TFS HealthScience
Clinical Research Excellence

MSR33

Improving analysis of Continuous Predictors: advantages of Fractional Polynomial transformations (FP) and interpretation of "*non-linear*" Odds Ratios (OR) or Hazard Ratios (HR)

Neus Valveny[1], Tomas O´Mahoney[2], Veronica Alfonso[3], Irene Mansilla[4], Andrew Shala[4]

1. RWE, TFS HealthScience, Barcelona, Spain; 2. RWE, TFS HealthScience, Newbridge, Ireland; 3. Biostatistics, TFS HealthScience, Barcelona, Spain; 4. Medical Writing, TFS HealthScience, Barcelona, Spain

Introduction

- In medicine, many important predictors, risk factors, confounders and/or effect-modifiers are continuous (e.g., cholesterol, blood pressure, age).
- Assessing continuous predictors with a categorical outcome (e.g., mortality) under a "linearity assumption" (same risk increase or decrease, denoted by OR or HR, per unit throughout the entire range of X values) may lead to wrong medical decisions, especially if the variable is categorized (data-driven approach).

Objective

- We aimed to review methods for analyzing continuous predictors in regression models from RWE studies, to describe advantages of FP over traditional methods, and to develop a new visualization tool to help understanding "non-linear" ORs or HRs.

Methods

- We searched in Pubmed RWE studies from the last 2 years (2020-2022) using keywords and summarized main methods, including advantages and limitations.
- We described FP methodology and developed a "FP-Risk Score Calculator" to translate model parameters into 10 risk zones (intuitive, traffic-light-like ranging from green to dark red) for the predictor values.

Results

Main methods used in RWE to test continuous predictors

- **Figure 1** shows the most common approaches: cut-points (49.7%) and untransformed variable (47.6%). FP-transformations were rarely used (0.2%).
- **Table 1** summarizes the advantages and limitations of the main approaches.
- FP was the most efficient method selecting best fit based on power and alpha error, comprising most biologically plausible risk shapes (linear/non-linear, monotonic/unimodal).

