Systematic review of variable and functional form selection in Covid-19 prognostic models

JSM 2025

6 August 2025

Michael Kammer, Gregor Buch, Marc Henrion and Georg Heinze on behalf of STRATOS TG2

STRATOS INITIATIVE

STRATOS
Topic Group 2

STRATOS (TG2)

STRengthening Analytical Thinking for Observational Studies

https://www.stratos-initiative.org/

Topic Group 2:

Selection of variables and functional forms in multivariable analysis

TG2 Aim: Derive guidance for variable and function selection in multivariable analysis.

Chairs: Georg Heinze, Aris Perperoglou, Willi Sauerbrei

Interrelated challenges (Harrell 2001, Sauerbrei et al. 2007)

- Selection of variables for inclusion in a multivariable model → identification of influential variables.
- Choice of the functional forms for continuous variables → insight into relationship with the outcome.

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First challenge:

Selection of variables for inclusion in a multivariable explanatory model.

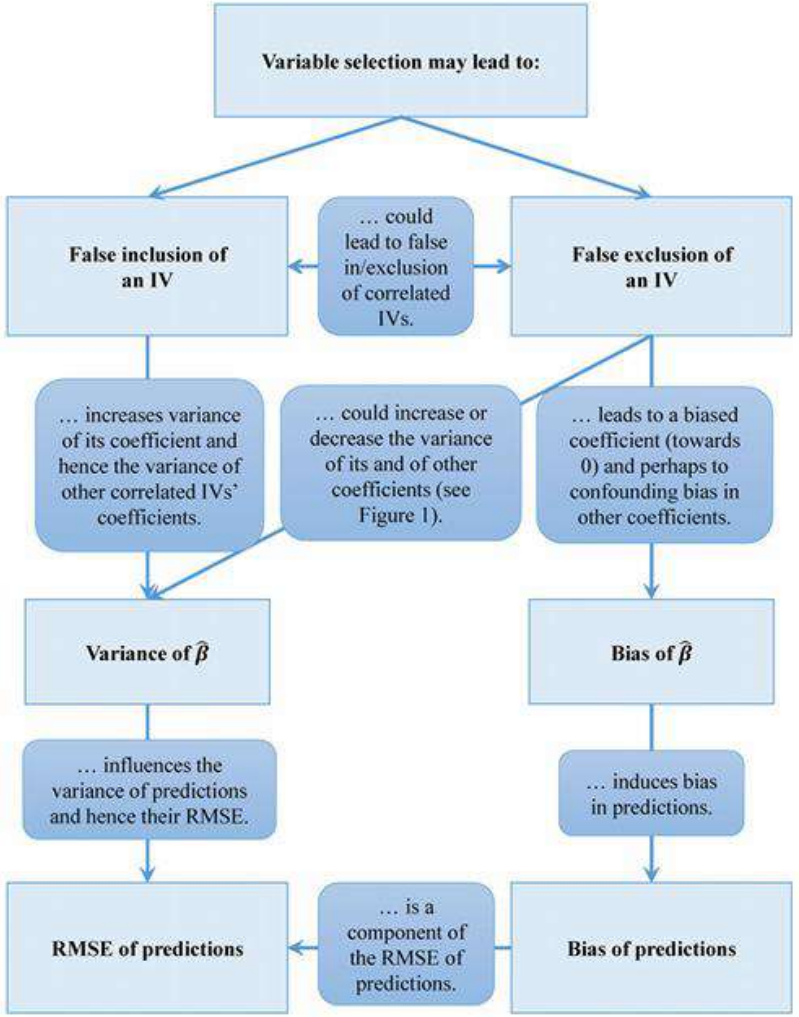
Multivariable models typically built through a combination of

- A priori inclusion of well established ‘predictors’.
- A posteriori data-driven selection of variables.

Consensus that **all model building strategies have weaknesses** (Miller 2002), but no consensus on the relative advantages and disadvantages of particular strategies.

Advanced methods (e.g. regularization techniques, resampling based methods, …) exist, but

- **No agreement, no state of the art.**
- **Need for clearer guidance and neutral, systematic comparisons.**



Heinze, G., Wallisch, C., & Dunkler, D. (2018). Variable selection–a review and recommendations for the practicing statistician. *Biometrical journal*, *60*(3), 431-449.

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Second challenge:

Choice of the functional forms for continuous variables.

The effects of continuous predictors are typically modeled by

- Assuming linear relationships (possibly after simple transformations).
- Categorizing.

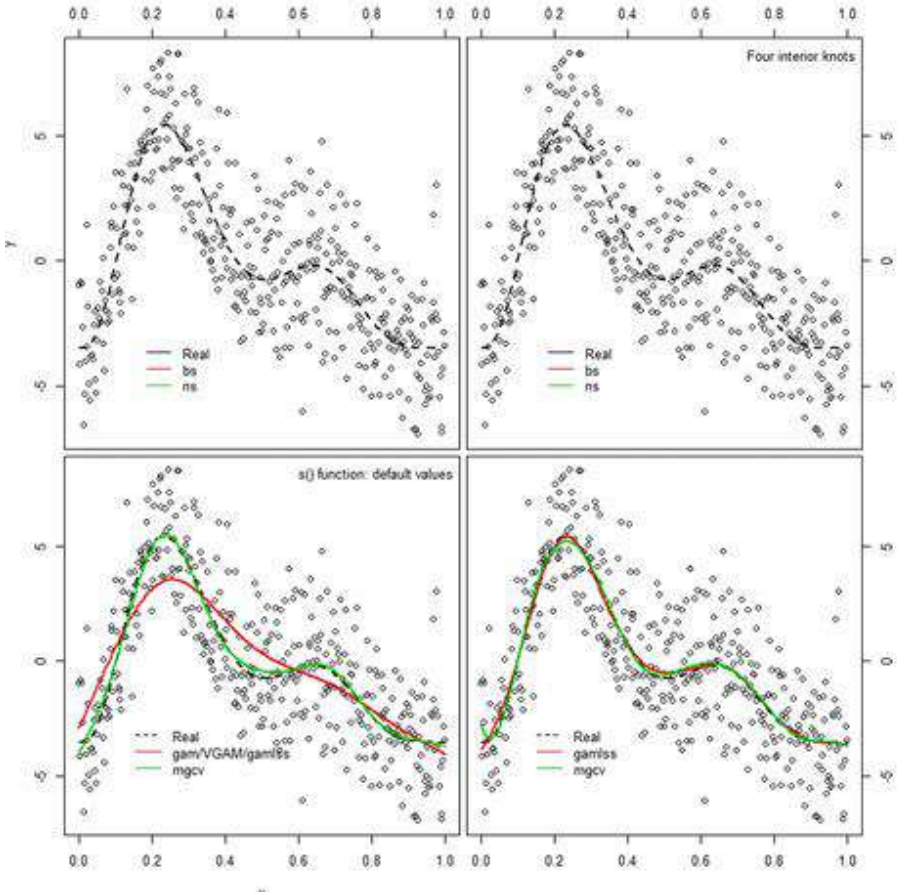
Problematic if reasons for and assumptions of such conventional approaches are not discussed and assessed.

