








RESEARCH ARTICLE

Individual participant data meta-analysis to examine linear or non-linear treatment-covariate interactions at multiple time-points for a continuous outcome

Miriam Hattle^{1,2}  | Joie Ensor^{1,2}  | Katie Scandrett^{1,2}  |
Marienke van Middelkoop³  | Danielle A. van der Windt^{1,4}  |
Melanie A. Holden⁴  | Richard D. Riley^{1,2} 

¹National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, Birmingham, UK

²Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

³Department of General Practice, Erasmus MC Medical University Center, Rotterdam, The Netherlands

⁴School of Medicine, Keele University, Keele, UK

Correspondence

Miriam Hattle, National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, UK.
Email: m.hattle@bham.ac.uk

Funding information

MRC-NIHR Better Methods Better Research; Birmingham Biomedical Research Centre; Chartered Society of Physiotherapy Charitable Trust, Grant/Award Number: PRF/16/A07; NIHR School for Primary Care Research; MRC-NIHR Better Methods Better Research panel, Grant/Award Number: MR/V038168/1; NIHR Birmingham Biomedical Research Centre; National Institute for Health and Care Research (NIHR) School of Primary Care Research, Grant/Award Number: 351

Abstract

Individual participant data (IPD) meta-analysis projects obtain, harmonise, and synthesise original data from multiple studies. Many IPD meta-analyses of randomised trials are initiated to identify treatment effect modifiers at the individual level, thus requiring statistical modelling of interactions between treatment effect and participant-level covariates. Using a two-stage approach, the interaction is estimated in each trial separately and combined in a meta-analysis. In practice, two complications often arise with continuous outcomes: examining non-linear relationships for continuous covariates and dealing with multiple time-points. We propose a two-stage multivariate IPD meta-analysis approach that summarises non-linear treatment-covariate interaction functions at multiple time-points for continuous outcomes. A set-up phase is required to identify a small set of time-points; relevant knot positions for a spline function, at identical locations in each trial; and a common reference group for each covariate. Crucially, the multivariate approach can include participants or trials with missing outcomes at some time-points. In the first stage, restricted cubic spline functions are fitted and their interaction with each discrete time-point is estimated in each trial separately. In the second stage, the parameter estimates defining these multiple interaction functions are jointly synthesised in a multivariate random-effects meta-analysis model accounting for within-trial and across-trial correlation. These meta-analysis estimates define the summary non-linear interactions at each time-point, which can be displayed graphically alongside confidence intervals. The approach is illustrated using an IPD

meta-analysis examining effect modifiers for exercise interventions in osteoarthritis, which shows evidence of non-linear relationships and small gains in precision by analysing all time-points jointly.

KEYWORDS

individual participant data (IPD) meta-analysis, longitudinal data, multivariate meta-analysis, non-linear analysis, treatment-effect moderators, treatment-effect modifiers

Highlights

What is already known?

- Individual participant data meta-analyses of existing randomised trials are recommended to identify treatment effect modifiers at the individual level, as opposed to single randomised trials that are under-powered to detect an effect modifier or a meta-regression of study-level information which are prone to aggregation bias and study-level confounding.
- When examining covariates as potential treatment effect modifiers it is recommended that categorisation of the continuous covariate should be avoided, and potential non-linear relationships should be examined.

What is new?

- We propose a two-stage multivariate IPD meta-analysis approach that summarises non-linear interaction functions at multiple time-points, allowing for participants or trials with missing time-points to still be included in the analysis.
- We demonstrate how the estimates defining the summary non-linear interactions at each time-point can be displayed graphically.
- We provide an example using an IPD meta-analysis examining effect modifiers for exercise interventions in knee and hip osteoarthritis, which demonstrates analysing non-linear relationships and multiple time-points using the proposed two-stage multivariate IPD meta-analysis approach.

Potential impact for *Research Synthesis Methods* readers

- The approach we propose can be used by researchers in any field (not only osteoarthritis), conducting an IPD meta-analysis that seeks to identify treatment effect modifiers with a continuous covariate and multiple time-points of interest.

1 | INTRODUCTION

There is an increasing interest in precision (personalised) medicine, where the aim is to select optimal treatments for individual patients, or groups of similar patients, based on their particular characteristics such as stage of disease, disease characteristics or particular gene mutations.^{1,2} A key component of precision medicine research is exploring whether particular participant-level characteristics (covariates) are associated with a differential effect of a particular treatment, to identify those who benefit the most from it.¹ In other words, the goal is to identify *treatment-covariate interactions*. For example, the

drug trastuzumab is usually only given to the subgroup (stratum) of breast cancer patients who are human epidermal growth factor receptor 2 (HER-2) positive, as it is known to lock on to the HER-2 protein, block the receptor and stop the cells from dividing and growing.³

A single randomised trial is rarely powered to detect a treatment-covariate interaction,⁴ as it would be expensive and so usually infeasible.

A solution is to obtain and synthesise individual participant data (IPD) from existing randomised trials.⁵ IPD meta-analysis provides the opportunity to increase power to detect genuine treatment-covariate interactions and to examine relationships at the participant level (thus

avoiding study-level confounding and aggregation bias^{6,7}), whilst also conditioning on prognostic factors.⁸ For this reason, many IPD meta-analyses of randomised trials are initiated specifically to examine one or more treatment-covariate interactions. Treatment-covariate interactions are sometimes described within research as ‘heterogeneous treatment effects’ or ‘treatment effect heterogeneity’, where heterogeneity refers to participant-level variability.^{9,10} However, in this article—and indeed the meta-analysis literature in general—we reserve the word heterogeneity for variability between trials.

Previous work describes how to use a two-stage or a one-stage IPD meta-analysis framework to examine treatment-covariate interactions at the participant level whilst avoiding aggregation bias.^{5,11–15} One-stage and two-stage models should closely agree if the sample sizes or events per trials are not small, and if the approaches make the same assumptions.^{5,16–18} Another important recommendation when examining interactions in IPD meta-analysis is to avoid categorisation of continuous covariates, and to examine potential non-linear relationships. This can be done using, for example, (restricted) cubic splines or fractional polynomials.^{11,19–23} However, there has been little research on how to deal with multiple time-points in this context, which arises when IPD meta-analysis researchers are interested in the treatment effect (and thus potential treatment-covariate interactions) at two or more follow-up times. Many trials record follow-up information at multiple times, and so researchers need to examine the treatment effect over time, and whether effect modification changes over time. As multiple time-points are likely to be correlated, this adds extra complexity to the IPD meta-analysis model at both the patient-level and the between-study level, which should be accounted for when examining linear or non-linear interactions between the continuous covariates and treatment effect at each time-point. Further, not all studies will provide all the time-points of interest, so accounting for their correlation may be important to address this and gain efficiency in estimates.²⁴

To address this, in this article, we extend the modelling of linear and non-linear interactions in two-stage IPD meta-analysis to the situation where a continuous outcome is of interest at multiple follow-up time-points. The proposed models allow multiple linear or non-linear interaction functions corresponding to multiple time-points to be synthesised in combination, whilst accounting for their within-trial and across-trial correlation. The outline is as follows. In Section 2, we introduce a general two-stage framework for synthesising interactions at a single time-point, and Section 3 extends this to a multi-variate meta-analysis of spline functions to summarise a non-linear interaction. Section 4 extends this further to

allow for multiple time-points, and then, Section 5 concludes with discussion. A running example is provided across all sections.

2 | USING IPD META-ANALYSIS TO EXAMINE A LINEAR INTERACTION AT A SINGLE TIME-POINT

In this section, we provide a general framework for undertaking a two-stage IPD meta-analysis of treatment-covariate interactions at a single time-point, building on material presented in Chapter 7 of our textbook.⁵ In the first stage, the treatment-covariate interactions are estimated using the IPD in each trial separately; in the second stage, these interaction estimates are pooled using a chosen meta-analysis model.²⁵ The approach can be implemented using the *ipdmetan* software package in Stata,²⁶ and our website (www.ipdma.co.uk) provides examples of statistical code for various case studies used in this article. In this section, we assume a linear relationship for continuous covariates of interest, with extension to non-linear relationships and multiple time-points given in subsequent sections.

