Statistical methods used to combine the effective reproduction number, $R(t)$, and other related measures of COVID-19 in the UK

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In the recent COVID-19 pandemic, a wide range of epidemiological modelling approaches have been used to predict the effective reproduction number, $R(t)$, and other COVID-19 related measures such as the daily rate of exponential growth, $r(t)$. These candidate models use different modelling approaches or differing assumptions about spatial or age mixing, and some capture genuine uncertainty in scientific understanding of disease dynamics. Combining estimates using appropriate statistical methodology from multiple candidate models is important to better understand the variation of these outcome measures to help inform decision making. In this paper, we combine these estimates for specific UK nations and regions using random effects meta analyses techniques, utilising the restricted maximum likelihood (REML) method to estimate the heterogeneity variance parameter, and two approaches to calculate the confidence interval for the combined estimate: the standard Wald-type intervals; and the Knapp and Hartung (KNHA) method. As estimates in this setting are derived using model predictions, each with varying degrees of uncertainty, equal weighting is favoured over the more standard inverse-variance weighting in order avoid potential up-weighting of models providing estimates with lower levels of uncertainty that are not fully accounting for inherent uncertainties. Both equally weighted models using REML alone and REML+KNHA approaches were found to provide similar variation for $R(t)$ and $r(t)$, with both approaches providing wider, and therefore more conservative, confidence intervals around the combined estimate compared to the standard inverse-variance weighting approach. Utilising these meta-analysis techniques has allowed for statistically robust combined estimates to be calculated for key COVID-19 outcome measures. This in turn allows timely and informed decision making based on all of the available information.

1 Introduction

Following the outbreak of COVID-19 and attempts to control the spread of the disease, focus in the UK has moved to estimating the effective reproduction number, $R(t)$, which reflects the infectious potential of a disease and is defined as the average number of secondary cases per primary case at time t since the start of the epidemic[1]. The basic reproduction number, $R(0)$, is the number of secondary cases per primary case at the beginning of an epidemic, in an entirely susceptible population[2]. As more individuals are infected or immunised, the population in which $R(t)$ is based consists of both naive/susceptible and exposed/immune individuals and therefore changes over time[2]. If $R(t)$ for the UK exceeds 1, the infection rate will grow exponentially. To bring the epidemic under control, the corresponding $R(t)$ needs to drop and remain as far below 1 as practicable[1]. There are a number of ways to estimate $R(t)$, for example using information on the number of cases, number of deaths, survey data, or a combination of these. From incidence/cases data, the mean generation time and initial growth rates (defined as the *per capita* change in number of new cases per unit of time) in the infected population can be used[1,3]. From death data, $R(t)$ can be determined by using the number of deaths that can be attributable to the infection, with key information including the infection fatality rate, mean generation time and the time from onset of symptoms to death[4,5]. For example, $R(t)$ can be linked to the number of deaths using a renewal equation which incorporates the time between death of the infector

and infectee[2]. $R(t)$ can also be determined by surveying the population for infection and inferring likely case data; an approach which commonly uses a contact function that identifies the susceptible individuals, how likely transmission is to be (given that contact has occurred), and measures the contact between members of the population[6,7]. Detailed methodology is not provided in this paper but available from the Royal Society[2].

Other key COVID-19 outcomes of interest include the daily rate of exponential growth, $r(t)$, which represents an approximation of the percentage change in the number of infections over time[8]. If $r(t)$ is positive, the infection rate will grow exponentially, whereas if $r(t)$ is negative and remains negative, it will be possible for the epidemic to be brought under control.

In the UK, epidemiological modelling is provided by a number of highly skilled academic groups based on a number of different data streams, modelling techniques and assumptions (a summary of these models is provided in the appendix and detailed descriptions are also available from the Royal Society[2]). Each of these groups provide key understanding and insight into the current state of the epidemic, and these estimates must therefore be combined to provide an overall assessment so that decision making is based on all available evidence. In this paper, we use meta-analyses to combine estimates of $R(t)$ and $r(t)$ for specific nations/geographical regions of the UK, from multiple candidate epidemiological models.