Flexible modeling techniques have been developed and, for multivariable analysis, incorporated in GAMs:

- Fractional polynomials (Royston and Altman 1994, Royston and Sauerbrei 2008).
- Splines (many 'flavours'; Boer 2001, Harrell 2001, Wood 20017, Hastie and Tibshirani 1990).

But:

- **No agreement, no state of the art.**
- **Need for clearer guidance and neutral, systematic comparisons.**



Perperoglou, A., Sauerbrei, W., Abrahamowicz, M., & Schmid, M. (2019). A review of spline function procedures in R. *BMC medical research methodology*, *19*(1), 46.

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Selected outputs

Sauerbrei *et al. Diagnostic and Prognostic Research* (2020) 4:3
https://doi.org/10.1186/s41512-020-00074-3

Diagnostic and Prognostic Research

COMMENTARY Open Access

State of the art in selection of variables and functional forms in multivariable analysis—outstanding issues

Willi Sauerbrei[1*], Aris Perperoglou[2], Matthias Schmid[3], Michal Abrahamowicz[4], Heiko Becher[5], Harald Binder[1], Daniela Dunkler[6], Frank E. Harrell Jr[7], Patrick Royston[8], Georg Heinze[6] and for TG2 of the STRATOS initiative

Heinze *et al.*
BMC Medical Research Methodology (2024) 24:178
https://doi.org/10.1186/s12874-024-02294-3

BMC Medical Research Methodology

RESEARCH Open Access

Regression without regrets –initial data analysis is a prerequisite for multivariable regression

Georg Heinze[1*], Mark Baillie[2], Lara Lusa[3,4], Willi Sauerbrei[5], Carsten Oliver Schmidt[6], Frank E. Harrell[7], Marianne Huebner[8] on behalf of TG2 and TG3 of the STRATOS initiative

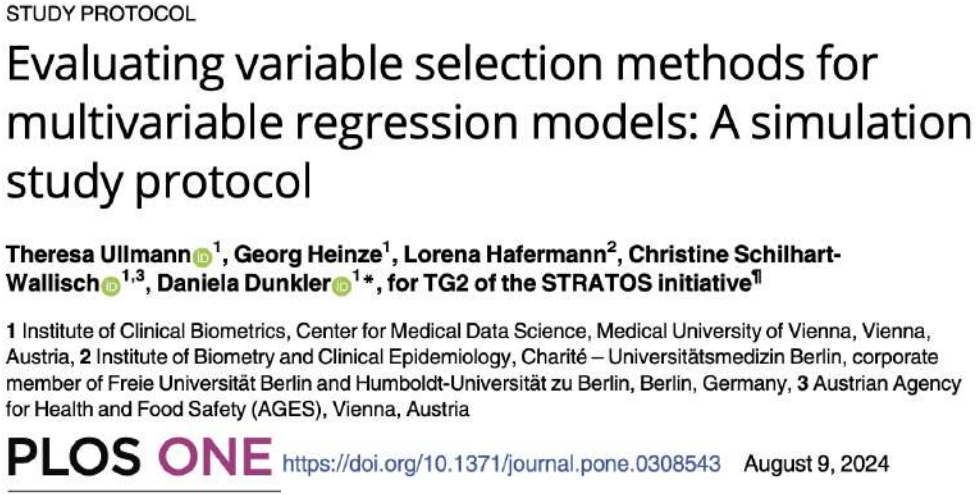
REVIEW Open Access

A review of spline function procedures in R

Aris Perperoglou[1*], Willi Sauerbrei[2], Michal Abrahamowicz[3], Matthias Schmid[4] on behalf of TG2 of the STRATOS initiative

Perperoglou *et al. BMC Medical Research Methodology* (2019) 19:46
https://doi.org/10.1186/s12874-019-0666-3

BMC Medical Research Methodology



STUDY PROTOCOL

Evaluating variable selection methods for multivariable regression models: A simulation study protocol

Theresa Ullmann[1], Georg Heinze[1], Lorena Hafermann[2], Christine Schilhart-Wallisch[1,3], Daniela Dunkler[1]*, for TG2 of the STRATOS initiative[¶]

1 Institute of Clinical Biometrics, Center for Medical Data Science, Medical University of Vienna, Vienna, Austria, **2** Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, **3** Austrian Agency for Health and Food Safety (AGES), Vienna, Austria

PLOS ONE https://doi.org/10.1371/journal.pone.0308543 August 9, 2024

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Towards recommendations / guidelines:

Research needed!

1. Investigation and comparison of the **properties** of **variable selection strategies**
2. Comparison of **spline procedures** in **univariable and multivariable contexts**
3. How to model one or more variables with a **‘spike-at-zero**’?
4. Comparison of **multivariable procedures** for **model and function selection**
5. Role of **shrinkage to correct for bias** introduced by data-dependent modelling
6. Evaluation of new approaches for **post-selection inference**
7. **Adaptation** of procedures for **very large sample sizes** needed?