2.1 | First stage

Consider IPD from a parallel group randomised trial, comparing a treatment ($x_{ij}=1$) to a control ($x_{ij}=0$). Let z_{ij} be a participant-level covariate (e.g., the age of participant j in trial i), observed for all participants in each trial, and consider a continuous outcome at a particular time-point, such as systolic blood pressure or pain score at 1 year after randomisation (y_{ij}). Then, the first stage is to apply a linear regression *in each trial separately*, to model the variation of y_{ij} values in terms of the treatment (x_{ij}), the covariate (z_{ij}), the baseline value of the continuous outcome (y_{0ij}), and treatment-covariate interaction ($x_{ij}z_{ij}$):

$$y_{ij} = \alpha_i + \beta_{1i}z_{ij} + \beta_{2i}x_{ij} + \beta_{3i}y_{0ij} + \gamma_{wi}x_{ij}z_{ij} + e_{ij}$$

$$e_{ij} \sim N(0, \sigma_i^2) \quad (2.1)$$

Fitting this model will estimate the treatment-covariate interaction (γ_{wi}) conditional on (after adjusting for) the prognostic effect (β_{1i}) of the covariate of interest (z_{ij}), the treatment effect (β_{2i}) for the reference ($z_{ij}=0$) group, and the prognostic effect (β_{3i}) of y_{0ij} . Model (2.1) can be extended to adjust for other (pre-defined)

prognostic factors, especially as interactions may disappear after conditioning on them. The choice of prognostic factors may be restricted by the information available in the IPD, but generally a few key prognostic factors like age or stage of disease should be available in all trials.

The treatment-covariate interaction term, γ_{wi} , indicates the expected change in treatment effect for a one-unit increase in z_{ij} for trial i . For a continuous covariate, as written this assumes the effect of the interaction is linear but in practice extension to non-linear trends is important, as discussed in the next section. The ‘W’ is used to emphasise that the interaction, γ_{wi} , is based solely on *within*-trial information. The model can be fitted using restricted maximum likelihood estimation (REML), and produces a treatment-covariate interaction estimate, $\hat{\gamma}_{wi}$, and its variance, $\text{var}(\hat{\gamma}_{wi})$, to be used in the second stage.

2.2 | Second stage

In the second stage, the $\hat{\gamma}_{wi}$ values are combined across trials in either a common-effect model (i.e., the true interaction is assumed the same in all trials),

$$\hat{\gamma}_{wi} \sim N(\gamma_w, \text{var}(\hat{\gamma}_{wi})) \quad (2.2)$$

or a random-effects model (i.e., the true trial interactions are assumed drawn randomly from a normal distribution with mean γ_w and variance τ^2):

$$\begin{aligned} \hat{\gamma}_{wi} &\sim N(\gamma_{wi}, \text{var}(\hat{\gamma}_{wi})) \\ \gamma_{wi} &\sim N(\gamma_w, \tau^2) \end{aligned} \quad (2.3)$$

The estimate of γ_w summarises the difference in the expected treatment effect (i.e., mean difference for a continuous outcome) for two participants who differ in z_{ij} by one unit. We generally focus on the random-effects model (2.3) in this article, with estimation using REML.

Between-trial heterogeneity in the true treatment-covariate interaction may arise due to differences across trials in, for example, the dose of the treatment, the length of follow-up, the measurement of the covariate, and the magnitude of any interaction. It may also be due to case-mix differences in the trial populations, for example leading to between-trial differences in the distribution of (not included) prognostic factors and even the covariate itself. For instance, if a treatment-covariate interaction is non-linear, and the covariate distribution is narrow in some trials and wide in others, then this will induce between-trial heterogeneity in the treatment-covariate interaction,

unless the non-linear association is modelled directly (see next section). The magnitude and impact of heterogeneity can be summarised by the estimated between-trial variance (τ^2) or standard deviation (τ), and a 95% prediction interval for the interaction size in a new study.²⁷

2.3 | Applied example: IPD meta-analysis to examine effect modifiers for exercise interventions for knee and hip osteoarthritis

The Subgrouping and TargetEd Exercise pROgrammes for knee and hip OsteoArthritis (STEER OA) project is an IPD meta-analysis to identify moderators of the effect of exercise among people with knee and/or hip OA at multiple follow-up time-points (nearest to 3, 6 and 12 months).²⁸ A total of 31 trials, containing 4241 participants, were included in the IPD meta-analysis. We use the IPD from the STEER OA project as a running example throughout this paper. The key outcome of interest was pain; this was measured using different scales in different trials, and so to enable meta-analysis, all the outcome measures were mapped to a 0 (no pain) to 100 (most pain) scale.

The 31 trials are summarised in Table 1. The three time-points were not available in all trials, which is a key motivation for analysing all time-points together later in the article. Twenty-Seven of the trials provided 3 months (‘short-term’); 15 of the trials provided 6 months (‘medium term’); and 13 of the trials provided 12 months (‘long term’). Initially, in the remainder of this section and Section 3, we consider the single time-point of 12 months. Our focus is on the single potential moderator of baseline physical function score, which was also harmonised to a 0 (most function) to 100 (least function) scale in all trials. Specifically, we aim to examine whether baseline physical function score interacts with the effect of exercise on pain compared to non-exercise controls by a single time-point in each trial corresponding to that closest to 12 months. Section 4 extends to multiple time-points.

Using the 13 (2216 participants) studies that provide the pain outcome at 12 months, we applied a two-stage IPD meta-analysis analysis to summarise the interaction between the effect of exercise on pain at 12 months and baseline physical function score (Figure 1). In the first stage, model (2.1) was applied in each trial separately to estimate the treatment-covariate interaction assuming a linear effect of baseline function, and adjusting for an assumed linear prognostic effect of baseline pain score. In the second stage, we applied random effects meta-analysis model (2.3) using REML to summarise the

TABLE 1 Summary of the 31 trials in the IPD meta-analysis of the Subgrouping and TargetEd Exercise pRogrammes for knee and hip OsteoArthritis (STEER OA) project, including whether the IPD provided pain outcome data at 3 months (short term), 6 months (medium term) and 12 months (long term).

Trial	No. participants (treatment/control)	Baseline function score^a Mean (SD), range	3 months (short term)	6 months (medium term)	12 months. (long term)
Allen et al. (2018)	210 (142/68)	33.1 (19.3), 0–100	Yes	No	Yes
Bearne et al. (2011)	48 (24/24)	23.2 (16.0), 0–72.1	Yes	Yes	No
Bennell et al. (2010)	89 (45/44)	35.7 (16.6), 5.9–85.3	Yes	No	No
Bossen et al. (2013)	199 (100/99)	44.4 (21.5), 4.4–93.7	Yes	No	Yes
Brosseau et al. (2012)	222 (148/74)	27.5 (16.5), 0–76.5	Yes	Yes	Yes
Cochrane et al. (2005)	312 (153/159)	44.9 (17.4), 0–89.7	No	Yes	Yes
de Rooij et al. (2017)	126 (63/63)	48.7 (18.0), 7.4–94.1	Yes	Yes	No
Fernandes et al. (2010)	109 (55/54)	22.3 (15.4), 1.2–56.9	Yes	No	Yes
Fransen et al. (2007)	152 (111/41)	39.4 (16.5), 5.9–82.4	Yes	No	No
French et al. (2013)	88 (45/43)	47.9 (19.9), 10.3–98.5	Yes	No	No
Hale et al. (2012)	39 (23/16)	38.6 (11.9), 11.8–64.1	Yes	Yes	Yes
Hay et al. (2006)	217 (109/108)	44.6 (19.2), 2.9–100	Yes	Yes	Yes
Henrikson et al. (2014)	48 (25/23)	31.0 (15.2), 4.4–63.2	Yes	No	No
Hinman et al. (2007)	71 (36/35)	40.8 (19.1), 2.8–83.4	Yes	No	No
Hopman-Rock and Westhoff (2000)	105 (56/49)	70.1 (22.4), 0–100	Yes	Yes	No
Hurley et al. (2007)	418 (278/140)	39.9 (21.5), 0–95.6	Yes	Yes	Yes
Kraus et al. (2014)	218 (71/147)	27.5 (16.4), 0–82.6	Yes	No	No
Levinger et al. (2018)	28 (19/9)	5.2 (3.1), 0–11.0	Yes	No	No
Lim et al. (2008)	107 (53/54)	34.8 (15.8), 1.5–67.6	Yes	No	No
Messier et al. (2004)	158 (80/78)	37.1 (17.4), 2.9–100	No	Yes	Yes
Multanen et al. (2014)	80 (40/40)	4.7 (5.5), 0–24.1	No	No	Yes
Munukka et al. (2016)	87 (43/44)	9.5 (10.5), 0–54.0	Yes	No	Yes
Simão et al. (2012)	32 (21/11)	51.8 (21.2), 13.2–89.7	Yes	No	No
Tak et al. (2005)	109 (55/54)	13.3 (11.3), 0–61.1	Yes	Yes	No
Takacs et al. (2017)	40 (20/20)	43.4 (12.5), 10.3–69.1	Yes	No	No
Talbot et al. (2003)	34 (17/17)	–	Yes	Yes	No
Teirlinck et al. (2016)	203 (101/102)	36.7 (17.2), 1.5–82.8	Yes	Yes	Yes
Thomas et al. (2002)	391 (235/156)	33.4 (18.8), 0–95	No	Yes	Yes
Tsai et al. (2013)	55 (28/27)	39.1 (14.7), 0–77.9	Yes	Yes	No
van Baar et al. (2001)	200 (98/102)	63.2 (26.4), 0–100	Yes	Yes	No
Wallis et al. (2017)	46 (23/23)	52.5 (14.3), 25–85.3	Yes	No	No

^aStandardised score from 0 (good physical function) to 100 (poor physical function).

interaction. (Although, we would recommend using a correction for the confidence interval to account for the uncertainty in the between-study variance, for example, Hartung-Knapp Sidik-Jonkman correction,^{29,30} for example purposes we do not include a correction for any examples, to allow for comparisons to be made across the methods).

