

August 26, 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,

I am submitting a post-publication concern regarding the article cited above. Because the findings could inform lipid-management decisions, accurate statistical reporting is essential. An independent re-analysis (code and figure checks) identifies material issues that may mislead readers. I respectfully request editorial assessment and correction.

Each concern is documented with evidence and reproduced checks in the attached Appendix (with code in the repository).

#### Critical issues

- **Incorrect Figure scales/IQR (C1–C3):** Fig 1B y-axis is 0–10% while data span 0–20% (halves magnitude); Fig 1A–B IQR band conflicts with the stated sample IQR (lower bound of band dips <0%); Fig 2E–F y-axis should be –1 to 6 (not –1 to 4).
- **Claims exceed reported models (C4):** “No association” is asserted without reporting key models:  $\Delta\text{TPS} \sim \text{ApoB}$ ;  $\Delta\text{TPS} \sim \text{LDL-C}$ ;  $\Delta\text{TPS} \sim \text{LDL-C}$  exposure.
- **Linear-model assumptions violated (C5):** Change-score regressions fail  $\geq 2$  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 **unadjusted univariable change-score** models; field-standard is ANCOVA (follow-up baseline + exposure + age/sex/BP).<sup>1,2</sup> ANCOVA avoids baseline–change artifacts and yields clearer estimates.<sup>3,4</sup> Omitting age/sex/BP (available in the dataset) leaves associations likely confounded.<sup>2,5</sup> No reported 95% CIs for  $\beta$ . “Predicts” is used for association models without validated prognostic performance.<sup>6</sup>
- (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.<sup>7–9</sup>

*Additional items are detailed in the Appendix.*

#### Requested editorial actions

1. **Figure corrections:** Replot Figures 1A–1B and 2E–2F with correct y-axes and IQR 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  $\beta$ , 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 [repository](#)

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

Sincerely,

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## Appendix

### Summary Table of Critical and Major Issues

ID	Area	Core issue	Severity	Ref.
C1–C3	Figures	Incorrect y-axis (Fig 1B, 2E–F); incorrect IQR shading (1A–B)	Critical	C1, C2, C3
C4	Results claims	Claims exceed reported models; $\Delta$ TPS models missing	Critical	C4
C5	Model diagnostics	Linear-model assumptions violated	Critical	C5
M1	Model strategy & multiplicity	Univariable $\Delta$ focus; no multiplicity; predictive wording	Major	M1
M2	Methods (Bayes)	Multiple BF issues (r-scale, no sensitivity, misinterpretation)	Major	M2
M3	Age “mediation” analysis	Age is a confounder; CAC downstream of exposure	Major	M3

**Data provenance.** Individual-level plaque metrics used for reproductions were obtained from the Citizen Science Foundation keto-CTA repository (accessed Aug 23, 2025).<sup>10</sup>

### Critical (C1–C5)

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 labeled 0–10% while data span 0–20%