1.1 Existing Methods to Combine Estimates

The methodology used to combine modelling estimates is not limited to meta analyses. For example, Lindstrom *et al* incorporate an ensemble modelling approach using a Bayesian framework and various weighting schemes[9]. Ensemble methods were also explored by Ray *et al*[10], which used model stacking[11], again, with exploration into different weighting approaches to combine predictions from multiple models[10]. Methods used to aggregate expert-generated predictions have also been explored by Genest and Zidek, O'Hagan *et al*, and McAndrew *et al*[12–14]. Genest and Zidek provide a comprehensive annotated bibliography on various methods, including but not limited to: the use of a supra Bayesian approach whereby in some cases, there is a decision maker for whom the panel of experts reports to[15,16]; and the Vincentization method which averages the per cent quantiles of the experts' distribution to construct a consensus distribution[17]. McAndrew *et al* provide a more recent review on various methods to aggregate predictions from experts, including Cooke's method which incorporates a calibration score to assign weights to the experts[18], stacking methods[11], and other pooling methods which transform the aggregated forecast distribution such as the Spread-adjusted Linear Pool (SLP) method[19–21] and Beta Linear Pool (BLP) method[22,23]. In terms of combining COVID-19 related outcomes, a number of combination approaches were explored to combine model projections by Silk *et al*[24] and Funk *at al*[25], including stacking methods, and regression-based methods such as ensemble model output statistics (EMOS)[26], and Quantile Regression Averaging (QRA)[27].

1.2 Application of the Meta Analysis Approach

Meta analysis, the process of synthesizing data from a series of separate studies[28], is a well-known and established method, used ubiquitously in fields such as epidemiology, medicine, climate science, psychology, and education. It provides a rapid and simple approach, and its results are easy to interpret. In this paper, we use this method to provide an estimate of $R(t)$ from multiple models and assumptions. Effectively $R(t)$ is a physical quantity that could potentially be measured if we had perfect knowledge of infection state and transmission risk of all individuals through time. Clearly, in reality, this is impossible and therefore $R(t)$ must be estimated from available data. However, there are a number of entirely valid ways to estimate $R(t)$ and each provides insight into the current value. We require the best knowledge of $R(t)$ that can be provided and each model estimate captures an aspect of the current $R(t)$ value, therefore meta-analysis will, by definition, provide an overall estimate, averaged over all of the modelling assumptions and potential methodologies, providing a combined estimate that benefits from all available information. However, the combination naturally assumes that the candidate models are valid and worth considering.

Meta-analysis models can assume fixed or random effects; i.e. a shared common effect or distribution of effects. As it is possible for each candidate model to use a different method to estimate these outcome measures, the modelling approaches and/or underlying assumptions are assumed to vary. For example, different modelling approaches (e.g. mechanistic or empirical) or differing assumptions about spatial or age mixing may be used[24]. Moreover, the random effects model assumes a distribution of true effect sizes as opposed to a shared common (true) effect size assumed in

the fixed effects model[28,29]. Subsequently, a meta-analysis using a random effects model is chosen over a fixed effects model. Details and motivating examples on fixed and random effects models for analysis can be found in Borenstein *et al.*[30]. The random effects model can be defined as:

$$\widehat{\theta}_i = \theta_i + \varepsilon_i \qquad \theta_i \sim N(\theta, \tau^2) \tag{1}$$

where θ_i is the true effect size in group i (for a set of $i = 1, ..., k$ groups), $\widehat{\theta}_i$ is the estimated effect size in group i, θ is the average effect across all groups, and ε_i are the within-group errors[29]. θ_i is sampled from a distribution, typically assumed to be normal, of mean θ and variance τ^2, the heterogeneity variance parameter.[29].