The results show a summary treatment-covariate interaction of -0.078 (95% CI: -0.152 to -0.003 , τ^2 : 0.00) at 12 months (Figure 1), providing some evidence that the benefit of exercise treatment compared to control improves in those with a higher baseline physical function score (i.e., those with *worse* physical function). There is an estimated additional 0.078 reduction in pain for

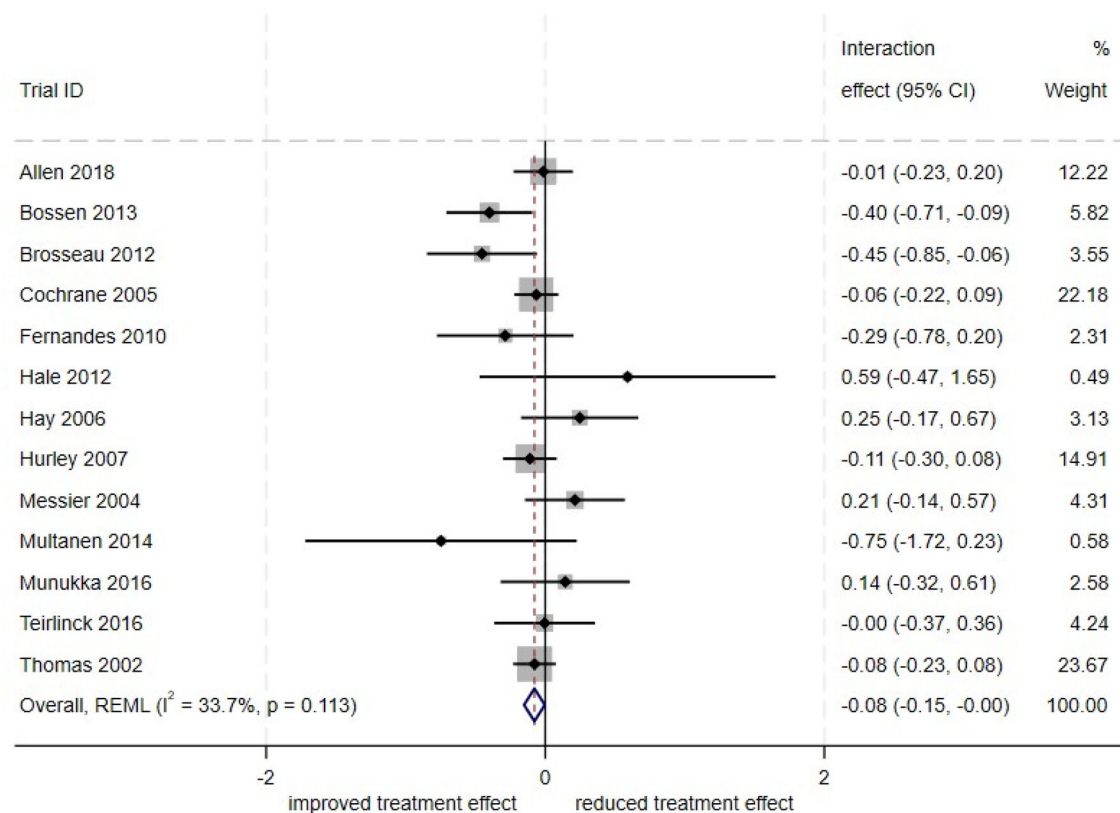


FIGURE 1 Forest plot of study-specific and meta-analysis results for the interaction effect between the pain outcome at 12 months and baseline function. Values below 0 ('improved treatment effect') indicate a 1-unit increase in baseline function score improves the treatment effect on pain. Values above 0 ('lower treatment effect') indicate a 1-unit increase in baseline function score reduces the treatment effect on pain.

every 1-unit increase in baseline physical function score. Therefore, the participants with poorer physical function are expected to benefit more (have greater reduction in their pain) from the exercise treatment at 12 months.

3 | USING IPD META-ANALYSIS TO EXAMINE A NON-LINEAR INTERACTION AT A SINGLE TIME-POINT USING SPLINES

The previous section assumed a linear effect of the continuous covariate. However, sometimes the underlying relationship may be non-linear, as emphasised by Royston and Sauerbrei,³¹ and considered in detail by Kasenda et al.^{32,33} A non-linear relationship implies that the change in treatment effect for every one-unit increase in the covariate may vary across the distribution of the covariate. Therefore, non-linear interactions should routinely be evaluated when the interaction of continuous covariates and treatment effect is of interest.

Here, we focus on interaction with treatment defined via a restricted cubic spline function, which is a flexible way of modelling smooth non-linear relationships. For a

detailed introduction to (restricted cubic) splines, we refer the reader to the following references.^{34–37} Briefly here, a restricted cubic spline is obtained by fitting a series of cubic functions and forcing them to join (and be smoothed) at certain points (called internal knots), whilst constraining the function to be linear in the tails (i.e., before the first internal knot and after the last internal knot). The magnitude and shape of the curve are defined by multiple parameters depending on the number of knots chosen. Rather than using a reference group whose covariate value is 0, it helps to centre the spline variables at a meaningful value; if so, this should be consistent and use the same value for every trial in the IPD meta-analysis. Further details of restricted cubic spline functions are given in the Appendix and also by Belias et al.²³ Here, we focus on a two-stage IPD meta-analysis of splines defining an interaction.

3.1 | First stage

In a two-stage approach to IPD meta-analysis of a non-linear interaction, the first stage fits a model in each trial separately that includes a restricted cubic spline for the

covariate of interest and its interaction with treatment effect. The key focus (to take forward for the second stage) is to obtain the parameter estimates defining this interaction. For instance, in the first stage we might pre-define three internal knots (at the same location in each trial) for the restricted cubic function for the covariate of interest, which leads to three parameters per trial defining the spline function in each trial (an intercept and two slope terms). The interaction of this spline function with the treatment effect is then estimated, leading to an estimated function defining the non-linear within-trial treatment-covariate interaction in each trial. The steps can be summarised as follows:

1. **Create the restricted spline transformation of z , which requires choosing the number of knots and their location.** The number and location of the knots must be identical for each trial. Usually, three or four knots will suffice. Their location could be defined by quantiles of the covariate distribution observed within the entire IPD from all trials. However, if the distribution of the covariate varies considerably across trials, then knot locations might be modified so that they fall at relevant places. For example, if some trials do not have any patients above a value of v , then v could be a knot location. Sensitivity analysis changing the location of the knots may be important.
2. **Estimate the treatment-covariate interaction in each trial.** This requires the specification and estimation of a suitable regression model, followed by storing the parameter estimates (and corresponding variance matrix) that define the treatment-covariate interaction function. The module *mvmeta* in Stata allows the user to perform a particular regression analysis in each trial and automatically stores the relevant estimates and corresponding variance matrix.^{38,39} Example code is provided in the supplementary material in Data S1.