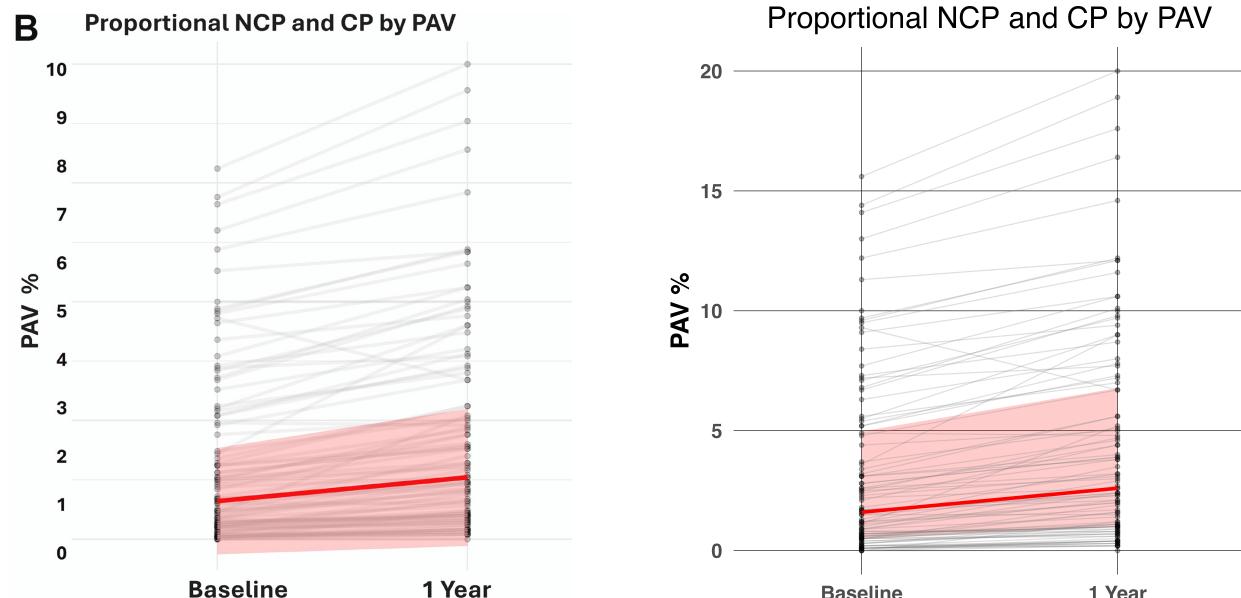


Figure 1: Left: published (axis 0–10%; IQR band mismatched). Right: reproduced (axis 0–20%; IQR  $\approx$  0.3%–1.7%).

**Issue (objective error).** The published panel's y-axis is labeled 0–10% while the plotted scale and data span 0–20%, which halves the apparent magnitude.

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%**.

## C2 — Figures 1A & 1B: shaded IQR band incorrect; caption unclear

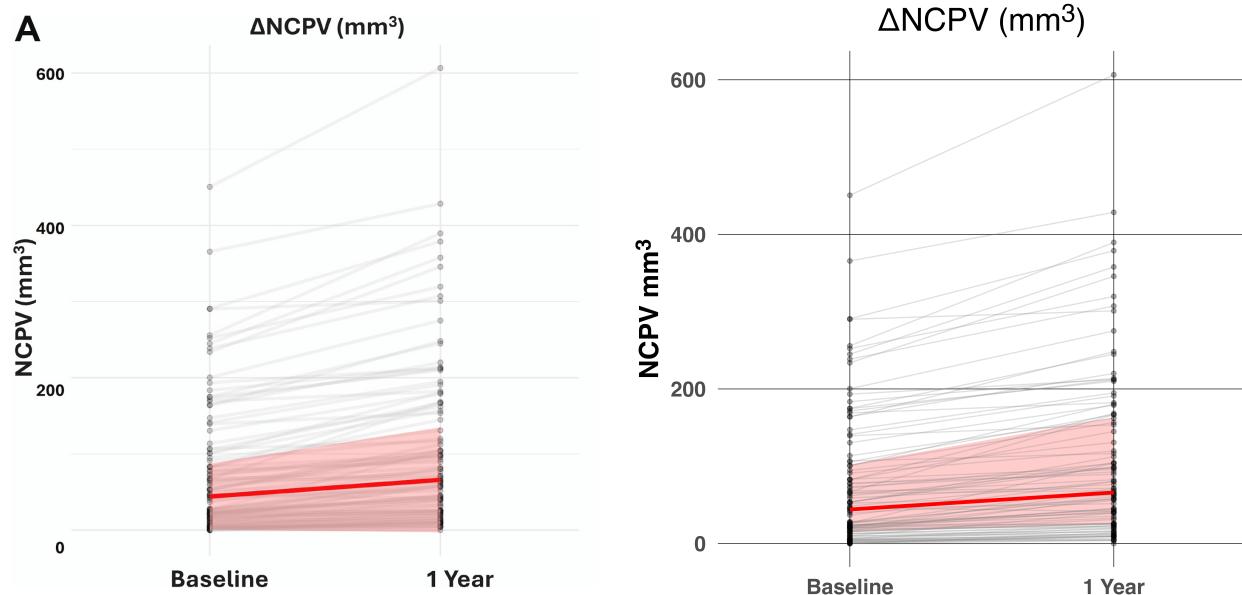


Figure 2: Left: published (IQR shading does not match the sample IQR). Right: reproduced (median  $\approx 18.9 \text{ mm}^3$ ; IQR  $\approx 9.3\text{--}47.0 \text{ mm}^3$ ).

**Issue (objective error).** The shaded IQR band conflicts with the reported sample IQRs. The shaded band is described as the interquartile range (IQR) of **change** (median 0.8%, IQR 0.3%–1.7%). If so, the band should lie entirely **above 0%** (the 25th percentile is 0.3%). In the published panels the band is anchored at 0% in Figure 1A and dips **below 0%** in Figure 1B, which is inconsistent with the reported quantiles and cannot occur if the band truly represents the IQR of paired change.

**Requested correction.**

1. Re-compute and plot the **interquartile range of paired within-person change** from baseline to 1 year (25th–75th percentiles).
2. Revise the caption for both panels to read: “The red line shows the median paired change from baseline to 1 year; the shaded band shows the interquartile range (25th–75th percentiles) of paired change from baseline to 1 year.”