Covid-19 Prognostic Modelling Review

Motivation: COVID PRECISE study

RESEARCH

OPEN ACCESS

Check for updates

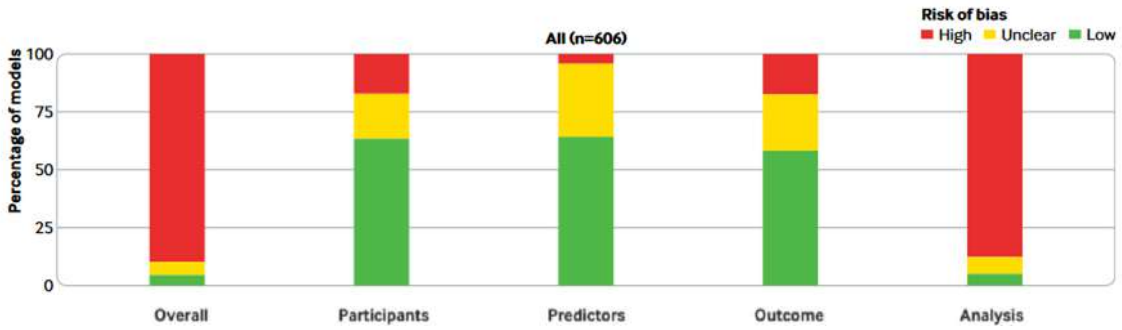
FAST TRACK

Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal

Laure Wynants,[1,2] Ben Van Calster,[2,3] Gary S Collins,[4,5] Richard D Riley,[6] Georg Heinze,[7] Ewoud Schuit,[8,9] Marc M J Bonten,[8,10] Darren L Dahly,[11,12] Johanna A Damen,[8,9] Thomas P A Debray,[8,9] Valentijn M T de Jong,[8,9] Maarten De Vos,[2,13] Paula Dhiman,[4,5] Maria C Haller,[7,14] Michael O Harhay,[15,16] Liesbet Henckaerts,[17,18] Pauline Heus,[8,9] Michael Kammer,[7,19] Nina Kreuzberger,[20] Anna Lohmann,[21] Kim Luijken,[21] Jie Ma,[5] Glen P Martin,[22] David J McLernon,[23] Constanza L Andaur Navarro,[8,9] Johannes B Reitsma,[8,9] Jamie C Sergeant,[24,25] Chunhu Shi,[26] Nicole Skoetz,[19] Luc J M Smits,[1] Kym I E Snell,[6] Matthew Sperrin,[27] René Spijker,[8,9,28] Ewout W Steyerberg,[3] Toshihiko Takada,[8] Ioanna Tzoulaki,[29,30] Sander M J van Kuijk,[31] Bas C T van Bussel,[1,32] Iwan C C van der Horst,[32] Florien S van Royen,[8] Jan Y Verbakel,[33,34] Christine Wallisch,[7,35,36] Jack Wilkinson,[22] Robert Wolff,[37] Lotty Hooft,[8,9] Karel G M Moons,[8,9] Maarten van Smeden[8]

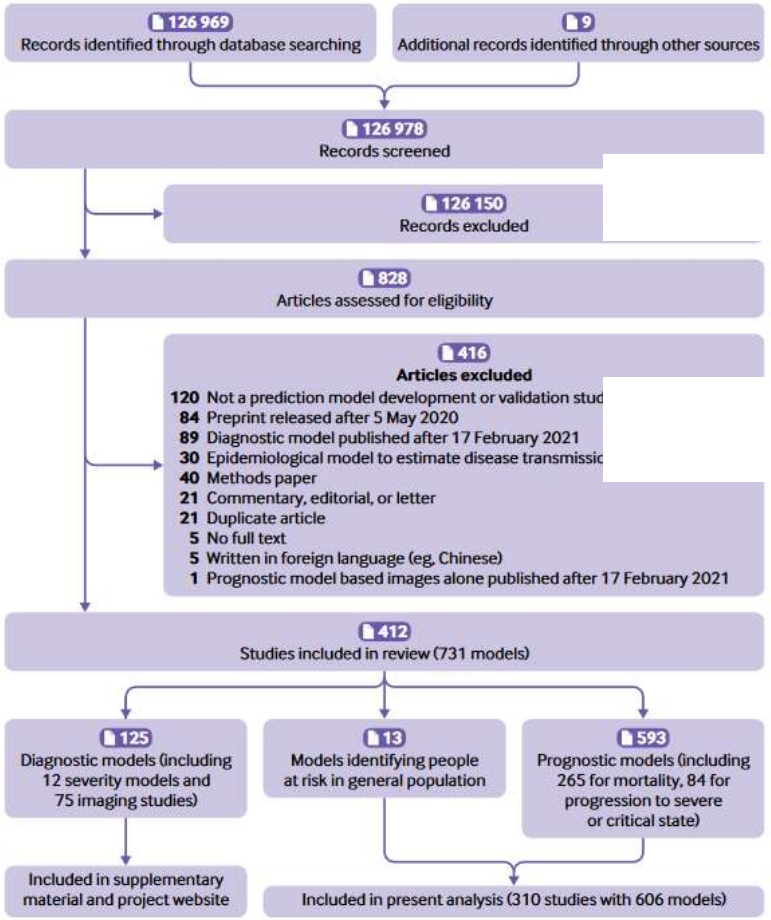
BMJ: first published as 10.1136/bmj.m1328 on 7 April

(Wynants et al 2020)



Full results database available
https://www.covprecise.org/

- 731 models from 412 studies
- Repeated updates during epidemic
- Risk of bias assessment (ROB)
- > 3000 citations



Stratos TG2 oriented re-review

COVID PRECISE reflects **methods researchers rely on in times of crisis,** when robust, reliable models are needed.

