lm($\Delta\text{NCPV} \sim \text{CAC}_{bl}$))` output for the reported change-score model: clear nonlinearity, heteroskedasticity, and non-normal residuals—matching BP/SW/RESET results.

Generalizability. These checks cover plaque-only change-score regressions because of data availability. Given the similar functional form and residual structure, similar violations are plausible for other reported change-score regressions (e.g., with ApoB/LDL-C), but cannot be verified without those covariates.

- Δ NCPV is screened against baseline TPS, PAV, CAC, and NCPV without prespecification, even though these predictors are deterministically related and/or highly correlated. For example, TPS is a composite score derived from plaque features, and PAV uses plaque volume relative to vessel volume, so it scales with increases in non-calcified plaque and shares a common denominator across subjects.¹⁹⁻²² This invites mechanical “plaque-predicts-plaque” findings via shared components.
- Total R^2 (or p-values) from univariable models is not informative about an exposure’s contribution when baseline to follow-up correlation is very high. Specifically, variation in $NCPV_{\text{follow-up}}$ is dominated by $NCPV_{\text{baseline}}$ due to within-person persistence (especially after 1 year), so univariable models such as Δ NCPV \sim ApoB or $NCPV_{\text{follow-up}} \sim$ ApoB will show low **total R^2** by construction. For example, $R^2(\Delta NCPV \sim NCPV_{\text{baseline}}) = 0.49$ while $R^2(NCPV_{\text{follow-up}} \sim NCPV_{\text{baseline}}) = 0.96$ (independent re-analysis; not reported in study). Additionally the ICC² for the follow-up \sim baseline model is 0.91. The relevant quantity is the **partial R^2** for the exposure conditional on baseline (and prespecified covariates) in an ANCOVA model:

$$R_{\text{partial}}^2(\text{ApoB} | NCPV_{\text{baseline}}, \text{covariates}) = \frac{R_{\text{full}}^2 - R_{\text{baseline+covariates}}^2}{1 - R_{\text{baseline+covariates}}^2}$$

Interpreting the total R^2 or significance from a univariable model understates the contribution of ApoB beyond baseline and covariates.²³

- Multiplicity is not addressed despite many hypothesis tests; without a plan, familywise/type-I error is inflated and false positives are expected.
 - Table 3 has \$ \$19 unique tests; repeating the same panel in two subgroups yields \$ \$57 tests overall. The text references Δ TPS analyses not shown, so the total is plausibly >70 .
- No confidence intervals for β coefficients are reported. With modest n and change-score models (which reduce precision), the results do not rule out clinically meaningful effects; “no association” wording is not supported without CIs.
- “Predicts/predictor” implies prognostic (prediction) standards⁶, e.g. multivariable specification, internal validation, calibration/discrimination, which are not presented. If claims are associational, wording should reflect association rather than prediction.

Requested action.

1. **Clarify analytic aim.** State consistently whether analyses are **predictive** or **associative** throughout the manuscript. Use “predicts/predictor” only for validated prognostic models; otherwise use “associated with.”
2. **Declare outcomes and exposures.** Specify one primary outcome and the primary exposure(s); use other plaque metrics (TPS, PAV, CAC) as outcomes or concordance checks, not predictors of NCPV, unless prespecified, otherwise results are driven by shared construct and coupling rather than etiologic signal.
3. **If association is the aim:**

²The intraclass correlation coefficient (ICC) is the proportion of total variance attributable to between-participant differences. With two repeated measures per person, ICC can be estimated from a one-way ANOVA (mean squares). A high ICC (0.91) means baseline explains most follow-up variance.

- **Scale distortion:** the pre-KD term is $\$ \$1/365$ the magnitude of the day-based terms; if converted to days, the term is a near-linear age surrogate times one LDL value.

Note. It appears some Ketogenic Diet Exposure durations are inconsistent across the study.

- Table 1 KD duration: mean **1,642.7 days (\$ \$4.5 y)**.
- Table 3 caption: “LDL-C exposure on a ketogenic diet: mean **5.7 y**.”

Requested action. Confirm KD duration. Use a single time unit (e.g., convert all time to **days** and label units), report a sensitivity dropping the pre-KD term, and consider also reporting the time-weighted mean LDL alongside total duration.