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

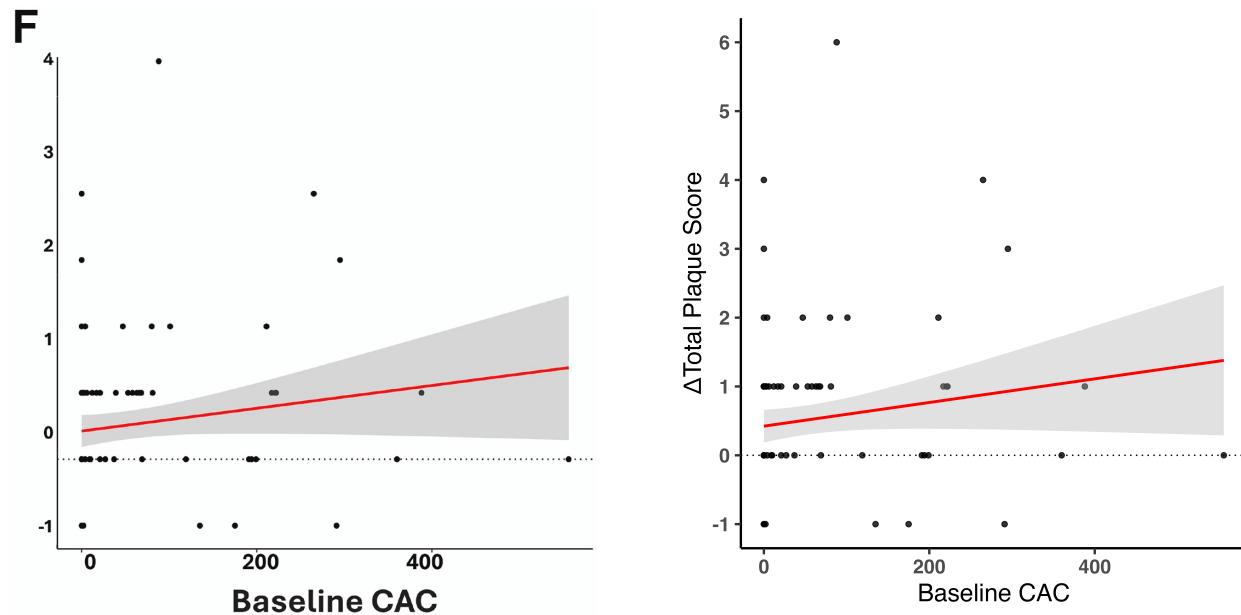


Figure 3: Left: published (y-axis \*\*labeled\*\* –1–4 while the plotted range/ticks correspond to \*\*–1–6\*\*). Right: reproduced (axis –1–6); OLS  $lm(y \sim x)$  line with SE band.

**Issue (objective 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)–4, but the scale used is (–1)–6 (all data are shown). The same mislabeling 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 **label** to reflect the actual plotted range in each panel, (–1)–6.

*Panels 2D and 2E exhibit the same 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 (objective error).** 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?
Δ-plaque vs ΔLDL-C	ΔNCPV ~ ΔLDL-C	Not reported
Δ-plaque vs LDL-C <b>exposure</b>	ΔNCPV ~ LDL-C exposure	Not reported
Δ-plaque vs LDL-C <b>baseline</b>	ΔNCPV ~ LDL-C baseline	Not reported
Δ-plaque vs ΔApoB	ΔNCPV ~ ΔApoB	Reported
Δ-plaque vs ApoB <b>exposure</b>	ΔNCPV ~ ApoB exposure	Not reported
Δ-plaque vs ApoB <b>baseline</b>	ΔNCPV ~ ApoB baseline	Reported
ΔTPS vs LDL-C / ApoB / exposure	ΔTPS ~ (LDL-C or ApoB or exposure)	<b>Not reported</b>

A review of Table 3 Model Results 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.