Figure 1. Main methods to test continuous predictors

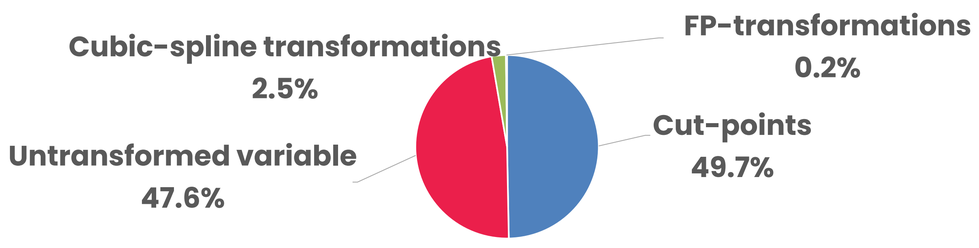


Table 1. Main methods for analyzing continuous predictors in regression models

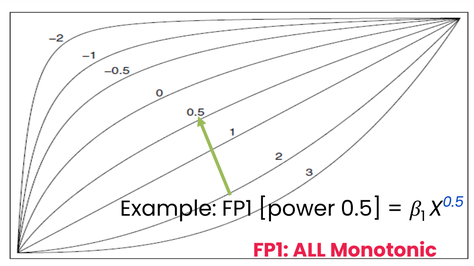
Method	Risk Shape	Main Advantages	Main Limitations
Cut-points (cut-offs from bibliography or data-driven, step risk assumption)	➢Step Risk	✓ OR/HRs easy to interpret ✓ Straightforward medical decisions/clinical algorithms	x Not biologically plausible x Grouping may lead to wrong conclusions x Loss of statistical power x Increased alpha error if multiple testing x Results may not be extrapolable to other cohorts with different "risk shapes"
Untransformed variable (continuous, linearity assumption)	➢Linear risk	✓ Linear/proportional risk is more intuitive and physicians are more familiar with it ✓ A single effect measure (OR/HR) is obtained per variable ✓ Keep statistical power	x More biologically plausible, but not entirely true ("zero" and "infinite" risks do not exist) x If non-linear/non-monotonic risk may lead to wrong conclusions x OR/HRs difficult to interpret (very small) x Results may not be extrapolable to other cohorts with different "risk shapes"
Cubic-spline transformations (curve transformations using ≤5 "cubic polynomials" with smooth merging)	➢Any shape (including multimodal)	✓ Fit all biologically plausible "risk shapes" (including most complex) ✓ Like FP for large amount of information	x OR/HRs difficult to interpret (change over X values) x Results may not be extrapolable to other cohorts with different "risk shapes" x No clear guidelines for selecting the multivariable spline-based model x More difficult to implement than FP
FP-transformations (44 single or double-term transformations using "fraction powers")	➢Monotonic or unimodal risk	✓ Keep statistical power ✓ Do not increase alpha error ✓ Fit most biologically plausible "risk shapes" ✓ Clear guidelines for multivariable models ✓ Easy to implement	x OR/HRs difficult to interpret (change over X values) x Results may not be extrapolable to other cohorts with different "risk shapes" x Cannot fit most complex shapes

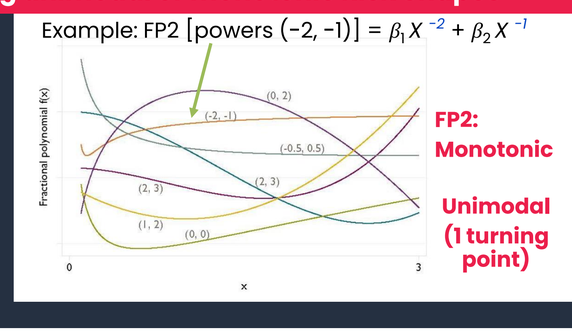
FP, fractional polynomial; HR, hazard ratio; OR, odds ratio

Fractional Polynomial transformations

- 44 transformations done:
  - ➢ 8 Single Exponents (-2, -1, -0.5, 0, 0.5, 1, 2, 3) (FP1)
  - ➢ 36 "Double" using 1 Exponent each (e.g. $\beta_1 X^{0.5} + \beta_2 X^3$) (if exponents are equal ln(x) added to second term)
- Exponents include "fraction powers" (e.g.0.5) => "**Fractional Polynomials"**
- Closed testing: Function Selection Procedure (preserves Type I Error)
- Best transformation (or linearity) is chosen
- Possible shapes reflect medical knowledge: e.g. only monotonic or unimodal forms
- Cover almost **all possible shapes**!
- Free software package for univariate or multivariate (MFP) models: https://mfp.imbi.uni-freiburg.de/
- A new R package (MFP2) will appear very soon (before end of 2023).