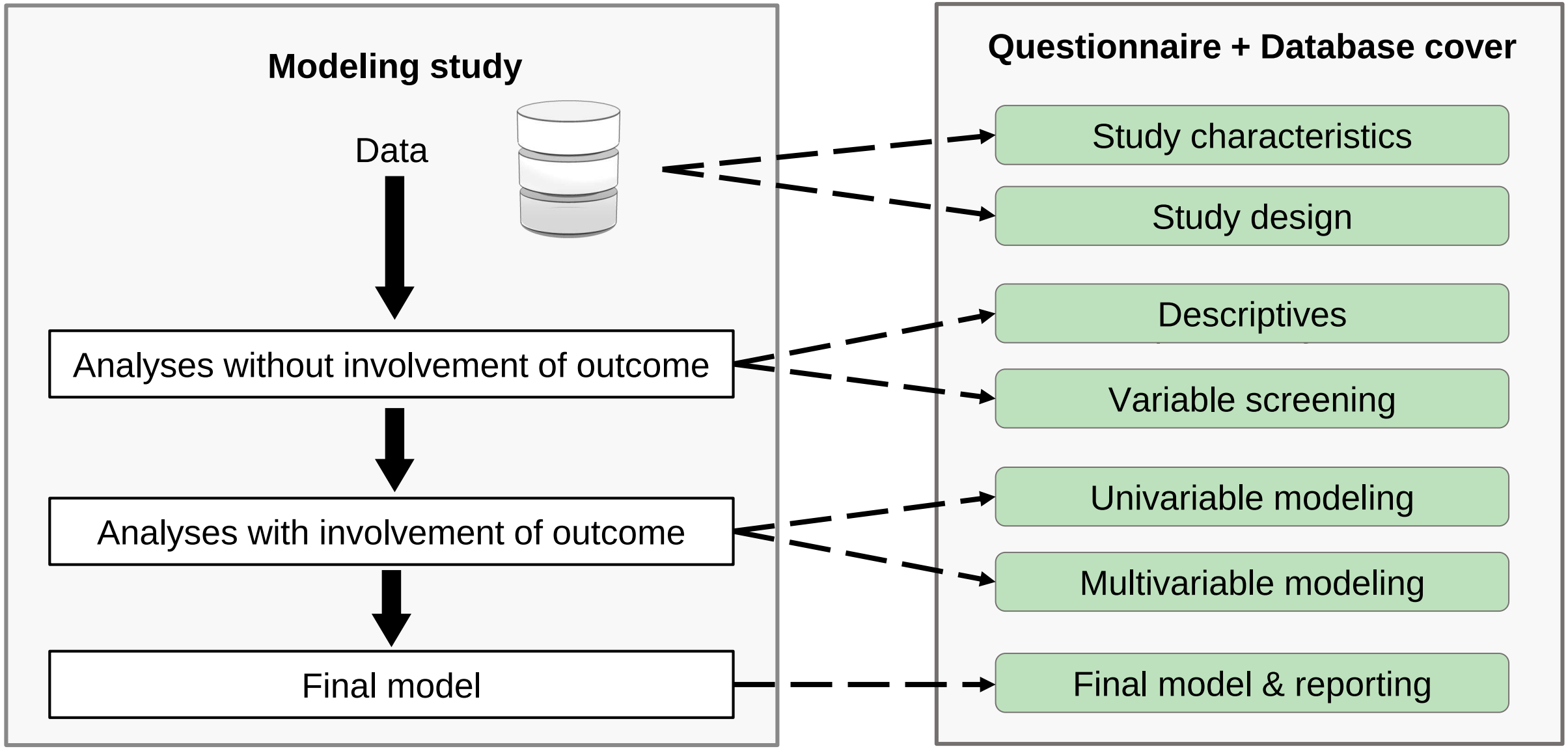
Hence, it allows us to:

Identify approaches in regression-based prediction models for COVID-19 outcomes to:

1) **select predictors** for regression models, and
2) **model the effects** of predictors, in particular the use of **non-linear functional forms** and the use of **interactions** between predictors.

This extends the data with details on the procedures which were not recorded for ROB.

Our model of a modelling workflow



Our re-review

Stage 0: Develop protocol and extraction sheet

- Input from original study authors and TG2 members
- Two pilot studies with 4 papers and several reviewers to test protocol
- Focus on regression based **prognostic** models. Excluded (from 731):
  - 124 diagnostic models,
  - 442 machine learning / non-parametric methods,
  - 232 external validations of existing models.

181 studies remain for re-review

For each a primary model was chosen by pre-defined criteria

Our re-review

Stage 0: Develop protocol and extraction sheet

Stage 1: Extract relevant data from existing database

- Study characteristics, Basic model characteristics, Reporting
- Provides background info for further extraction stages
- Done by core team

Our re-review

Stage 0: Develop protocol and extraction sheet

Stage 1: Extract relevant data from existing database

Stage 2: Re-extract data

- Invite reviewers for double review followed by consensus
- Extract details on variable selection & functional forms
- Done in pairs as double-review followed by consensus