The combined estimate, $\widehat{\theta}$, with associated variance, $Var(\widehat{\theta})$, can be calculated as follows[29]:

$$\widehat{\theta} = \frac{\sum\limits_{i=1}^{k} w_i \widehat{\theta}_i}{\sum\limits_{i=1}^{k} w_i},$$

$$Var(\widehat{\theta}) = \left(\frac{1}{\sum\limits_{i=1}^{k} w_i}\right)^2 \sum\limits_{i=1}^{k} w_i^2 (\widehat{\sigma}_i^2 + \widehat{\tau}^2) \tag{2}$$

where w_i denotes the weighting applied to the estimate in group i, $\widehat{\sigma}_i^2$ the estimated variance of the estimate in group i, and $\widehat{\tau}^2$ the estimated heterogeneity variance parameter; a measure of the heterogeneity (or variability) between estimates.

The standard weighting applied in a meta analysis is by way of *inverse-variance*, whereby $w_i = 1/(\widehat{\sigma}_i^2 + \tau^2)$, whereas an equally weighted model has weighting $w_i = 1/k$. The corresponding combined estimate, $\widehat{\theta}$, and associated variance, $Var(\widehat{\theta})$, from Equation (2) become:

$$\widehat{\theta} = \begin{cases} \dfrac{\sum\limits_{i=1}^{k} \widehat{\theta}_i (\widehat{\sigma}_i^2 + \widehat{\tau}^2)^{-1}}{\sum\limits_{i=1}^{k} (\widehat{\sigma}_i^2 + \widehat{\tau}^2)^{-1}} & \text{for inverse-variance weighting} \\[4ex] \dfrac{1}{k} \sum\limits_{i=1}^{k} \widehat{\theta}_i & \text{for equal weighting} \end{cases}$$

$$Var(\widehat{\theta}) = \begin{cases} \dfrac{1}{\sum\limits_{i=1}^{k} (\widehat{\sigma}_i^2 + \widehat{\tau}^2)^{-1}} & \text{for inverse-variance weighting} \\[4ex] \dfrac{1}{k^2} \sum\limits_{i=1}^{k} (\widehat{\sigma}_i^2 + \widehat{\tau}^2) & \text{for equal weighting} \end{cases} \tag{3}$$

For random effects meta analyses, several methods are available to estimate τ^2. In addition, multiple methods can be used to calculate the confidence intervals (CIs) for the combined estimate. This paper focuses on the well-established restricted maximum likelihood (REML) method recommended by Veroniki *et al.*[31] to estimate τ^2, with the incorporation of two different approaches for the calculation of the CIs: the standard Wald-type method; and the Knapp and Hartung (KNHA) method (also referred to as the Hartung-Knapp-Sidik-Jonkman method)[32,33]. The Wald-type method is chosen as it is a well-established approach, whilst the KNHA method has been shown to provide better coverage[29]. The standard Wald-type CI is calculated as[29]:

$$\widehat{\theta} \pm z_{1-\frac{\alpha}{2}} \sqrt{Var(\widehat{\theta})} \tag{4}$$

with $\widehat{\sigma}_i^2$ the estimated variance for group i, and z-score calculated for the required confidence interval of the standard normal distribution.

The KNHA CI is calculated as [29]:

$$\widehat{\theta} \pm t_{k-1,1-\frac{\alpha}{2}} \sqrt{Q \cdot Var(\widehat{\theta})}$$

$$\text{where } Q = \frac{1}{k-1} \sum_{i=1}^{k} \left(\frac{1}{\widehat{\sigma}_i^2 + \widehat{\tau}^2} \right) (\widehat{\theta}_i - \widehat{\theta})^2 \tag{5}$$

with t-score calculated from the t distribution with $k-1$ degrees of freedom.

The use of REML to estimate τ^2 has been shown to be robust to deviations from normality and to perform well, particularly when utilising the KNHA method to calculate the CIs, when only a limited number of models are available for comparison [29,34,35]. This papers refers to these two approaches as the *REML alone* and *REML+KNHA* approaches respectively.

2 Methods

2.1 Data Preparation

This paper utilised data from 12 different candidate models, in which estimated quantiles from each model were available for up to 12 UK nations/regions for a set cut-off date. These candidate models were drawn from many of the leading academic institutions and epidemiologists in the UK whose models already support government response for pandemics. In this paper, candidate models and UK nations/regions were anonymised, and estimates were combined according to each of the anonymised UK nations/regions separately.