<b>TABLE 3 Model Results</b>				
	<b>β</b>	<b>P Value</b>	<b>R<sup>2</sup></b>	<b>BF</b>
Estimated LDL-C exposure				
NCPV <sub>final</sub> ~ LDL-C <sub>exp</sub>	0.00	0.88	-0.01	(01) 9.9
PAV <sub>final</sub> ~ LDL-C <sub>exp</sub>	0.00	0.73	-0.01	(01) 9.1
ApoB				
ΔNCPV ~ ΔApoB	0.01	0.91	-0.01	(01) >10.0
ΔNCPV ~ ApoB	0.06	0.33	-0.00	(01) 6.3
Plaque Metrics				
ΔNCPV ~ CAC <sub>bl</sub>	0.18	<0.001	0.33	(10) >10.0 <sup>a</sup>
ΔNCPV ~ NCPV <sub>bl</sub>	0.25	<0.001	0.49	(10) >10.0 <sup>a</sup>
ΔNCPV ~ PAV <sub>bl</sub>	5.5	<0.001	0.43	(10) >10.0 <sup>a</sup>
ΔNCPV ~ TPS <sub>bl</sub>	7.4	<0.001	0.37	(10) >10.0 <sup>a</sup>
ΔNCPV ~ CAC <sub>bl</sub> * ΔApoB				
CAC <sub>bl</sub>	0.18	<0.001	0.33	N/A
ΔApoB	0.08	0.20	N/A	N/A
CAC <sub>bl</sub> : ΔApoB	-0.00	0.23	N/A	N/A
Saturated fat				
ΔNCPV ~ Saturated fat intake	-0.05	0.77	-0.01	(01) 9.8
ApoB ~ Saturated fat intake	-0.03	0.90	-0.01	(01) >10.0
Age mediation analysis				
NCPV <sub>final</sub> ~ Age	3.0	0.004	0.07	(01) 0.3
NCPV <sub>final</sub> ~ Age + Life-LDL-C <sub>exp</sub>	1.93   0.01	0.13   0.16	0.07	(01) 0.3   0.3
NCPV <sub>final</sub> ~ Age + Life-LDL-C <sub>exp</sub> + CAC <sub>bl</sub>	0.02   0.01   0.73	0.98   0.15   <0.001	0.47	(01) 2.7   3.1   >10.0 <sup>a</sup>

<sup>a</sup>Models on CAC are provided for the alternative hypothesis (10). All other models are provided for the null hypothesis (01).

β = estimate (slope magnitude); ΔNCPV = change in noncalcified plaque volume; ApoB = apolipoprotein B; ApoB = ApoB on a ketogenic diet; ΔApoB = ApoB change during the study; BF = Bayes factor; CAC<sub>bl</sub> = CAC at baseline; LDL-C<sub>exp</sub> = LDL-C exposure while on a ketogenic diet (mean 5.7 y); Life-LDL-C<sub>exp</sub> = LDL-C exposure over life course to date; NCPV<sub>final</sub> = noncalcified plaque volume at the end of the study; PAV = percent atheroma volume; R<sup>2</sup> = squared correlation coefficient (explained variability); TPS<sub>final</sub> = total plaque score at the end of the study; other abbreviations as in Table 1.

Figure 4: C4a. Table 3 Model Results — no ΔTPS models are reported.

**Requested correction:** Provide fitted models (coefficients, CIs, diagnostics) for all claimed

relationships, especially  $\Delta\text{TPS}$  vs LDL-C/ApoB/exposure, or amend the conclusions.

### $\Delta\text{TPS} \sim \text{CAC}$ : claimed association not reproduced

Although Table 3 shows no  $\Delta\text{TPS}$  outcome models, the Figure 2 caption asserts an association with baseline CAC.

#### Quoted claim (paper).

“(C, F) Only CAC is associated with changes in NCPV and TPS.” (p. 7)

Reproducing the stated model univariable linear model does not support an association:  $\Delta\text{TPS} \sim \text{CAC}_{bl}$  gives  $\beta = 0.0017$  (95% CI:  $-0.0004$  to  $0.0038$ ),  $P = 0.11$ . Additionally:

- $\Delta\text{TPS}$  has a point mass at 0 with small  $\pm$  values (58/100 zeros).
- Excess-zero test under a rounded-Gaussian  $lm$ :  $z = 5.54$ ,  $P_{boot} < 0.001$  (analytic  $P < 0.001$ ).
- Zero probability varies with baseline CAC: test of  $\Pr(\Delta\text{TPS} = 0 | \text{CAC}_{bl})$  via logistic LRT,  $\chi^2_{(1)} = 5.23$ ,  $P = 0.022$ .
- A two-part (hurdle-at-zero) analysis or other re-specification is warranted.<sup>11</sup>

**Requested correction:** amend the TPS claim, or provide supporting analyses with appropriate modeling (see M1) and full reporting (model specification, coefficients with 95% CIs, and diagnostics).

### C5 — Model assumptions: diagnostics indicate violations

**Scope.** Only plaque metrics were available to audit (CAC, NCPV, TPS, PAV; see **Data provenance**), so lipid/demographic covariates (ApoB, LDL-C, age, sex, BP) were not available. Four univariable change-score models were tested:  $\Delta\text{NCPV} \sim \text{CAC}_{bl}$ ,  $\Delta\text{NCPV} \sim \text{NCPV}_{bl}$ ,  $\Delta\text{NCPV} \sim \text{PAV}_{bl}$ ,  $\Delta\text{NCPV} \sim \text{TPS}_{bl}$ .

#### Quoted claim (paper).

“All linear model assumptions were corroborated with the R function `performance::check_model`.” (p. 3)

**Issue (objective error).** Diagnostics on the reported  $\Delta\text{NCPV}$  models fail  $\geq 2$  tests (e.g., Breusch–Pagan  $P \leq 0.001$ , Shapiro–Wilk  $P \leq 0.001$ ), contradicting the manuscript’s assertion that assumptions were met.