Figure 2. Example FP transformations assuming unimodal or monotonic Risk Shapes



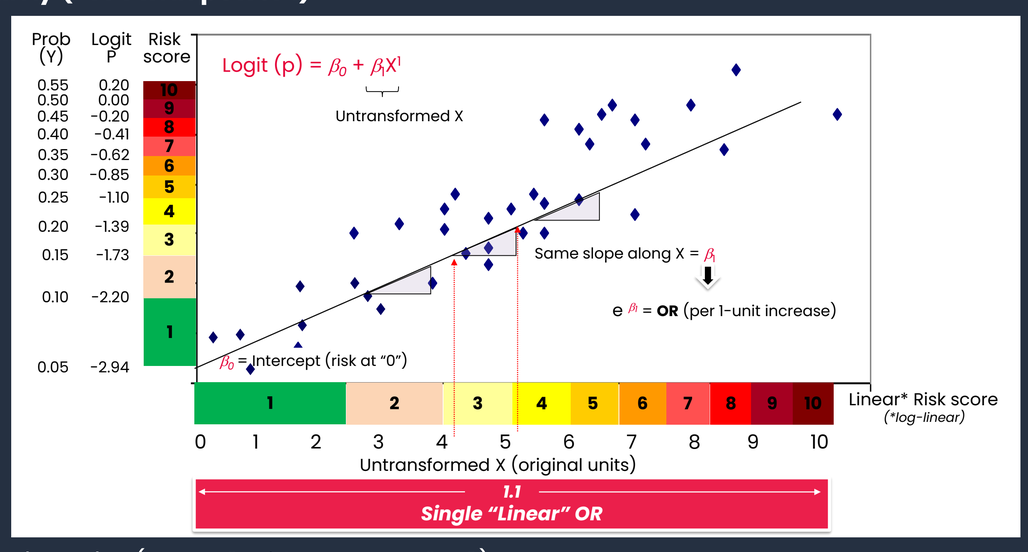


"Non-linear" Odds Ratios (OR) or Hazard Ratios (HR)

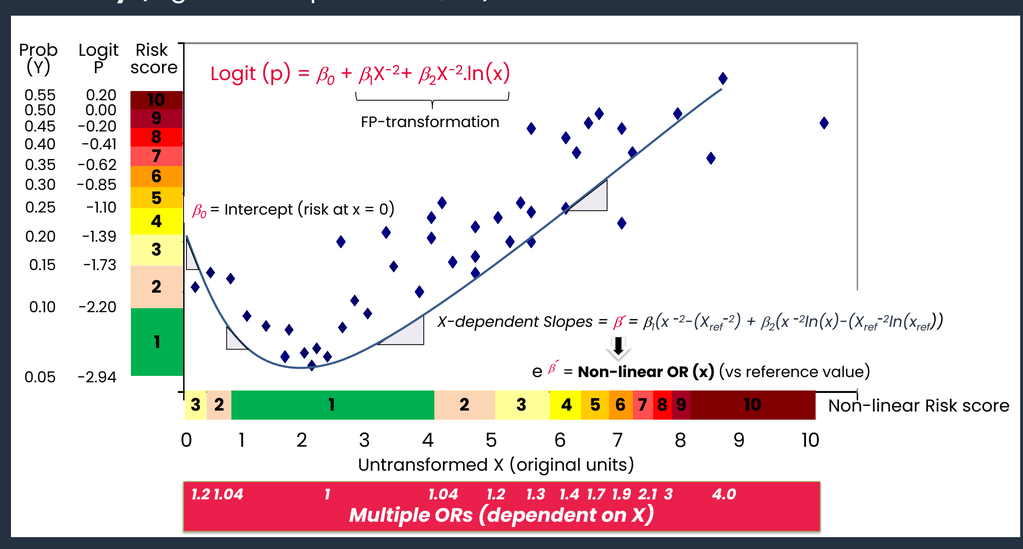
- "Non-linear" OR/HRs are x-dependent, i.e., vary along X. We developed a "FP-Risk Score Calculator" to translate model parameters into 10 Risk Zones with intuitive, traffic-light-like colours, for the observed range of X values (**Figure 3**).
- Each risk zone corresponds to relatively similar outcome probabilities. For simplicity, the OR/HR of the **mid-point** (vs reference value with lowest risk) is shown.

Figure 3. How to interpret "non-linear" OR/HR from FP transformations

A) Linearity (=FP1 with power 1)



B) Non-Linearity (e.g. FP2 with powers -2, -2)



Conclusions

- **Continuous variables should not be assumed by default to have a linear relationship with the outcome nor categorized using pre-defined or data-driven cut-points.**
- **Systematic FP-transformations are easy to implement and allow selecting the best (and simplest) "risk shape", taking into account biological plausibility (monotonic or only 1 turning point)**
- **The new FP-Risk Score Calculator divides predictor values into 10 risk zones (with 10 ORs) to facilitate clinical interpretation.**

References

Royston P, Sauerbrei W (2008) Multivariable model-building. A pragmatic approach to regression analysis based on fractional polynomials for modelling continuous & Sonvariables (John Wiley s).
Royston,P; Ambler,G; Sauerbrei,W (1999) The use of fractional polynomials to model continuous risk variables in epidemiology. Int. J. Epidemiol.28(5): 964-974.

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Conflict of interests

All authors are employees of TFS HealthScience.

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