The aim of the data preparation step is to generate appropriate estimated means and standard errors for each candidate model to be used in the combination. For a set of $i = 1, ..., k$ candidate models, let y_i denote the mean estimate of the outcome measure of interest for the ith model (previously denoted θ_i), with associated standard error, se_i.

Each of the candidate models outputs j^{th} percentiles, $Q_i(j)$, for the outcome measure of interest, as opposed to y_i and se_i. In order for the estimates to be combined in a random effects model for an outcome measure of interest, initial approximations of y_i and se_i, $\widehat{y}_i$ and $\widehat{se}_i$ are required. Using the jth percentiles from the ith candidate model, $Q_i(j)$, y_i^* and se_i^* are initially calculated as follows:

$$y_i^* = Q_i(50) \tag{6}$$

$$se_i^* = \frac{max(|Q_i(95) - Q_i(50)|, |Q_i(50) - Q_i(5)|)}{z_{1-\frac{\alpha}{2}}} \tag{7}$$

with z-score calculated using $\alpha = 0.10$ for the 90% confidence interval of the standard normal distribution.

2.2 Skewness Exploration and Correction

As some of the model estimates maybe skewed, the use of $Q_i(50)$ for an approximation of yi may not be optimal and an adjusted estimate required. First, the degree of skewness of the estimates, SK_i, is calculated and assessed using Bowley's formula [36]:

$$SK_i = \frac{Q_i(75) + Q_i(25) - 2Q_i(50)}{Q_i(75) - Q_i(25)} \tag{8}$$

An absolute value of 0.5 is then used to indicate a moderate or higher level of skewness [37]. If $|SK_i| \le 0.5$, then skewness is deemed sufficiently small and a normal distribution can be fitted to the percentiles, i.e. $\widehat{y}_i = Q_i(50)$ from Equation (6) and $\widehat{se}_i = se_i^*$ from Equation (7). However, if $|SK_i| > 0.5$, then an adjustment to the estimates are required. First, appropriate transformations to the percentiles are made: if the estimates are negatively skewed the quantiles are inverted i.e. $Q_i(5)$, $Q_i(50)$, $Q_i(95) \rightarrow -Q_i(95)$, $-Q_i(50)$, $-Q_i(5)$; and a positive constant is added, where applicable, to ensure the adjusted quantiles are positive. A gamma distribution is fit to the adjusted percentiles by minimizing

the sum of squared distance between the percentiles of the gamma distribution and those of the model estimates using a Particle Swarm Optimisation (PSO) algorithm[38]. The PSO is performed using the `psoptim` optimisation call from the `pso` package[39] in R[40]. This optimizes the non-linear function via an algorithm using a series of learning parameters[38]. Further details on the process are provided by Kennedy[38], Yang[41], and Bendtsen[39]. The square-root of the variance from the optimisation process can then be used as a conservative estimate of $\widehat{se_i}$, and the corresponding mean from the optimisation process, after a suitable back-transformation applied, can be used for $\widehat{y_i}$. Although the adjusted estimates remain skewed, the use of REML for a meta-analysis is robust even in the case of extreme non-normal distributions[34,35].

2.3 Equal Weighting

The standard weighting applied in meta analyses is by way of *inverse-variance* weighting, whereby estimates which provide the highest precision are weighted highest. However, estimates in this setting are derived using model predictions, each with varying degrees of uncertainty, i.e. estimates provided with smaller levels of uncertainty are not necessarily more representative of the situation over another model. For example, a model with wider 90% intervals could in fact be more representative over another model with narrower 90% intervals as the modelling approach takes into account more information in the derivation of its estimates. The standard *inverse-variance* weighting could therefore unjustifiably change estimates as models with smaller uncertainty will be up-weighted. As each modelling approach differs in how uncertainty is accounted for and conservative estimates in the context are preferable, the comparison of uncertainty levels alone would not be appropriate in this particular setting. To counter this, user-defined equal weighting is applied to the candidate models using $\frac{1}{k}$, where k is the number of candidate models that are included in the random effects model[42].