Model	$\beta$	Linearity	Constant Variance	Residual Normality
$\Delta\text{NCPV} \sim \text{CAC}_{bl}$	$\beta = 0.18$ $p = <0.001$	<b>Violation</b>	<b>Violation</b> $p = 0.001$	<b>Violation</b> $p = <0.001$
$\Delta\text{NCPV} \sim \text{NCPV}_{bl}$	$\beta = 0.25$ $p = <0.001$	<b>OK</b>	<b>Violation</b> $p = <0.001$	<b>Violation</b> $p = <0.001$
$\Delta\text{NCPV} \sim \text{PAV}_{bl}$	$\beta = 5.48$ $p = <0.001$	<b>Borderline</b>	<b>Violation</b> $p = <0.001$	<b>Violation</b> $p = <0.001$
$\Delta\text{NCPV} \sim \text{TPS}_{bl}$	$\beta = 7.37$ $p = <0.001$	<b>OK</b>	<b>Violation</b> $p = <0.001$	<b>Violation</b> $p = 0.001$

Figure 5: C5a. Objective tests for four  $\Delta\text{NCPV}$  models; each fails  $\geq 2$  assumptions.

**Context (published letter).** A letter to the editor questioned model assumptions, noting median/IQR summaries (skewed distributions), clustering with no clear linear trend in scatterplots, and the absence of reported diagnostics<sup>12</sup>.

**Results of diagnostics.** Breusch–Pagan rejected homoscedasticity in all four models ( $P \leq 0.001$ ); Shapiro–Wilk rejected residual normality in all four ( $P \leq 0.001$ ); RESET indicated misspecification for  $\Delta\text{NCPV} \sim \text{CAC}_{bl}$  ( $P = 0.031$ ) and was borderline for  $\Delta\text{NCPV} \sim \text{PAV}_{bl}$  ( $P = 0.050$ ). Each model fails at least two assumption checks. Accordingly, the blanket statement that “all assumptions were corroborated” is not supported for these models.

**Example of the cited diagnostic suite.** The output of `performance::check_model` for  $\Delta\text{NCPV} \sim \text{CAC}_{bl}$  shows nonlinearity (non-flat residual smooth), heteroskedasticity (non-constant spread over fitted values), and non-normal residuals (Q–Q tails), consistent with the tests above.