For example, consider a continuous outcome (y_{ij}) and a regression to examine the non-linear interaction between treatment and a continuous covariate (z_{ij}), conditioning on the prognostic effect of baseline (y_{0ij}), the reference treatment effect (x_{ij}) and the non-linear prognostic effect of z_{ij} , as follows:

$$y_{ij} = \alpha_i + f(z_{ij}) + \beta_{2i}x_{ij} + \beta_{3i}y_{0ij} + f(x_{ij}z_{ij}) + e_{ij}$$

$$e_{ij} \sim N(0, \sigma_i^2) \quad (3.1)$$

with the restricted cubic spline function defined by two terms (based on three internal knots),

$$f(z_{ij}) = \delta_{1i}z_{1ij} + \delta_{2i}z_{2ij}$$

where z_{1ij} and z_{2ij} denote the first and second spline transformations of z_{ij} (Appendix Box A1), respectively, and δ_{1i} and δ_{2i} denote the conditional effect on the outcome of a 1-unit increase in z_{1ij} and z_{2ij} , respectively. Then, the interaction between the spline function and treatment is defined by the function:

$$f(x_{ij}z_{ij}) = \gamma_{W1i}x_{ij}z_{1ij} + \gamma_{W2i}x_{ij}z_{2ij}$$

After model fitting, the estimates $\hat{\gamma}_{W1i}$ and $\hat{\gamma}_{W2i}$ are of key interest, as they define the treatment-covariate interaction in trial i , together with their variances ($\text{var}(\hat{\gamma}_{W1i})$ and $\text{var}(\hat{\gamma}_{W2i})$) and covariance ($\text{cov}(\hat{\gamma}_{W1i}, \hat{\gamma}_{W2i})$).

To aid interpretation, before model estimation it may be helpful to centre z_{ij} by a reference value, such as the mean z_{ij} across all trials or in the general population. Each of the spline transformations (e.g., z_{1ij} and z_{2ij}) need to be centred by their specific value that corresponds to this overall reference group. The same reference group should be used in every trial, in order to ensure the parameters are compatible for the meta-analysis.

Note that if some parameters cannot be estimated in some trials (e.g., due to a narrow distribution of z_{ij} , or perfect prediction), then data augmentation can be used (e.g., via the *mvmeta_make* package by White³⁸). Essentially, this adds just a few individuals to the problematic groups and leads to an arbitrary parameter estimate but with a very large variance (e.g., 1,000,000,000) and any associated covariances set to zero, such that the estimates will receive barely any weighting in the subsequent multivariate meta-analysis.

3.2 | Second stage

In the second stage, we can apply a multivariate meta-analysis to synthesise the estimates of the restricted cubic spline functions. The steps involved can be summarised below.

1. **Perform a multivariate meta-analysis of the treatment-covariate interaction estimates, to produce a summary of the treatment-covariate interaction function.** The multivariate approach allows the joint synthesis of multiple parameter estimates, whilst accounting for their correlation.^{40,41} It can be fitted using REML estimation. Example Stata code is provided in the supplementary material in Data S1.

For example, if the spline function is defined by two parameters (based on three internal knots), we can fit a

bivariate random-effects meta-analysis allowing for between-trial heterogeneity,

$$\begin{pmatrix} \hat{\gamma}_{W1i} \\ \hat{\gamma}_{W2i} \end{pmatrix} \sim N \left(\begin{pmatrix} \gamma_{W1i} \\ \gamma_{W2i} \end{pmatrix}, \begin{pmatrix} \text{var}(\hat{\gamma}_{W1i}) & \text{cov}(\hat{\gamma}_{W1i}, \hat{\gamma}_{W2i}) \\ \text{cov}(\hat{\gamma}_{W1i}, \hat{\gamma}_{W2i}) & \text{var}(\hat{\gamma}_{W2i}) \end{pmatrix} \right)$$

$$\begin{pmatrix} \gamma_{W1i} \\ \gamma_{W2i} \end{pmatrix} \sim N \left(\begin{pmatrix} \gamma_{W1} \\ \gamma_{W2} \end{pmatrix}, \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix} \right) \quad (3.2)$$

where τ_1^2 and τ_2^2 define the between-trial variances of γ_{W1i} and γ_{W2i} , respectively, and τ_{12} defines their between-trial covariance.

The summary estimates of $\hat{\gamma}_{W1}$ and $\hat{\gamma}_{W2}$ define the summary spline function describing the treatment-age interaction of $\gamma_{W1}x_{ij}z_{1ij} + \gamma_{W2}x_{ij}z_{2ij}$.

- **Plot the summary treatment-covariate interaction and its confidence interval across the distribution of covariate values.** After estimation of the multivariate model, the summary treatment-covariate interaction function can be applied (e.g., via the *predict* post-estimation command in Stata, see supplementary material in Data S1) to each participant in the original IPD, to obtain their predicted treatment-covariate interaction; i.e., the difference in their treatment effect compared to that for the reference covariate value. This predicted value can then be plotted (on the y-axis) against the original covariate value (on the x-axis). The standard error (s.e.) of the predicted value can also be estimated, and then a confidence interval calculated (e.g., using predicted estimate $\pm (1.96 \times \text{s.e.})$, or one based on a t-distribution as in the Hartung-Knapp-Sidik-Jonkman approach²⁹). The upper and lower values of the confidence interval can then be plotted. This might be accompanied by the trial-specific estimated curves from the first stage, or trial-specific empirical Bayes curves obtained post-estimation from the second stage might also be presented, as shown by Gasparrini et al.²²

3.3 | Applied example: non-linear interaction assessment in the STEER-OA project

Returning to the STEER-OA example, let us now examine whether there is a non-linear interaction between pain and baseline physical function, for the long-term

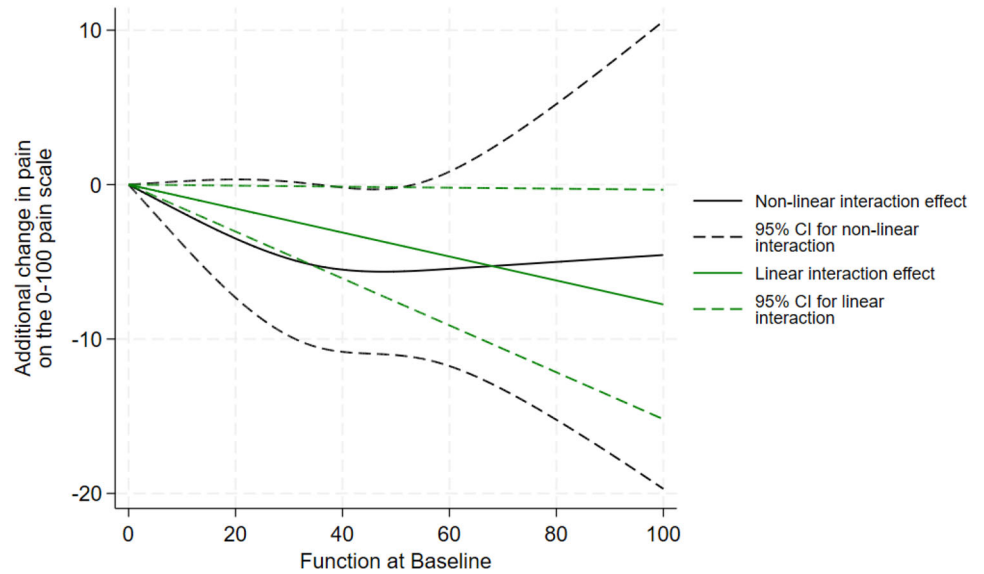
time-point of 12 months. In the first stage, we fit a restricted cubic spline with 3 internal knots. The most appropriate knot positions were decided upon from examining the entire IPD and choosing values closest to the quartiles. The knot positions were 5, 35 and 60, and forced to be the same for each trial. In the second stage, a bivariate meta-analysis with REML estimation was used to pool the spline functions for the long-term time-point.

The results are shown visually in Figure 2. It is clear, from the shape of the non-linear plot, that the relationship between pain and baseline physical function was misrepresented as linear, and the non-linear relationship is more appropriate. Moreover, conclusions from the linear and non-linear analyses differ. Recall, when assuming a linear relationship, we concluded that those prescribed exercise with the least physical function (i.e., higher physical function scores) will see the greatest additional reduction in pain. However, after allowing for a non-linear relationship, the additional benefit only rises up to a baseline physical function score of about 42, and thereafter there is a plateau (no continued improvement) and perhaps a slight reduction. The uncertainty is also much larger in the non-linear investigation, especially in regions above a function of 42.

4 | EXAMINING LINEAR OR NON-LINEAR INTERACTIONS AT MULTIPLE TIME-POINTS

We now extend the approach to allow for multiple time-points, focusing on a continuous outcome. We assume there are a set of key time-points of interest, and that these are to be modelled as discrete (rather than as continuous values themselves). In an IPD meta-analysis, sometime-points (e.g., 12 months) may be recorded by all the included trials, but other time-points may be only available in some trials and not others. However, the multivariate framework described below can handle this situation as it allows for different sets of time-points across studies, under a missing at random assumption. Similarly, participants do not need to report outcome values for all time-points in a trial. Still, some pragmatism will often still be needed to aid the modelling process if time-points vary slightly across trials and some time-points are sparsely available. For example, if most studies report outcomes at 4 months and 12 months, but a few trials rather report outcomes at 3 months and 12 months, it may be sensible to focus meta-analysis on the two time-points of 3/4 months and 12 months, thus grouping together 3 and 4 months.