Our re-review

Stage 0: Develop protocol and extraction sheet

Stage 1: Extract relevant data from existing database

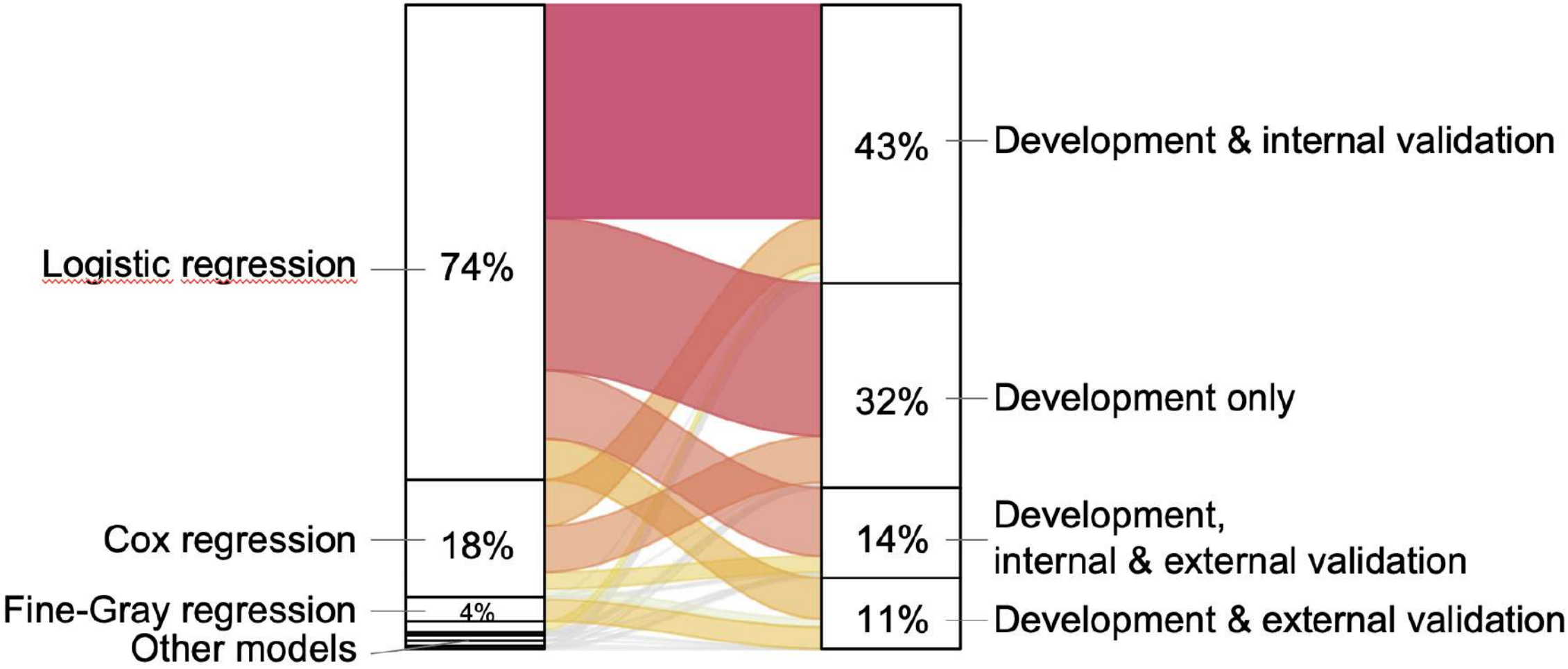
Stage 2: Re-extract data

Stage 3: Data consolidation & analysis

- Done by core team

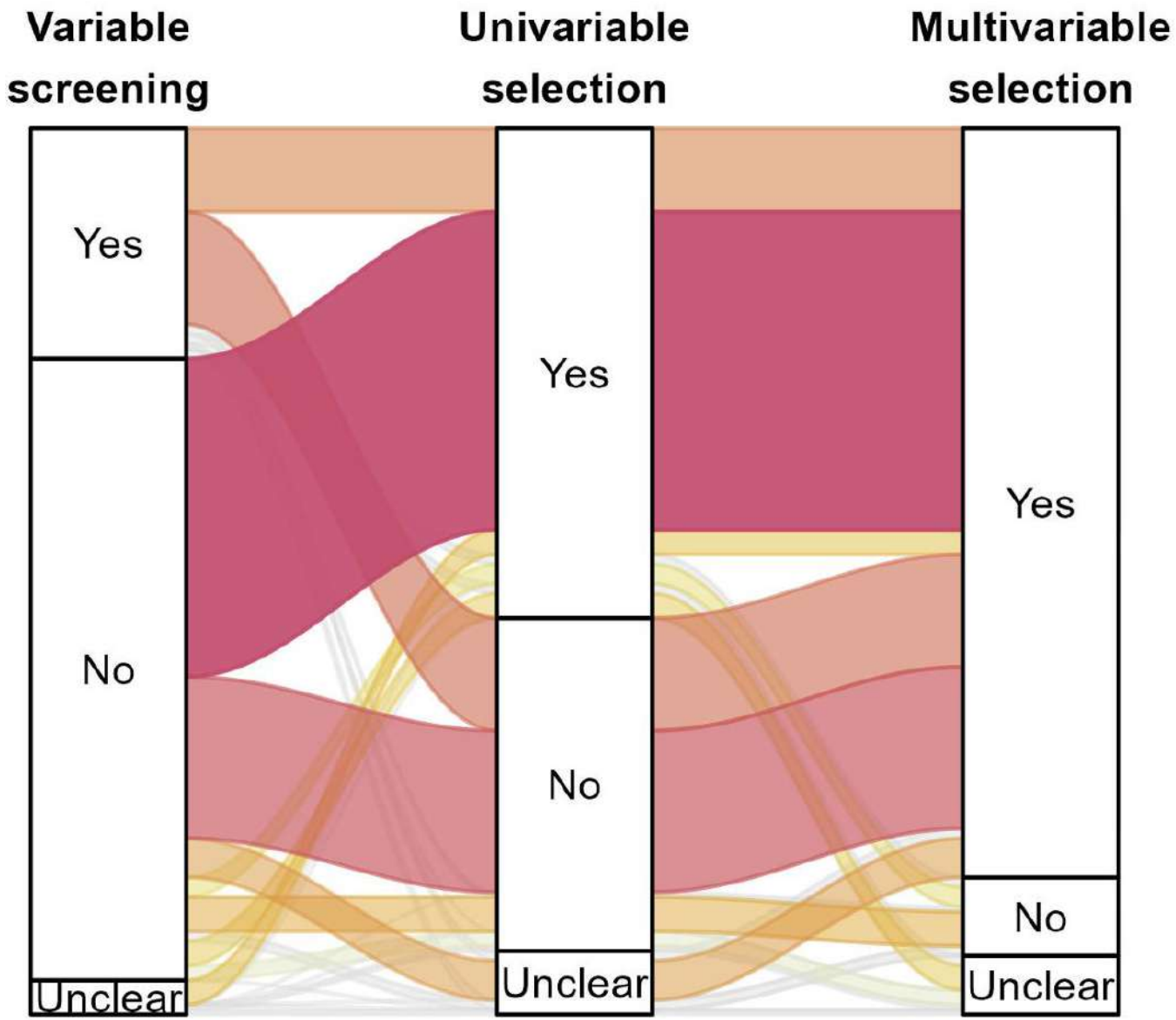
Results: Overview