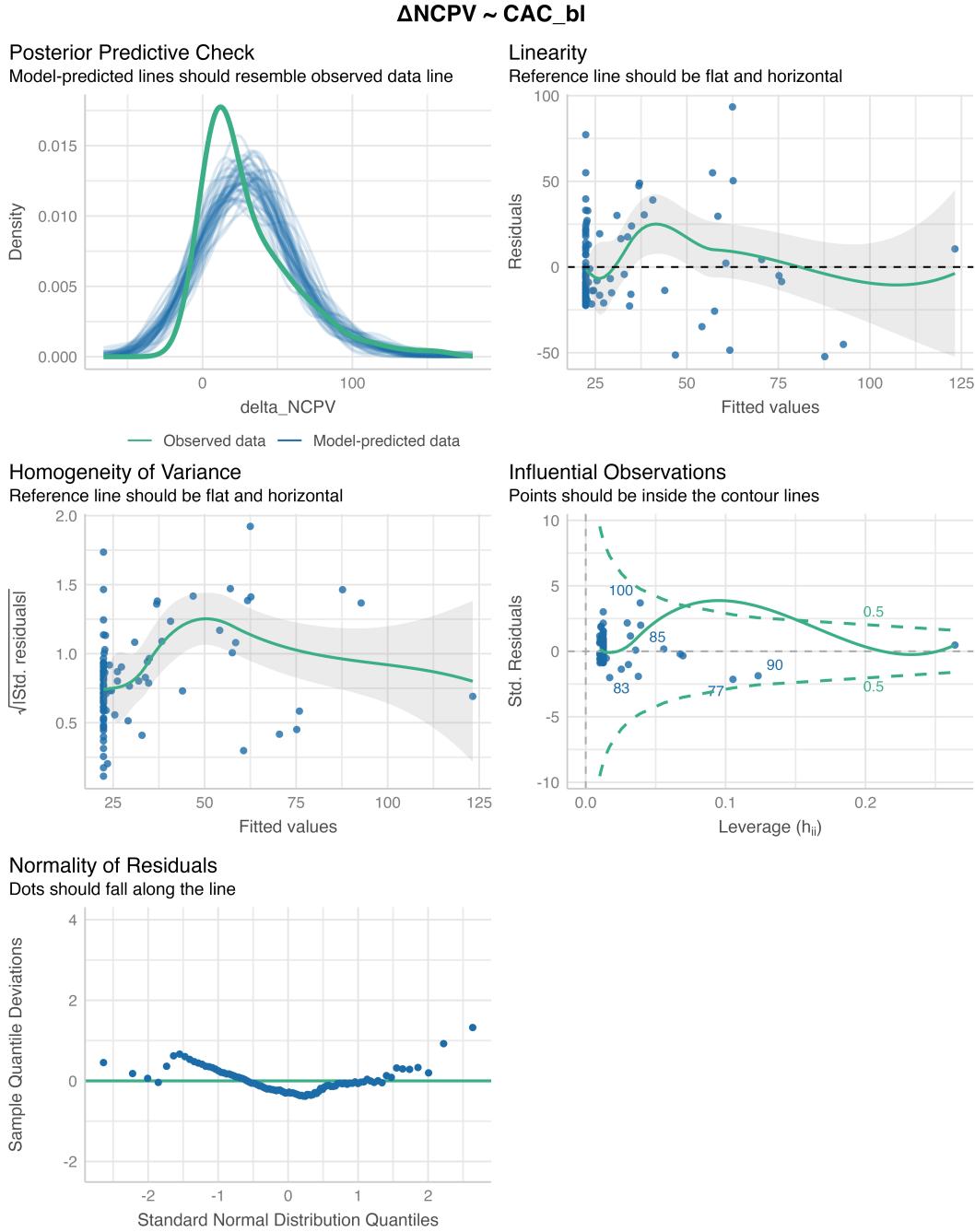


Figure 6: C5b. `performance::check_model(lm( $\Delta\text{NCPV} \sim \text{CAC}_{bl}$ ))` output for the reported change-score model: clear nonlinearity, heteroskedasticity, and non-normal residuals—matching BP/SW/RESET results.

**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.

**Author response (post-publication).** In a response to the letter to the editor regarding model assumptions, the authors stated that they reran all models using robust linear regression (`MASS::rlm`) and that estimates were “consistent” with the published results<sup>13</sup>.

**Assessment.** M-estimator robust regression (e.g., `MASS::rlm`) downweights outliers/heavy tails but does not remedy nonlinearity, heteroskedasticity, or non-normal residuals (no HC/sandwich SEs were used); it also does not supply standard p-values by default. Appropriate fixes require model specification (e.g., splines/transformations) and, where variance is non-constant, heteroskedasticity-consistent (HC/sandwich) SEs. Robust regression alone does not address the violations indicated here.<sup>14,15</sup>

**Requested correction.** Report assumption checks for all fitted models; where violations occur, fit appropriately specified models (e.g., baseline-adjusted follow-up (see M1) with nonlinear terms; splines/transformations where justified; HC/sandwich SEs) rather than relying solely on robust regression, and include diagnostics with the corrected analyses.

## Major (M1–M3)

### M1 — Model strategy, multiplicity, and claim wording

“Linear models on the primary (NCPV) and secondary outcomes were univariable” (p. 3)

“By contrast, baseline CAC was positively associated with a change in NCPV (Figure 2C) ( $\beta = 1.8$ ,  $P < 0.001$ ,  $R^2 = 0.33$ ).” (p. 4)<sup>1</sup>

**Evidence (paper).** Methods describe univariable linear models on change-scores as the primary analysis; Table 3 and accompanying text report numerous univariable regressions across outcomes/exposures. The narrative alternates between “predicts/predictor” and “associated with,” with a single late “exploratory” caveat in the conclusion. No baseline-adjusted follow-up models (ANCOVA) or prespecified covariate set are reported. The manuscript does not report 95% confidence intervals for any  $\beta$  coefficients.

#### Issue (affects interpretation).

- Primary reliance on univariable change-score models invites confounding (e.g., age, sex) and mathematical coupling with baseline<sup>4,16</sup>; change scores compounds measurement error and reduces power. Baseline imbalance and regression-to-the-mean can inflate, attenuate, or reverse associations.<sup>17</sup>
- The approach departs from standard practice<sup>1,2</sup> for progression analyses, where follow-up is modeled as a function of baseline and covariates (ANCOVA) to obtain clinically interpretable effects at a given starting plaque burden.
- Primary models omit adjustment for age, sex, and BP despite availability and known links to plaque progression
- Multiplicity is not addressed despite many tests; without a plan, familywise/type-I error is inflated and false positives are expected.

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<sup>1</sup>Table 3 reports  $\beta = 0.18$  for the corresponding  $\Delta\text{NCPV} \sim \text{CAC}_{bl}$  model (a  $10\times$  difference); please reconcile (units/scaling vs typographical error).