FIGURE 2 Comparison of linear and non-linear moderating effect of baseline function on the effect of exercise on pain outcomes at the (long term) time-point of about 12 months. Reference group is individuals with a baseline function of zero (most function).



4.1 | First stage

In the first stage, we will estimate all parameters (treatment effect, prognostic effects, and interaction) for all time-points simultaneously, whilst accounting for their correlation. For a continuous outcome, this requires a multivariate linear regression model (akin to a repeated measures or longitudinal data model). For example, assuming a linear interaction, equation (2.1) can be extended to include multiple time-points as,

$$y_{ijt} = \alpha_{it} + \beta_{1it}z_{ij} + \beta_{2it}x_{ij} + \beta_{3it}y_{0ij} + \lambda_{wit}x_{ij}z_{ij} + e_{ijt}$$

$$e_{ijt} \sim N(0, \sigma_{it}^2) \quad \text{cov}(e_{ijt}, e_{ijt'}) = \sigma_{itt'} \quad (4.1)$$

where t and t' denote different time-points. REML estimation leads to an interaction estimate ($\hat{\lambda}_{wit}$) for each time-point, along with their variances ($\text{var}(\hat{\lambda}_{wit})$) and covariances ($\text{cov}(\hat{\lambda}_{wit}, \hat{\lambda}_{wit'})$) to be taken forward for the second stage.

Allowing for non-linear interactions, Equation (3.1) can be extended to:

$$y_{ijt} = \alpha_{it} + f_t(z_{ij}) + \beta_{2it}x_{ij} + \beta_{3it}y_{0ij} + f_t(x_{ij}z_{ij}) + e_{ijt}$$

$$e_{ijt} \sim N(0, \sigma_{it}^2) \quad \text{cov}(e_{ijt}, e_{ijt'}) = \sigma_{itt'} \quad (4.2)$$

Here, $f_t(z_{ij})$ defines the restricted cubic spline function at time t ; for example, with three internal knots it is defined by,

$$f_t(z_{ij}) = \delta_{1it}z_{1ij} + \delta_{2it}z_{2ij}$$

where z_{1ij} and z_{2ij} denote the first and second spline transformations of z_{ij} , respectively, and δ_{1i} and δ_{2i} denote the conditional effects on the outcome of a 1-unit increase in z_{1ij} and z_{2ij} , respectively. The interaction between the spline function and treatment at time t is defined by the function $f_t(x_{ij}z_{ij})$; again, with three internal knots we have

$$f_t(x_{ij}z_{ij}) = \gamma_{w1it}x_{ij}z_{1ij} + \gamma_{w2it}x_{ij}z_{2ij}$$

REML leads to an estimated $f_t(x_{ij}z_{ij})$ for each trial, giving parameter estimates (e.g., $\hat{\gamma}_{w1it}$ and $\hat{\gamma}_{w2it}$) at each time-point, alongside their variances and covariances, to be taken forward for the second stage.

Crucially, these first-stage models do not require each patient to provide outcome values for all time-points. Indeed, by accounting for correlation among the time-points (via $\text{cov}(e_{ijt}, e_{ijt'})$), this allows information from one time-point to contribute toward the parameter estimates at another time-point, and vice versa, via a missing at random assumption. As specified, the residual variances and covariances are unstructured (i.e., allowed to be distinct for each time-point and pair of time-points, respectively), but this can be modified (simplified) as appropriate.

4.2 | Second stage

The second stage requires a multivariate meta-analysis to pool all the parameters defining the interactions at all time-points, accounting for their within-trial and

between-trial variances and correlations. This allows the trial-specific estimates of the interaction (and any non-linear relationship) at one time-point to contribute toward the summary (meta-analysis) results about the interaction (and non-linear relationship) at another time-point. This is particularly important if some time-points are not available in some studies.

Let $\hat{\theta}_i$ be a vector containing the available K parameter estimates defining the interactions for the time-points recorded in the i th trial ($i = 1$ to S). For example, when fitting equation (4.1) in the first stage assuming a linear treatment-covariate interaction, then if T time points are recorded there are $K = T$ parameter estimates giving $\hat{\theta}_i = (\hat{\lambda}_{w11}, \hat{\lambda}_{w12}, \dots, \hat{\lambda}_{w1T})$. When fitting Equation 4.2 the number of parameters depends on $f_i(x_{ij}z_{ij})$ and the number of time-points. For example, with three internal knots, we would have $\hat{\theta}_i = (\hat{\gamma}_{w111}, \hat{\gamma}_{w211}, \hat{\gamma}_{w112}, \hat{\gamma}_{w212}, \dots, \hat{\gamma}_{w1iT}, \hat{\gamma}_{w2iT})$ and thus $K = 2 \times T$ parameters.

Then, the general specification of the multivariate meta-analysis model is:

$$\begin{aligned} \hat{\theta}_i | \theta_i &\sim N(\theta_i, \mathbf{S}_i) \\ \theta_i &\sim N(\theta, \Sigma) \end{aligned} \quad (4.3)$$

Here N denotes a multivariate normal distribution, θ_i contains the true underlying (true) values for the K parameters for the i^{th} trial, \mathbf{S}_i is the within-trial variance-covariance matrix for the i^{th} trial (assumed known) containing the K variances of the effect estimates (in the diagonal: $s_{i1}^2, s_{i2}^2, \dots, s_{iK}^2$) and their covariances (in the off-diagonal; for example $\rho_{wi(1,2)}s_{i1}s_{i2}$ is the within-trial covariance for outcomes 1 and 2), and θ is a vector containing the K mean parameter values. The matrix Σ is the between-trial variance-covariance matrix, and in its unstructured form contains the K between-trial variances of the true parameter values (in the diagonal: $\tau_1^2, \tau_2^2, \dots, \tau_K^2$) and their between-trial covariances (in the off-diagonal; e.g., the between-trial covariance for outcomes 1 and 2 is $\rho_{B(1,2)}\tau_{i1}\tau_{i2}$, where $\rho_{B(1,2)}$ is their between-trial correlation). The number of rows in each vector and matrix is equal to the number of parameters. We again assume unstructured between-study covariance matrix, but simplifications are possible, and of course the larger K , the greater the potential for convergence issues and the need for simplifications.

4.3 | Applied example: interactions at multiple time-points in the STEER-OA project

So far our STEER-OA application focused on treatment-covariate interactions for the time-point of 12 months (long

term). Many of the trials in the IPD meta-analysis had other time-points of interest available, in particular 3 months (short term) and 6 months (medium term). Hence, let us now model 3 (26 studies, 86.7%), 6 (14 studies, 46.7%), and 12 (13 studies, 43.3%) month outcomes simultaneously for the 30 studies that provided physical function scores, using the approaches described in Sections 4.1 and 4.2 above, and compare the results from analysing each time-point separately (in both the first and second stage).

4.3.1 | Linear interactions at multiple time-points

First, we assumed a linear effect of baseline function. The multivariate meta-analysis of all time-points jointly showed slightly larger interaction estimates than when analysing all time-points separately (Table 2). Further, the precision (standard error) of the interaction estimate was smaller for the multivariate estimates compared to the univariate estimates (Table 2). Nevertheless, the findings were quite similar, and the extra information gained by analysing all time-points together was quite small. This is evident from the borrowing of strength (BoS) statistic,⁴² which quantifies the percentage reduction in the variance of the summary interaction estimate for a particular time-point that is due to (borrowed from) data from other correlated time-points. This is less than 10% for every time-point (Table 2).

4.3.2 | Non-linear interactions at multiple time-points

We now use spline functions to allow for non-linear relationships between pain and baseline function, whilst also modelling the 3, 6 and 12 month time-points jointly. The trends are presented in Figure 3a–c, and in general, the findings are similar to when analysing each time-point separately. The most notable difference is in the medium term (6 months), as the confidence interval is much narrower, and the summary trend is more pronounced after using a multivariate meta-analysis of all time-points. All three time-points suggest that the effect of exercise increases in patients with a worse baseline function (scores further from zero), but with the plateau (no continued improvement beyond a baseline level of 42) only observed at the 12-month follow-up.

5 | DISCUSSION

In this paper, we proposed how to model linear and non-linear relationships at multiple time-points, when

TABLE 2 Comparison of univariate and multivariate meta-analysis results from the linear moderation effect of baseline function on exercise on pain outcomes at the time-points closest to 3 months (Short term), 6 months (Medium term) and 12 months (Long term).