Data extraction of 181 models completed February 2025



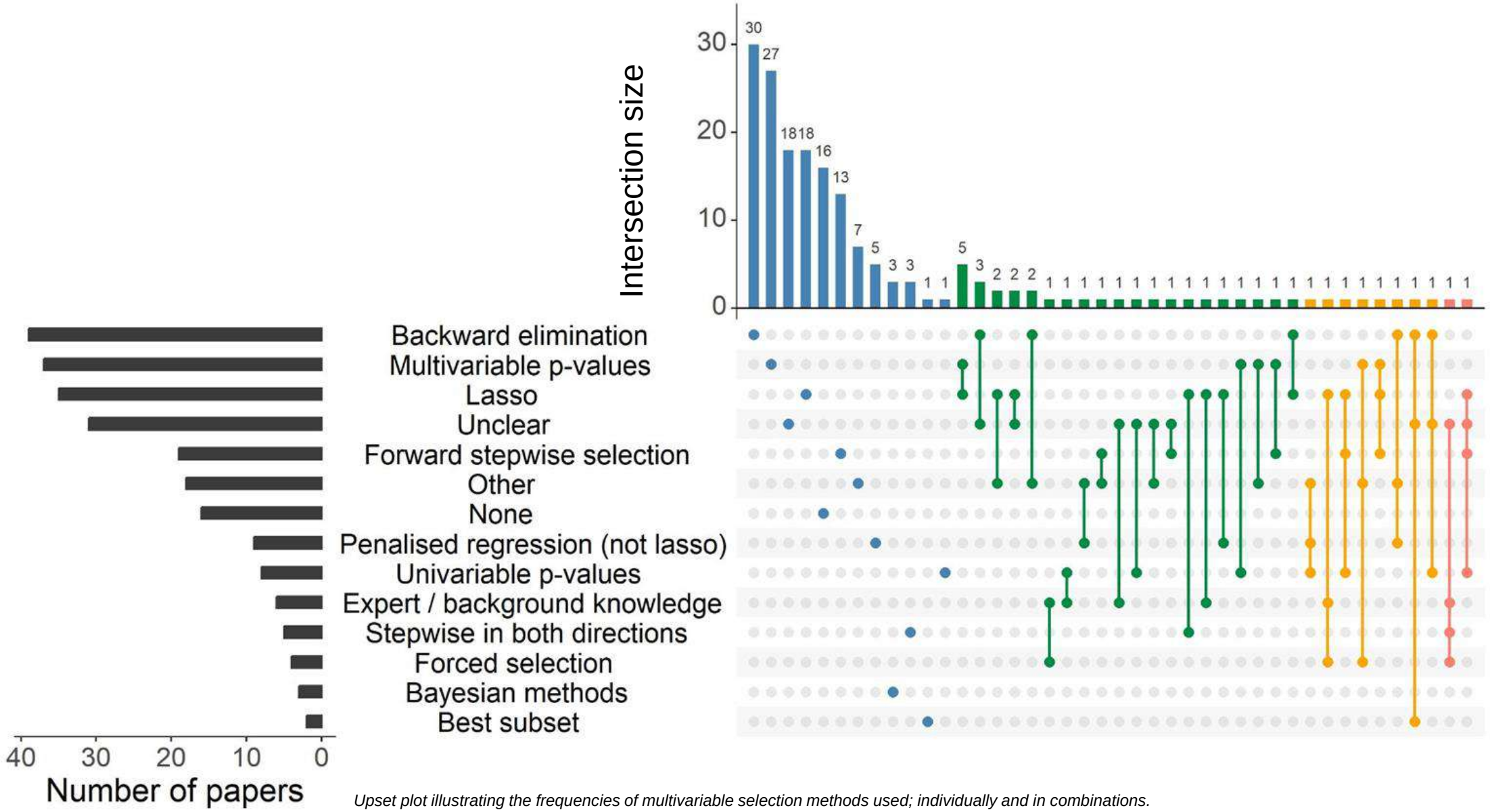
Median sample size 344 (IQR 156 - 982) with median 68 events (IQR 35 - 169)

Results: Modelling patterns



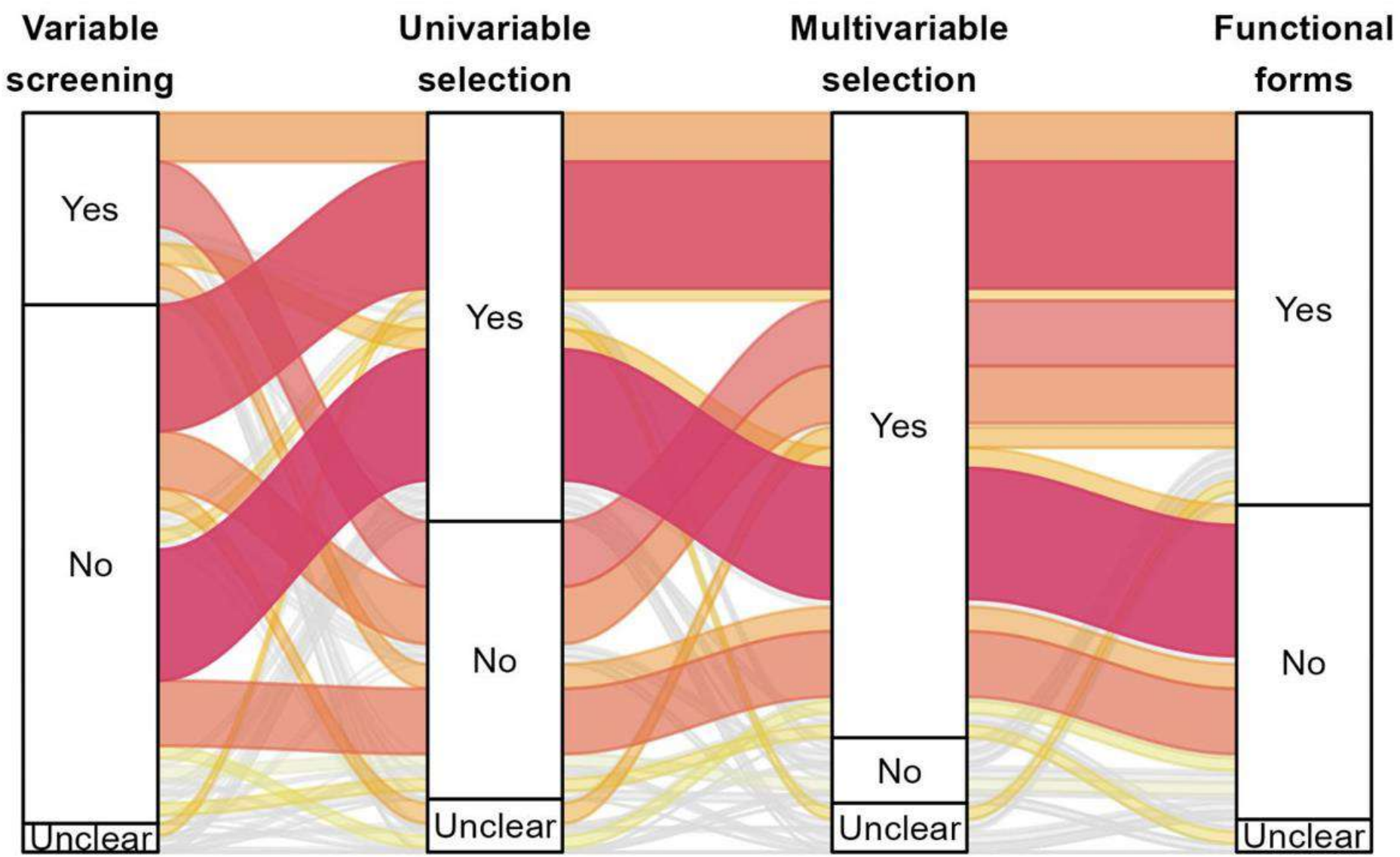
Alluvial plot illustrating the flow of modelling decisions. Flows are color-coded for distinct pathways.