- Table 3 has ~19 unique tests; repeating the same panel in two subgroups yields ~57 tests overall. The text references  $\Delta$ TPS analyses not shown, so the total is plausibly >70.
- No confidence intervals for  $\beta$  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) standards<sup>6</sup>, 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 (Title, Abstract, Methods, Results, Figures/Tables, Conclusions). 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:**
  - Prespecify a primary adjustment set (e.g. baseline value of the same outcome, age, sex as confounders).
  - Report baseline-adjusted follow-up models (ANCOVA: follow-up outcome  $\sim$  baseline outcome + exposure + prespecified covariates) as the main analysis, with effect estimates and 95% CIs; move univariable  $\Delta$ -models to the Supplement.
  - Provide full diagnostics (linearity, residuals, influence; see [C5](#)) and, where variance is non-constant, use heteroskedasticity-consistent (HC) standard errors.
4. **If prediction is the aim:**
  - Present a multivariable prognostic model with internal validation (bootstrap or k-fold).
  - Report calibration and discrimination; do not rely on univariable screens as evidence.
5. **Multiplicity control.** Prespecify the testing family (endpoints  $\times$  predictors  $\times$  subgroups) and apply a strategy (e.g., Holm or FDR); emphasize effect estimates with uncertainty over dichotomous “significance.”

#### **M2 — Bayes-factor analysis: extra-wide r-scale, no sensitivity, misinterpreted evidence**

##### **Quoted claims (paper).**

“the addition of Bayesian inference adds credence to finding that there is no association between NCPV vs LDL-C or ApoB and TPS vs LDL-C or ApoB.” (p. 6)

“Bayes factors were calculated using BayesFactor::regressionBF with default settings and an rscale value of 0.8 to contrast a moderately informative prior with a conservative distribution width” (p. 3)

“these data suggest it is 6 to 10 times more likely that the hypothesis of no association between these variables (the null) is true as compared to the alternative.” (p. 6)

### Issue (affects interpretation)

- The paper’s sole rationale for adding a Bayes-factor analysis is that it “adds credence to finding there is no association”, is circular: a BF has evidential meaning only when the prior and analysis plan are fixed *a priori*.
- `regressionBF` run with `rscale = 0.8`, called “moderately informative.”
  - Package defaults: “medium” = 0.354, “wide” = 0.5, “ultrawide” = 0.707; **0.8 is wider than “ultrawide.”**<sup>7</sup>
- The same extra-wide r-scale is applied to every model without justification
- No prior-sensitivity analysis (a standard recommendation for Bayes-factor reporting<sup>8</sup>) and no indication the BF test was pre-specified.
- Interpreting a BF of 6 to 10 as “6 to 10 times more likely that the hypothesis of no association between these variables (the null) is true” conflates a Bayes factor (a likelihood ratio) with posterior probability. Such a claim requires explicit prior odds.<sup>9</sup>

### Requested action

1. Re-compute Bayes factors with default r-scales (0.354, 0.5, 0.707) and ( $r = 0.8$ ); report all values.
2. Justify the prior for each model or adopt a standard scale.
3. Indicate whether the BF analysis (and r-scale choice) was pre-specified; if post hoc, label it exploratory and provide the rationale for adding it.
4. Revise manuscript text to avoid equating BF with the probability the null is true unless prior odds are specified.

### M3 — Age mediation analysis: causal language and improper adjustment

Age mediation analysis			
$NCPV_{final} \sim Age$	3.0	0.004	
$NCPV_{final} \sim Age + Life-LDL-C_{exp}$	1.93   0.01	0.13   0.16	
$NCPV_{final} \sim Age + Life-LDL-C_{exp} + CAC_{bl}$	0.02   0.01   0.73	0.98   0.15   <0.001	

Figure 7: M3a. Excerpt from Table 3 from the published article showing the sequential models

### Quoted claim (paper):

“There was no association between LDL-C exposure while on a KD (mean 5.7 years) and NCPV or TPS (Figure 2G, Table 3). Estimated lifetime LDL-C exposure was only a significant predictor of final NCPV in the univariable analysis but lost significance when age was included as a covariate (Table 3). Both age and lifetime LDL-C exposure lost significance when baseline CAC was included in the model (Table 3).” (p. 4)

**Issue (affects interpretation).**

Age is a confounder (not caused by LDL), and baseline CAC is plausibly downstream of lifetime LDL exposure. Conditioning on CAC when asking about the total effect of lifetime LDL on NCPV blocks the  $\text{LDL} \rightarrow \text{CAC} \rightarrow \text{NCPV}$  pathway and yields only a direct effect; it does not constitute a mediation analysis<sup>18</sup>. No mediator model or indirect effect with CI was reported. Given that the paper's lifetime-LDL metric embeds age (see O2), collinearity is expected and "loss of significance" is not evidence of no association.