Time-point	Univariate meta-analysis (separate IPD meta-analysis at each time)				Multivariate meta-analysis (IPD meta-analysis of all time-points jointly)				
	Interaction	Standard error	95% C.I.	τ^2	Interaction	Standard error	95% C.I.	τ^2	BoS Statistic
Short term (3 months)	−0.101	0.032	−0.163 to −0.040	0.000	−0.105	0.030	−0.164 to −0.046	0.000	7.6%
Medium term (6 months)	−0.086	0.036	−0.156 to −0.015	0.000	−0.097	0.034	−0.163 to −0.031	0.000	9.8%
Long term (12 months)	−0.078	0.038	−0.152 to −0.003	0.000	−0.080	0.036	−0.150 to −0.010	0.000	6.3%

Abbreviation: BoS, borrowing of strength statistic.

examining treatment-covariate interactions in an IPD meta-analysis of randomised trials with a continuous outcome. Researchers often embark on an IPD meta-analysis project to examine treatment-covariate interactions at the participant level, as they circumvent the problems of low power and aggregation bias facing meta-regression of across-trial information.¹¹ It also allows continuous covariates to be modelled properly and avoids arbitrary categorisation into two or more groups,⁴³ which reduces power and may lead to inappropriate interpretation of findings. In some trials, the categorisation may be embedded in the IPD provided (i.e., the original value has been lost), but usually the original value is available in the IPD, and this allows researchers to analyse covariates on the continuous scale and to examine non-linear interactions. We focused on restricted cubic splines for this purpose, but other spline types are possible,²³ and also other approaches,⁴⁴ such as fractional polynomials, pointwise averaging, barycentric rational interpolation,⁴⁵ and machine learning approaches such as tree-based methods.^{19,21,46,47} An advantage of cubic splines is that it allows knots to be fixed at the same positions in each study, thus ensuring the parameter estimates (from the first stage) can be combined across studies (in the second stage) to produce coherent and interpretable summary curves and results.

The value of analysing all time-points together depends on the proportion of trials not providing all time-points.^{41,48} In our example the benefit was quite small, mainly because most trials provided all time-points. Yet differences still arose and in situations with more missing time-points across studies, the gain in information will be more pronounced.⁴² This has been demonstrated mathematically and in applied examples.^{24,49} For example, when focusing on the overall treatment effect, Jones et al.⁴⁸ consider an IPD meta-analysis of five trials investigating the effects of selegiline versus

placebo for the treatment of Alzheimer's disease, with respect to the Mini-Mental State Examination (MMSE) score at 6 time-points from 1 month to 12 months, which were not all available in all studies. When the time points were wrongly assumed uncorrelated and a series of separate univariate meta-analyses conducted at each time point, the summary estimates and standard errors of the overall treatment effect were very different compared to a multivariate IPD meta-analysis. For example, assuming zero correlation gave a summary difference (between selegiline and placebo groups) at 9 months of 0.69 with standard error of 0.63, compared to the multivariate summary estimate of 0.34 with standard error of 0.52. Notably, the standard error of treatment effect estimates was consistently smaller when accounting for correlation, due to the large borrowing of strength across time-points due to large correlation and missing time-points. In situations with low correlation or mostly complete time-points, borrowing of strength may be small.⁵⁰

The methods proposed are quite advanced, requiring the synthesis of spline functions in a multivariate model allowing for random effects and correlations, both within and across studies, whilst adjusting for prognostic factors. The module *mvmeta* in Stata is able to fit such multivariate models (supplementary material in Data S1 provides example code). The complexity is justified as it makes full use of the available data, which is important after spending much time (often 1–2 years) collecting and harmonising IPD from multiple studies. Sadly, current practice is not utilising the IPD properly, with Gao et al. showing that treatment-covariate interactions are sub-optimally modelled in IPD meta-analysis cancer projects,⁵¹ with only 1 in 89 examining non-linear relationships. Further research is needed to examine situations where estimating correlations (either within-trials or between-trials) is problematic, for example when the number of participants is sparse in a particular trial, or there are few trials

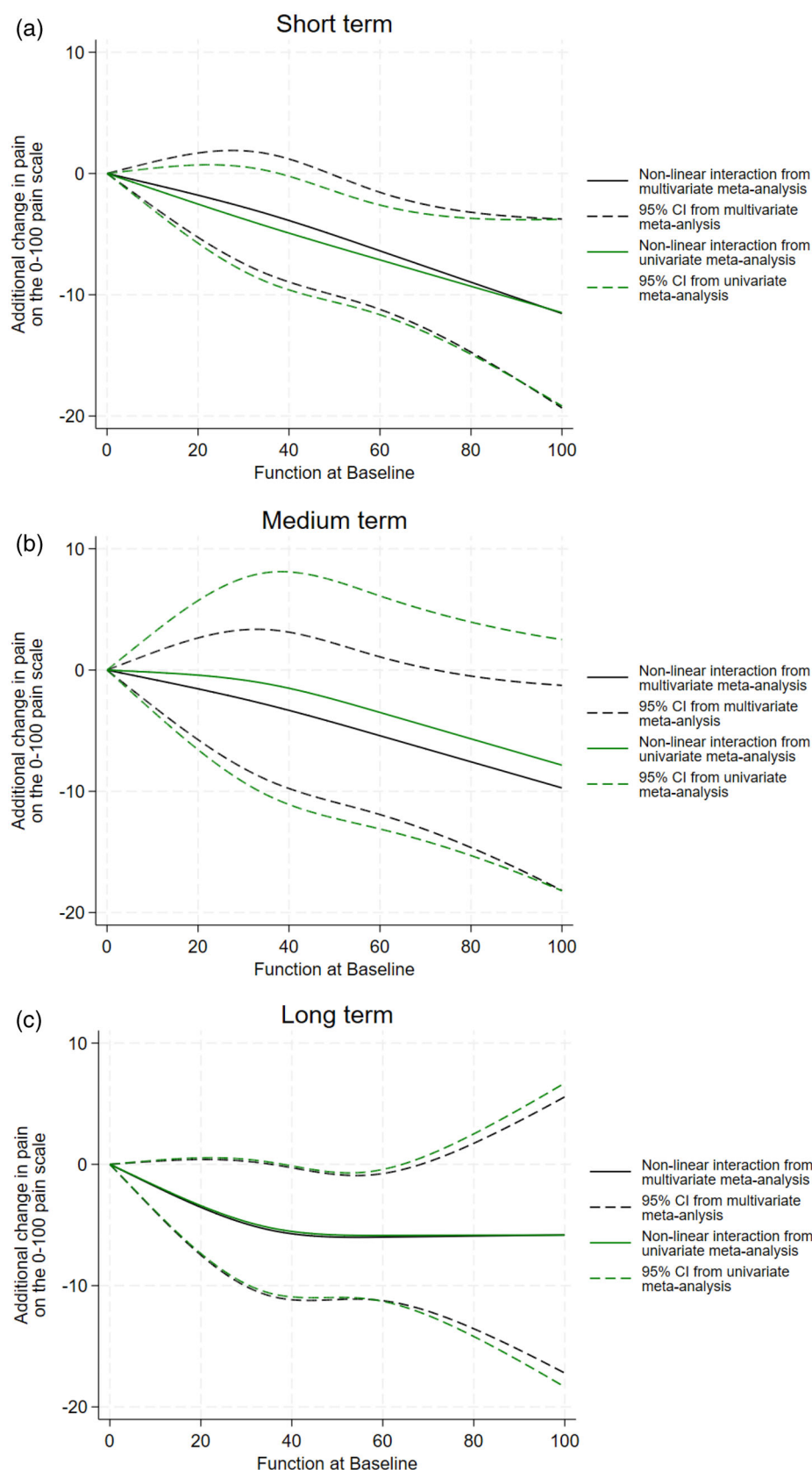


FIGURE 3 Comparison of multivariate and univariate analysis results from the non-linear moderation effect of baseline function on exercise on pain outcomes at the time-points closest to 3 months (Short term) [A], 6 months (Medium term) [B] and 12 months (Long term) [C].

with a particular time-point available. We assumed unstructured variance-covariance matrices (within each trial and also between trials), and further work is needed

to examine the impact of using constraints (e.g., common between-trial variance for all time-points; common between-trial correlation between all pairs of outcomes).

In our examples, we assumed a random-effects model as we considered heterogeneity in treatment-covariate interactions was likely at some time-points. However, this may not always be justified or computationally feasible, and a common-effects model (i.e., setting all between-study variances and correlations to zero) may be justified.

