p-values: beyond polemics to practical proposals

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Wed 15th July, IBC Seoul

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Acknowledgements

Michal Abrahamowicz (McGill, Canada)

Els Goetghebeur (Ghent, Belgium)

Willi Sauerbrei (Freiburg, Germany)

Victor Kipnis (NIH, USA)

Carsten Schmidt (Greifswald, Germany)

on behalf of the STRATOS p-values working group

Overview

- Criticism of use and reporting of p-values
- Reproducibility and p-values
- Use of p-values in three broad modelling aims
  - Descriptive
  - Predictive
  - Explanatory / Causal
- Example: descriptive analysis
- Discussion

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Critique of p-values

- Large literature on misuse of p-values
  - 2019 paper by Amrhein et al. [1] arguing for retiring ‘statistical significance’
  - ‘confidence interval’ should be renamed to ‘compatibility interval ’
  - Emphasize the need to focus on estimates and the uncertainty in them, including p-values

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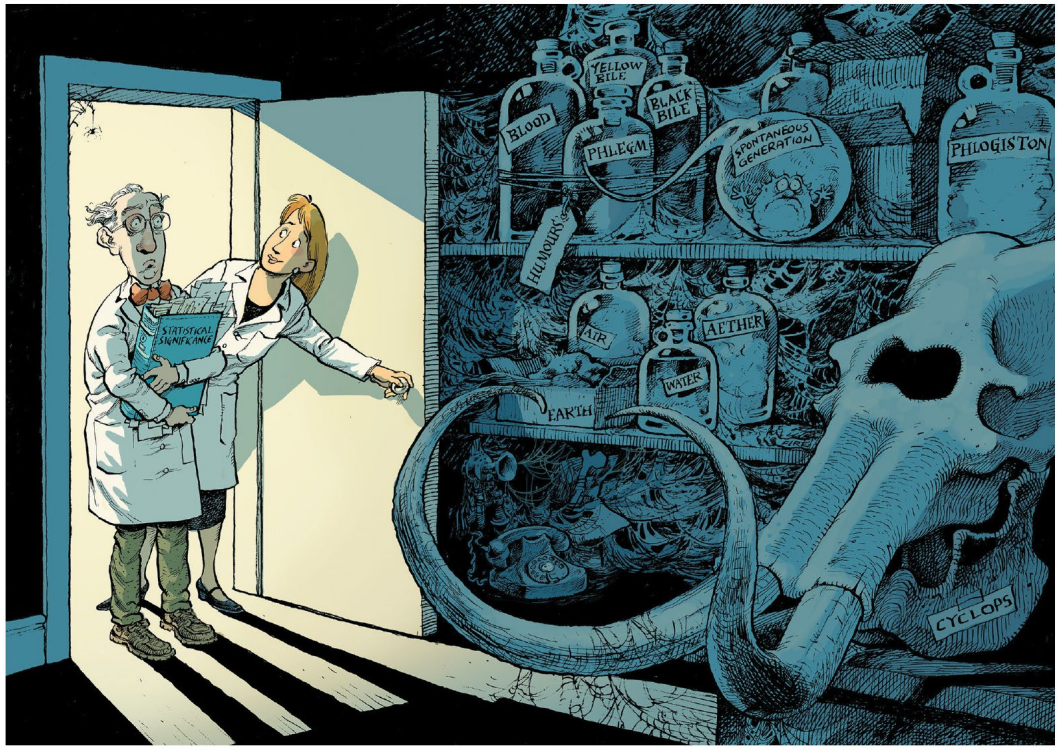

Retire statistical significance

Valentin Amrhein, **Sander Greenland**, **Blake McShane** and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

Critique of p-values

- Large literature on misuse of p-values
  - 2019 paper by AMR [1] arguing for retiring ‘statistical significance’
  - ‘confidence interval’ should be renamed to ‘compatibility interval ’
  - Emphasize the need to focus on estimates and the uncertainty in them, including p-values

- Well written, but more guidance needed
  - Principal issue is lazy use and (deliberately?) misleading reporting

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Some consequences

- Over-interpretation of point estimates may be an issue:
  - E.g. [2], Methods: “To avoid placing too much emphasis on statistical significance, we emphasize the strength of associations… as well [cite AGM].”
  - Then, Results section explicitly interprets OR = 5.456, with 95% CI: 0.3–90.6 as “5 times” risk increase
  - Re-constructed p-value is about 0.24
- More driving change needed: Amrhein et al. cited but advice often ignored:
  - E.g. [3] cite AGM, but then report “significant associations” or “effects” in the conventional way:

    ‘… AI/AN women were found to be significantly more likely to have a high-risk (OR=1.28; 95% CI: 1.01-1.66)’

Can STRATOS help?

- STRATOS stands for Strengthening Analytical Thinking for Observational Studies
  - Hypothesis testing, inference and reporting are central to this
  - We should have something to say
- Discussion highlighted concern that the AMR paper could be used by those who wish to jettison more formal inference
  - The current situation may be bad, but it could be worse!
- Therefore, we agreed to develop a manuscript which aimed to provide more practical guidance
  - We concluded the most appropriate way was to illustrate the principled use of p-values, testing and statistical significance in carefully chosen examples

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Reproducibility and p-values

Reproducibility is, rightly, an increasing focus of efforts to improve research. However, many researchers are not aware that the p-value is not a reproducible statistic.