Results: Multivariable selection methods



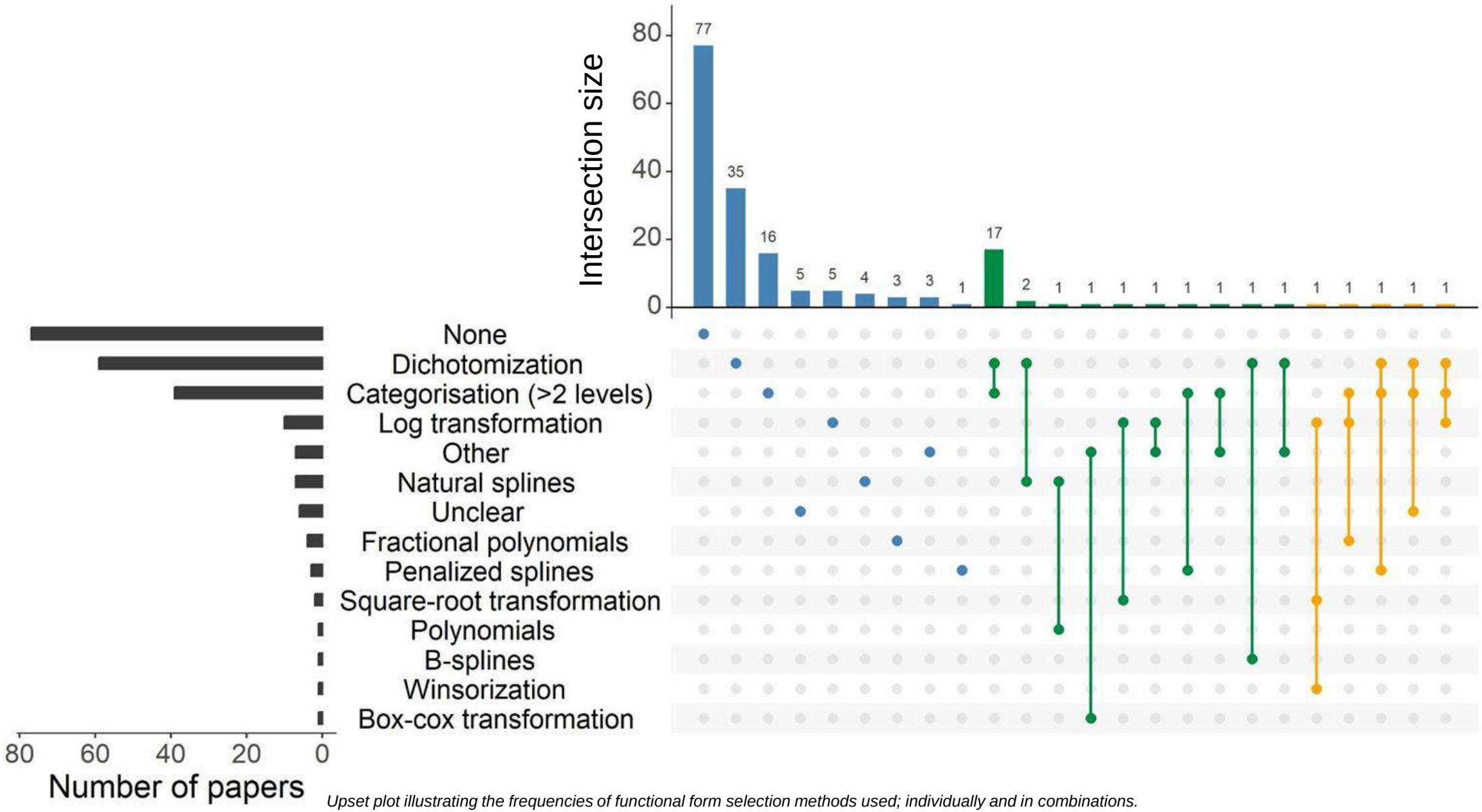
Upset plot illustrating the frequencies of multivariable selection methods used; individually and in combinations.

Results: Modelling patterns



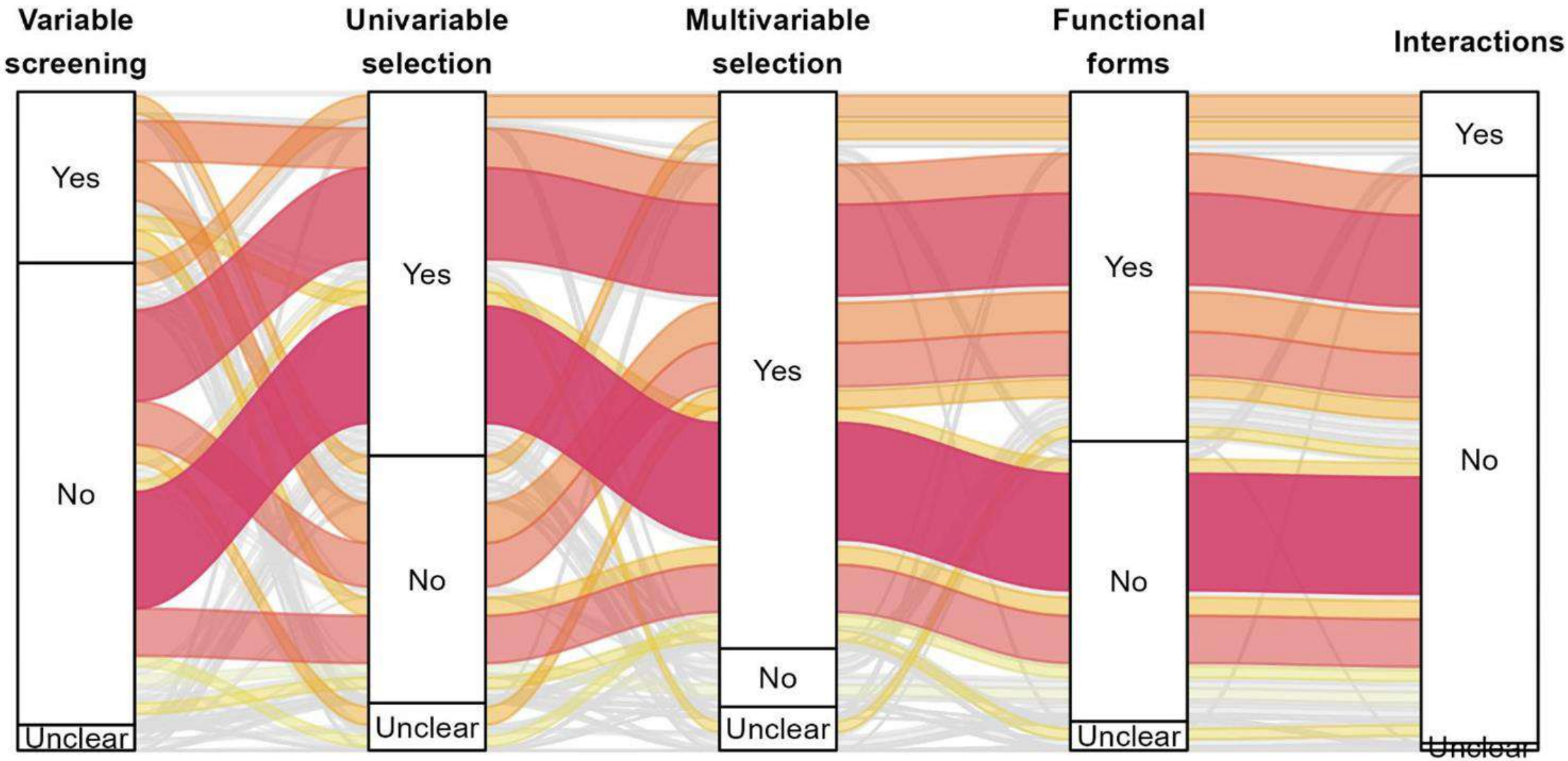
Alluvial plot illustrating the flow of modelling decisions. Flows are color-coded for distinct pathways.