Although we focused on trials, the modelling principles also apply to IPD meta-analyses of observational studies, for example to examine interactions between two prognostic variables. We focused on a continuous outcome mapped to a 0–100 scale, but the approach could be applied to any continuous outcome scale (e.g., original, standardised) that is interpretable and combinable across studies. The general principle of using splines to model continuous variables and non-linear interactions also extends to other outcome types such as binary and time-to-event outcomes, for which multiple time-points may require multinomial models or Cox models (potentially with further interactions with time), respectively. Further research should also consider how to extend our work to obtain predicted treatment effects for an individual, conditional on their covariate value.⁵² Our work focused on estimating the interaction itself, but clinical decisions are more likely to require the predicted treatment effect. This may require the use of penalisation methods to shrink regression coefficients due to overfitting concerns.⁵³ How to implement such penalisation in a two-stage IPD meta-analysis framework requires consideration, as does extension to the network meta-analysis setting where multiple treatments are being compared at multiple time-points whilst accounting for non-linear effect modifiers, building on related work.^{54–56}

Some patients may have missing covariates values in a trial. Rather than excluding such patients, this can be handled (in each trial separately) by using mean imputation or the missing indicator method, which—although rightly criticised for use in other medical research applications—is actually appropriate for randomised trials aiming to estimate a conditional treatment effect,^{57,58} though more evaluation of the impact on interactions is still needed. Multiple imputation is a possible alternative.⁵⁸

In summary, we have proposed a multivariate meta-analysis approach for examining non-linear treatment-covariate interaction functions at multiple time-points, which we hope readers find useful for performing IPD meta-analyses of randomised trials with continuous outcomes to evaluate potential treatment effect modifiers.

AUTHOR CONTRIBUTIONS

Miriam Hattle: Conceptualization; writing – original draft; writing – review and editing; methodology; data curation; software; visualization; formal analysis. **Joie Ensor:** Funding acquisition; methodology; writing – review and editing. **Katie Scandrett:**

Methodology; writing – review and editing. **Marienke van Middelkoop:** Data curation; writing – review and editing. **Danielle A. van der Windt:** Methodology; writing – review and editing. **Melanie A. Holden:** Methodology; data curation; writing – review and editing. **Richard D. Riley:** Writing – review and editing; writing – original draft; conceptualization; methodology; software; funding acquisition; supervision; visualization.

ACKNOWLEDGMENTS

We would like to thank Elaine Hay and all members of the OA trial Bank Exercise Collaborative who shared individual participant data from their randomised controlled trials for inclusion in the STEER OA study, the running example throughout this paper. Thanks also to members of the STEER OA patient advisory group and wider members of the STEER OA team. This includes Jos Runhaar, Emma Healey, Jonathan Quicke, Krysia Dziedzic, Danielle Burke, Nadia Corp, Amardeep Legha, Sita Bierma-Zeinstra, and Nadine E Foster. We thank two anonymous reviewers for their constructive comments to help improve the article.

FUNDING INFORMATION

MiH, JE, and RDR were supported by funding from the MRC-NIHR Better Methods Better Research panel (grant reference: MR/V038168/1). MiH, JE, KES, and RDR were supported by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. The STEER OA study was funded by the Chartered Society of Physiotherapy Charitable Trust (PRF/16/A07), National Institute for Health and Care Research (NIHR) School of Primary Care Research (351); Nadine Foster's NIHR Senior Investigator Award. This is independent research funded by MRC-NIHR Better Methods Better Research panel (grant reference: MR/V038168/1) and carried out at the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre (BRC). RDR is an NIHR Senior Investigator. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

RDR receives royalties for two books: *Prognosis Research in Healthcare* and *Individual Participant Data Meta-Analysis*.

DATA AVAILABILITY STATEMENT

Keele University is a member of the UK Reproducibility Network and committed to the principles of the UK Concordat on Open Research Data. The Keele University School of Medicine has a long-standing commitment to sharing data from our studies to improve research

reproducibility and to maximise benefits for patients, the wider public and the health and care system. De-identified IPD that underlie the results from this study will be made available to bonafide researchers on reasonable request via the OA Trial Bank and with permission from the original randomised controlled trial leads. Data requests and enquiries should be directed to m.holden@keele.ac.uk. We encourage collaboration with those who collected the data, to recognise and credit their contributions. Release of data will be subject to a data use agreement between the OA Trial Bank, original randomised controlled trial leads, and the third party requesting the data. De-identified IPD will be encrypted on transfer. Example code is provided in the Supplementary Material in Data S1.

ORCID

Miriam Hattle  <https://orcid.org/0000-0003-1542-6277>

Joie Ensor  <https://orcid.org/0000-0001-7481-0282>

Katie Scandrett  <https://orcid.org/0000-0001-6111-2805>

Mariénke van Middelkoop  <https://orcid.org/0000-0001-6926-0618>

Danielle A. van der Windt  <https://orcid.org/0000-0002-7248-6703>

Melanie A. Holden  <https://orcid.org/0000-0003-0374-2862>

Richard D. Riley  <https://orcid.org/0000-0001-8699-0735>

REFERENCES

- Hingorani AD, Windt DA, Riley RD, et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. *BMJ*. 2013;346:e5793.
- Riley RD, van der Windt D, Croft P, Moons KGM, eds. *Prognosis Research in Healthcare: Concepts, Methods and Impact*. Oxford University Press; 2019.
- Hudis CA. Trastuzumab – mechanism of action and use in clinical practice. *N Engl J Med*. 2007;357(1):39–51.
- Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol*. 2004;57(3):229–236.
- Riley RD, Tierney JF, Stewart LA, eds. *Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research*. Wiley; 2021.
- Schmid CH, Stark PC, Berlin JA, Landais P, Lau J. Meta-regression detected associations between heterogeneous treatment effects and study-level, but not patient-level, factors. *J Clin Epidemiol*. 2004;57(7):683–697.
- Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med*. 2002;21(3):371–387.
- Thompson SG, Higgins JP. Treating individuals 4: can meta-analysis help target interventions at individuals most likely to benefit? *Lancet*. 2005;365(9456):341–346.
- Kent DM, Paulus JK, van Klaveren D, et al. The predictive approaches to treatment effect heterogeneity (PATH) statement. *Ann Intern Med*. 2019;172:35.
- Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ*. 2018;363:k4245.
- Riley RD, Debray TPA, Fisher D, et al. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. *Stat Med*. 2020;39(15):2115–2137.
- Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ*. 2017;356:j573.
- Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. *Stat Med*. 2017;36(5):772–789.
- Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. *Stat Med*. 2008;27(11):1870–1893.
- Belias M, Rovers MM, Reitsma JB, Debray TPA, Int'Hout J. Statistical approaches to identify subgroups in meta-analysis of individual participant data: a simulation study. *BMC Med Res Methodol*. 2019;19(1):183.
- Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med*. 2017;36(5):855–875.
- Morris TP, Fisher DJ, Kenward MG, Carpenter JR. Meta-analysis of Gaussian individual patient data: two-stage or not two-stage? *Stat Med*. 2018;37(9):1419–1438.
- Riley RD, Ensor J, Hattle M, Papadimitropoulou K, Morris TP. Two-stage or not two-stage? That is the question for IPD meta-analysis projects. *Res Synth Methods*. 2023;14(6):903–910.
- White IR, Kaptoge S, Royston P, Sauerbrei W, Emerging Risk Factors Collaboration. Meta-analysis of non-linear exposure-outcome relationships using individual participant data: a comparison of two methods. *Stat Med*. 2019;38(3):326–338.
- Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med*. 2004;23(16):2509–2525.
- Sauerbrei W, Royston P. Investigating treatment-effect modification by a continuous covariate in IPD meta-analysis: an approach using fractional polynomials. *BMC Med Res Methodol*. 2022;22(1):98.
- Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. *Stat Med*. 2012;31:3821–3839.
- Belias M, Rovers MM, Hoogland J, Reitsma JB, Debray TPA, Int'Hout J. Predicting personalised absolute treatment effects in individual participant data meta-analysis: an introduction to splines. *Res Synth Methods*. 2022;13(2):255–283.
- Riley RD, Price MJ, Jackson D, et al. Multivariate meta-analysis using individual participant data. *Res Synth Methods*. 2015;6:157–174.
- Simmonds MC, Higgins JP. Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. *Stat Med*. 2007;26(15):2982–2999.