For a sample mean from a population with known variance 1, the table shows the probability of the p-value from a second experiment being < 0.05, if the true mean is equal to that observed in the first experiment:

p-value from 1st experiment:	**0.05**	**0.01**	**0.005**	**0.001**
Pr(p<0.05) in repeat of experiment:	0.5	0.73	0.8	0.91

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Use of p-values & significance testing in research

Large phase-III randomised trials are used to decide whether to adopt new treatments – in this setting, formal hypothesis testing is broadly agreed to be appropriate: reproducibility comes from the design which controls the type-1 error and power.

However, observational research has much broader aims, main aims are classified as [e.g., 4]:

- Descriptive
- Predicative modelling
- Explanatory / Causal inference

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p-values supporting reproducible research:

Follow reporting guidelines [e.g., 6], especially relating to

- Presenting p-values with parameter estimates and confidence intervals.
- Not interpreting $p \geq \alpha$ as evidence of the 'lack of effect' but, instead, as 'insufficient evidence to reject the null hypothesis'.
- Not interpreting parameter estimates, confidence intervals, and p-values isolated from previous / related findings
- Not comparing effect sizes between groups, or across studies, using p-values.

Focus on reporting both methodology (i.e. methodological decisions) and results [7] so that analyses are truly reproducible.

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Exploratory modelling - Example

- Understand the relationship between a continuous outcome and ten continuous and binary variables in a large dataset
- Key tasks: select variables and select functional form
  - Use pre-defined choice of tuning parameters to control both the number of variables, and the complexity of the functional form (including interactions)
  - This can take the form of penalty functions (e.g. lasso); choice of number and position of knots in splines
  - In Multivariable Fractional Polynomial (MFP) modelling, p-values are the tuning parameters [8]

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p-values as tuning parameters

- The MFP procedure uses two tuning-p-values:

    1. for variable selection: this controls how strong a variable's (potentially non-linear) effect needs to be for inclusion;

    2. To select functional form (functional selection procedure): are we interested to identify small deviations from linearity (large p-value) or would it be acceptable to oversee smaller deviations (small p-value) and specify a simpler model with a linear function.

For the multivariable analysis, MFP starts with the full model and combines backward elimination with the functional selection procedure for continuous variables.

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Comments I:

- These p-values are not sacred ‘p-value thresholds’ but **model-complexity tuning parameters**.
- The selected model is not ‘the final truth’ but the primary selected MFP model.
- Sensitivity and stability analyses are important:
  - Sensitivity analysis: using different model-complexity p-values
  - Stability analyses: bootstrap procedures could be used
- It is important that all steps of this process are reported, ideally by using a structured reporting approach.

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Comments II:

- Ideally scientific knowledge is used to pre-specify a model.
- However, in most analyses, data dependent decisions are still needed, although parts of the model may be ‘known’. For the ‘unknown’ part, tuning p-values play an important role for model building.
- It is often argued that p-values should be replaced by information criteria (eg AIC, BIC) but that does not solve the issue. For example, for a one degree of freedom term, 0.157 corresponds approximately to AIC. P-values allow suitable choices according to the main of an analysis.
- Emphasis needs to be on improved methodological reporting, rather than debates over the choice of p-values [e.g. 7].

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Explanatory / Causal analysis

Useful to distinguish between
(a) identifying confounders and selecting their functional form versus
(b) testing for the causal effect of the exposure/intervention.

– For (a), since the aim is to balance the covariates in the dataset (e.g. using a propensity score), using p-values (viewed as a tuning parameter) for model selection is acceptable; pre-specification of the number of tests is not required.

– For (b), because the result may contribute to a decision-making process, akin to trials, pre-specification in the protocol is important, as is *a-priori* specification of the alternative hypothesis (minimally important clinical difference) and estimation of the power to detect this. Pilot studies may be helpful here [see, e.g., 9]

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Explanatory / Causal analysis: pre-specify!

Some **RCTS** exploit p-values by combining co-or dual primary outcomes with **hierarchical testing**. They control the overall type I error by (re)assigning alpha portions over different (sub) hypotheses leading to boundaries for a network of p-values. Such **gatekeeping strategies**, yield additional evidence on a set of estimands while avoiding undue false positives

With **observed exposures** and focus on target trial emulation and **causal estimands, safe-guarding the causal null** is still critical, but now hinges on (untestable) causal assumptions, e.g. involving Instrumental Variables or no-unmeasured confounding.

To **defend conditional independence** in a DAG, or variable selection in adjusted models outcome or propensity model, simple p-values are less helpful. **Confounders** draw on their *joint* adjusted association with exposure & outcome.

p-values provide **an informal distance metric** when checking covariate balance and comparing their means among the treated and non-treated cohorts

Discussion

- Reproducibility is a key characteristic of good research. To support this we need
  - Increased focus on registration of studies
  - Publication of study protocols, including statistical analysis plans
  - Improved methodological reporting (as well as reporting of results)
- Within this context, point estimates, confidence intervals and p-values are all indispensable inferential tools : p-values are especially useful for joint tests
- P-values can also have a distinct use as tuning parameters in model building
  - Clear reporting is important to avoid confusion
- P-values are not reproducible: type-1 error and power are
- Template examples are a key tool to change practice
- Journals have a key role to play –
  papers with poorly reported methods should be rejected without review

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