Results: Functional form selection



Upset plot illustrating the frequencies of functional form selection methods used; individually and in combinations.

Results: Modelling patterns



Alluvial plot illustrating the flow of modelling decisions. Only combinations occurring more than once are visualized. Flows are color-coded for distinct pathways.

Results: Model reporting is challenging

Guidance documents rarely cited

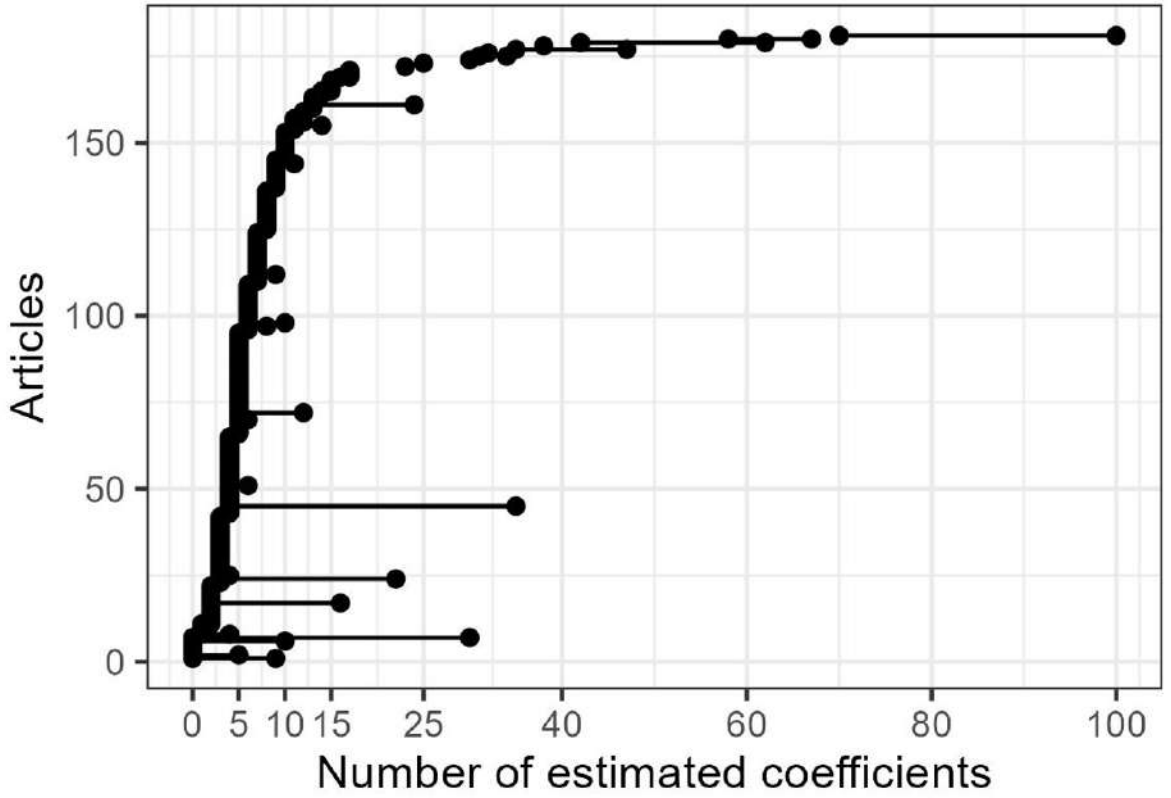
COVID PRECISE review cited in 23%, TRIPOD in 15%, others ≤ 3 times

Full, final models often not reported

Challenging: Not presented in 29%,
as sum score 11%, as online tool 7%

Easier: Nomogram 25%,
(partial) regression formula 17%

Considerable uncertainty even about e.g. number of coefficients



Results: Unusual approaches

There were quite a few unusual approaches for variable and functional form selection that reviewers struggled with during extraction.

- Unclear reporting.
- ‘Expected’ unusual choices [e.g. interesting p-value cut-offs, unorthodox stepwise selections, creative categorisation cut-offs].
- Fairly complex procedures [often unclear rationale, often badly reported].
- Genuinely creative applications [e.g. lasso as part of a stepwise elimination strategy].

→ **A need for more comprehensive / authoritative guidance?**

→ **An opportunity to learn?**

Conclusions: Modeling workflows are diverse

- **No standard modelling workflow.**
- **Variable selection is common practice.**
  - Particularly multivariable selection (>80% of models) but also univariable (>50%).
  - Methods are combined in novel ways that are not investigated in the literature.
  - Selection is not reflected when reporting inference.
- **The use of continuous functional forms and interactions is not.**
  - Widespread use of dichotomization and categorization (>50% of models).
  - Continuous functional forms rarely used (<10% of models).
  - Functional forms were rarely assessed through variable selection (5% of models).

Our empirical results underline opportunities for learning, improving guidance and to keep pushing for better reporting

Find the protocol at https://osf.io/2afuz/

A big thank you to all our reviewers and supporters

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