26. Fisher DJ. Two-stage individual participant data meta-analysis and generalized forest plots. *Stata J.* 2015;15(2):369-396.
27. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc.* 2009; 172:137-159.
28. Holden MA, Hattle M, Runhaar J, et al. Moderators of the effect of therapeutic exercise for knee and hip osteoarthritis: a systematic review and individual participant data meta-analysis. *Lancet Rheumatol.* 2023;5(7):e386-e400.
29. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med.* 2001; 20(24):3875-3889.
30. Jackson D, Law M, Rucker G, Schwarzer G. The Hartung-Knapp modification for random-effects meta-analysis: a useful refinement but are there any residual concerns? *Stat Med.* 2017;36(25):3923-3934.
31. Royston P, Sauerbrei W. Interactions between treatment and continuous covariates: a step toward individualizing therapy. *J Clin Oncol.* 2008;26(9):1397-1399.
32. Kasenda B, Sauerbrei W, Royston P, et al. Multivariable fractional polynomial interaction to investigate continuous effect modifiers in a meta-analysis on higher versus lower PEEP for patients with ARDS. *BMJ Open.* 2016;6(9):e011148.
33. Kasenda B, Sauerbrei W, Royston P, Briel M. Investigation of continuous effect modifiers in a meta-analysis on higher versus lower PEEP in patients requiring mechanical ventilation – protocol of the ICEM study. *Syst Rev.* 2014;3:46.
34. Harrell FE Jr. *Regression Modeling Strategies: with Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis (Second Edition).* Springer; 2015.
35. de Boor C. *A practical guide to splines.* Vol xviii. Springer; 2001:346.
36. Royston P, Sauerbrei W. Multivariable modeling with cubic regression splines: a principled approach. *Stata J.* 2007;7(1): 45-70.
37. Binder H, Sauerbrei W, Royston P. Comparison between splines and fractional polynomials for multivariable model building with continuous covariates: a simulation study with continuous response. *Stat Med.* 2013;32(13):2262-2277.
38. White IR. Multivariate random-effects meta-regression: updates to mvmeta. *Stata J.* 2011;11:255-270.
39. White IR. Multivariate random-effects meta-analysis. *Stata J.* 2009;9:40-56.
40. Riley RD, Jackson D, Salanti G, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. *BMJ.* 2017;358:j3932.
41. Jackson D, Riley RD, White IR. Multivariate meta-analysis: potential and promise. *Stat Med.* 2011;30:2481-2498.
42. Jackson D, White IR, Price M, Copas J, Riley RD. Borrowing of strength and study weights in multivariate and network meta-analysis. *Stat Methods Med Res.* 2017;26(6):2853-2868.
43. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst.* 1994;86(11):829-835.
44. Walker R, Stewart L, Simmonds M. Estimating interactions in individual participant data meta-analysis: a comparison of methods in practice. *Syst Rev.* 2022;11(1):211.
45. Baker RD, Jackson D. Statistical application of barycentric rational interpolants: an alternative to splines. *Comput Stat.* 2014;29(5):1065-1081.
46. Sauerbrei W, Royston P. A new strategy for meta-analysis of continuous covariates in observational studies. *Stat Med.* 2011; 30(28):3341-3360.
47. Huber C, Benda N, Friede T. Subgroup identification in individual participant data meta-analysis using model-based recursive partitioning. *Adv Data Anal Classif.* 2022;16(3):797-815.
48. Jones AP, Riley RD, Williamson PR, Whitehead A. Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. *Clin Trials.* 2009;6(1):16-27.
49. Riley RD. Multivariate meta-analysis: the effect of ignoring within-study correlation. *J R Stat Soc A Stat Soc.* 2009;172: 172-811.
50. Trikalinos TA, Hoaglin DC, Schmid CH. Empirical and Simulation-Based Comparison of Univariate and Multivariate Meta-Analysis for Binary Outcomes. Methods Research Report Agency for Healthcare Research and Quality. 2013.
51. Gao Y, Liu M, Shi S, et al. Prespecification of subgroup analyses and examination of treatment-subgroup interactions in cancer individual participant data meta-analyses are suboptimal. *J Clin Epidemiol.* 2021;138:156-167.
52. Godolphin PJ, Marlin N, Cornett C, et al. Use of multiple covariates in assessing treatment-effect modifiers: a methodological review of individual participant data meta-analyses. *Res synth. Methods.* 2023;15:107-116.
53. Hoogland J, Int'Hout J, Belias M, et al. A tutorial on individualized treatment effect prediction from randomized trials with a binary endpoint. *Stat Med.* 2021;40(26):5961-5981.
54. Efthimiou O, Mavridis D, Cipriani A, Leucht S, Bago P, Salanti G. An approach for modelling multiple correlated outcomes in a network of interventions using odds ratios. *Stat Med.* 2014;33(13):2275-2287.
55. Dagne GA, Brown CH, Howe G, Kellam SG, Liu L. Testing moderation in network meta-analysis with individual participant data. *Stat Med.* 2016;35(15):2485-2502.
56. Jansen JP, Vieira MC, Cope S. Network meta-analysis of longitudinal data using fractional polynomials. *Stat Med.* 2015; 34(15):2294-2311.
57. Groenwold RH, White IR, Donders AR, Carpenter JR, Altman DG, Moons KG. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. *CMAJ.* 2012;184(11):1265-1269.
58. Sullivan TR, White IR, Salter AB, Ryan P, Lee KJ. Should multiple imputation be the method of choice for handling missing data in randomized trials? *Stat Methods Med Res.* 2018;27(9):2610-2626.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hattle M, Ensor J, Scandrett K, et al. Individual participant data meta-analysis to examine linear or non-linear treatment-covariate interactions at multiple time-points for a continuous outcome. *Res Syn Meth.* 2024;1-16. doi:10.1002/jrsm.1750

APPENDIX A

BOX A1 Brief introduction to modelling non-linear relationships for a continuous covariate using restricted cubic splines

Let the original continuous covariate (e.g., age) be denoted by z . Rather than simply assuming a linear association with the outcome of interest (e.g., $Y = \delta_0 + \delta_1 z$), a restricted spline function, denoted by $f(z)$, allows for a potential non-linear association.³⁴ It is obtained by fitting a series of cubic functions and forcing them to join (and be smoothed) at certain points (called internal knots), whilst constraining the function to be linear in the tails (i.e., before the first internal knot and after the last internal knot). The magnitude and shape of the curve are defined by multiple parameters depending on the number of knots chosen. If we assume there are k internal knots in total at locations t_1, t_2, \dots, t_k , then the restricted cubic spline is:

$$f(z) = \delta_0 + \delta_1 z_1 + \delta_2 z_2 + \dots + \delta_{k-1} z_{k-1}$$

where $z_1 = z$ and thus there is an assumed linear association between z and the outcome before the first internal knot (i.e., when $z < t_1$), and for $c = 1, \dots, k-2$,

$$z_{c+1} = (z - t_c)_+^3 - (z - t_{k-1})_+^3 \frac{(t_k - t_c)}{(t_k - t_{k-1})} + (z - t_k)_+^3 \frac{(t_{k-1} - t_c)}{(t_k - t_{k-1})}$$

where the A_+ notation means that $A = A$ if $A > 0$, and $A = 0$ if $A \leq 0$. This specification of z_{c+1} also forces the trend to there to be a linear association between z and the outcome after the last internal knot (i.e., when $z \geq t_k$).

Therefore, using a restricted cubic spline in a regression analysis will include the original covariate (z) as linear and $k-2$ piecewise cubic variables. So with k internal knots, there are $k-1$ parameters to estimate which define the spline function, plus an 'intercept' term δ_0 . We can examine whether the use of the spline function (i.e., $f(z)$) adds value over and above assuming a linear trend by comparing the change in the model fit (e.g., the likelihood ratio statistic).

In terms of how to choose the number of knots, Harrell stated that 'for many datasets, $k = 4$ offers an adequate fit of the model and is a good compromise between flexibility and loss of precision caused by overfitting a small sample'.³⁴ If the sample size is small, three knots should be used in order to have enough observations in between the knots to be able to fit each polynomial. The location of the knots is best pre-specified, based on the quantiles of the continuous variable, with the following suggested by Harrell³⁴:

Number of internal knots, k	Knot locations in terms of quantiles of the z variable						
3	0.1	0.5	0.9				
4	0.05	0.35	0.65	0.95			
5	0.05	0.275	0.5	0.725	0.95		
6	0.05	0.23	0.41	0.59	0.77	0.95	
7	0.025	0.1833	0.3417	0.5	0.6583	0.8167	0.975

Note: Box taken from fig. 4 of Riley et al.,¹¹ reproduced with permission, © 2020 Wiley.