**Requested action.**

Specify the causal estimand with a DAG. If mediation is intended: fit Mediator  $\sim$  Exposure + Age and Outcome  $\sim$  Exposure + Mediator + Age and report indirect/direct/total effects with CIs. If the target is the total effect of lifetime LDL on NCPV, do not adjust for baseline CAC; report models with/without age (confounder), with diagnostics and collinearity checks.

## Other — Additional analysis & reporting issues

ID	Sev.	Location	Issue (concise)	Ref.	Requested action
O1	Other	Methods	Percent change reported as <b>ratio of medians</b> , not per-participant	§O1	Provide per-subject % change (or both) with summary + CI
O2	Other	Measurements	“Lifetime LDL-C exposure” mixes time units (days + years)	§O2	Recalculate exposure with a single time unit
O3	Other	Data/QC	<b>Inconsistent durations</b> distort exposure denominators	§O3	Audit durations; rerun exposure-based analyses
O4	Other	Table 1	<b>Impossible IQR</b> for total cholesterol (301–337 mg/dL; median = 338 mg/dL)	§O4	Correct IQR; verify all baseline stats & units

### O1 — Percent-change metric: ratio of medians, not per-subject

#### Quote

“The median change in NCPV was 18.9 mm<sup>3</sup> (IQR: 9.3–47.0 mm<sup>3</sup>) and the median change in PAV was 0.8% (IQR: 0.3%–1.7%). Compared to baseline, these represent a **43% and 50% change**, respectively.” (p. 4)

#### Issue (clarification)

The paper’s “43%” (NCPV) and “50 %” (PAV) values use a **non-standard percent-change metric**, a *ratio of medians*:

$$\frac{\text{median}(\Delta)}{\text{median}(\text{baseline})} \times 100\%.$$

This definition differs from the customary per-participant percent change and can under- or over-state the typical effect (see table below).

Outcome	Ratio-of-medians	Median % change (per subject)		Mean % change
		43%	49.2%	
NCPV	43%	49.2%	81.4%	
PAV	50%	47.3%	80.7%	

(participants with baseline = 0 excluded from % change calculations)

#### Requested action

1. Report per-subject percent change

$$\% \Delta X_i = \frac{X_{1y,i} - X_{bl,i}}{X_{bl,i}} \times 100$$

with median, IQR, and 95% CI.

2. Clarify that the published 43% / 50% are ratios of medians.
3. State how zero baselines were handled.

## O2 — Exposure metric: construction and units inconsistent

### Quoted method (paper).

“LDL-C exposure on a KD was calculated by summing the products of the reported days on a KD prior to study commencement and baseline LDL-C on a KD plus the study follow-up days by their final LDL-C. Estimated **lifelong** LDL-C additionally included the product of **age** upon commencing a KD and pre-KD LDL-C.” (p. 3)

$$\text{Life-LDL}_{\text{exp}} = \text{LDL}_{\text{KD-exp}} + \text{Age}_{\text{KD-start}} \cdot \text{LDL}_{\text{preKD}}$$

*Unit (as written):* dimensionally inconsistent

### Issue (clarification)

- **Dimensional inconsistency:** the “lifetime” sum mixes **days** and **years**; these are not commensurate.
- **Scale distortion:** the pre-KD term is  $\sim 1/365$  the magnitude of the day-based terms unless age is converted; if converted to days, the term becomes a near-linear **age surrogate** times one LDL value.
- **Interpretability:** model coefficients are not in a single unit ( $\text{mg} \cdot \text{day/dL} + \text{mg} \cdot \text{year/dL}$ ), hindering effect-size meaning and comparisons.

**Requested fix.** 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**:

$$\overline{\text{LDL}} = \frac{\sum_i \text{LDL}_i \Delta t_i}{\sum_i \Delta t_i}$$

alongside total duration.

## O3 — Exposure durations inconsistent across study

### Issue (clarification)

- Table 1 KD duration: **1,642.7 days (~4.5 y)**.
- Table 3 caption: “LDL-C exposure ... mean **5.7 y**.”
- Abstract median KD duration: **1,302 days**

Discrepant durations feed into exposure metrics and bias effect estimates.

### Requested action

1. Audit raw duration variables; reconcile KD start date, follow-up days, and exposure windows.
2. Re-calculate exposure metrics (e.g., time-weighted mean LDL) and rerun analyses with corrected durations.

3. Report both mean and median durations in consistent units (days or years).

#### **O4 — Table 1 Baseline Characteristics incorrect IQR**

“Total cholesterol (mg/dL)  $355.1 \pm 89.9$ ; median 338 (IQR 301–**337**)” — Table 1

##### **Issue (clarification)**

The reported median (338 mg/dL) lies **outside** the stated IQR (301–337 mg/dL), which is mathematically impossible.

##### **Requested action**

Correct the IQR and verify all baseline statistics (units, rounding, transcription).

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