2.4 Fitting the Random Effects Model

Having estimated the distributions of each model to be included in the combination, we now calculate the combined estimate using the random effects model. The custom weights, together with $\widehat{y_i}$ and $\widehat{se_i}$ from the fitted distributions of each candidate model, are passed to the `metafor` package in R using the `rma` call[43], using the REML method to estimate τ^2 with incorporation of either the Wald-type CIs (*REML alone*), or KNHA method for the calculation of the CIs (*REML+KNHA*).

3 Worked Example

To illustrate the method in practice, a step by step guide is given here for how the estimated quantiles from a group of anonymised models for a selected anonymised UK nation/region can be used to provide a combined estimate for this selected nation/region. A full set of results for all UK nations/regions can be found in Section 5 and the Appendix, and a csv file and example R script provided as supplementary material for the worked example. Table 1 shows the $R(t)$ estimated quantiles from 12 anonymised models for anonymised UK nation/region 10, together with the calculated se_i^* and SK_i using Equations (7) and (8) respectively, and corresponding $\widehat{y_i}$ and $\widehat{se_i}$ calculated values. No estimated quantiles were available from candidate model 8 for this particular nation/region but estimated quantiles are available for other nation/regions for this model (see Appendix Table 2 for the full list of $R(t)$ estimates by model and nation/region).

Moderate to high skewness was identified for candidate model 5, although this was only marginal (8.6×10^{-14} over the threshold). The corresponding adjusted estimate, $\widehat{y_i}$, following input into the `psoptim` optimisation call resulted in an identical estimate to $Q_i(50)$ in this case (to four decimal places), but with modified $\widehat{se_i}$ of 0.0028.

To illustrate the performance of the equal weighting random effects model approach, an initial random effects model using the REML method to estimate τ^2 but with the standard *inverse-variance* weighting was applied to provide a combined estimate. The equally weighted random effects models using REML and Wald-type CIs (*REML alone*) or KNHA CIs (*REML+KNHA*) were then applied to the same estimates. The $R(t)$ estimates from the candidate models, together with the combined estimates using these methods are shown in Figure 1.

Model	$Q_i(5)$	$Q_i(25)$	$Q_i(50)$	$Q_i(75)$	$Q_i(95)$	SK_i	se_i^*	$\widehat{y_i}$	$\widehat{se_i}$
1	0.6300	0.6800	0.7400	0.8100	0.8700	0.0769	0.0790	0.7400	0.0790
2	0.6228	0.6775	0.7045	0.7413	0.8265	0.1540	0.0742	0.7045	0.0742
3	0.6400	0.7000	0.7400	0.7900	0.8700	0.1111	0.0790	0.7400	0.0790
4	0.4400	0.6300	0.7500	0.8700	1.1400	0.0000	0.2371	0.7500	0.2371
5	0.7898	0.7930	0.7954	0.7963	0.7995	-0.5000	0.0034	0.7954	0.0028
6	0.8076	0.8199	0.8329	0.8494	0.8749	0.1189	0.0256	0.8329	0.0256
7	0.6232	0.7111	0.7862	0.8647	0.9890	0.0222	0.1233	0.7862	0.1233
8	-	-	-	-	-	-	-	-	-
9	0.7509	0.8626	0.9382	1.0159	1.1604	0.0148	0.1351	0.9382	0.1351
10	0.8175	0.8250	0.8302	0.8353	0.8427	-0.0041	0.0077	0.8302	0.0077
11	0.8412	0.8956	0.9293	0.9657	1.0340	0.0398	0.0637	0.9293	0.0637
12	0.6600	0.7100	0.7600	0.8000	0.8600	-0.1111	0.0608	0.7600	0.0608

Table 1: $R(t)$ estimates and corresponding SK_i, se_i^*, $\widehat{y_i}$ and $\widehat{se_i}$ calculated values for anonymised models 1 to 12 for anonymised UK nation/region 10. All numbers displayed to four decimal places. [†]No estimated quantiles were available from candidate model 8 for this particular nation/region.
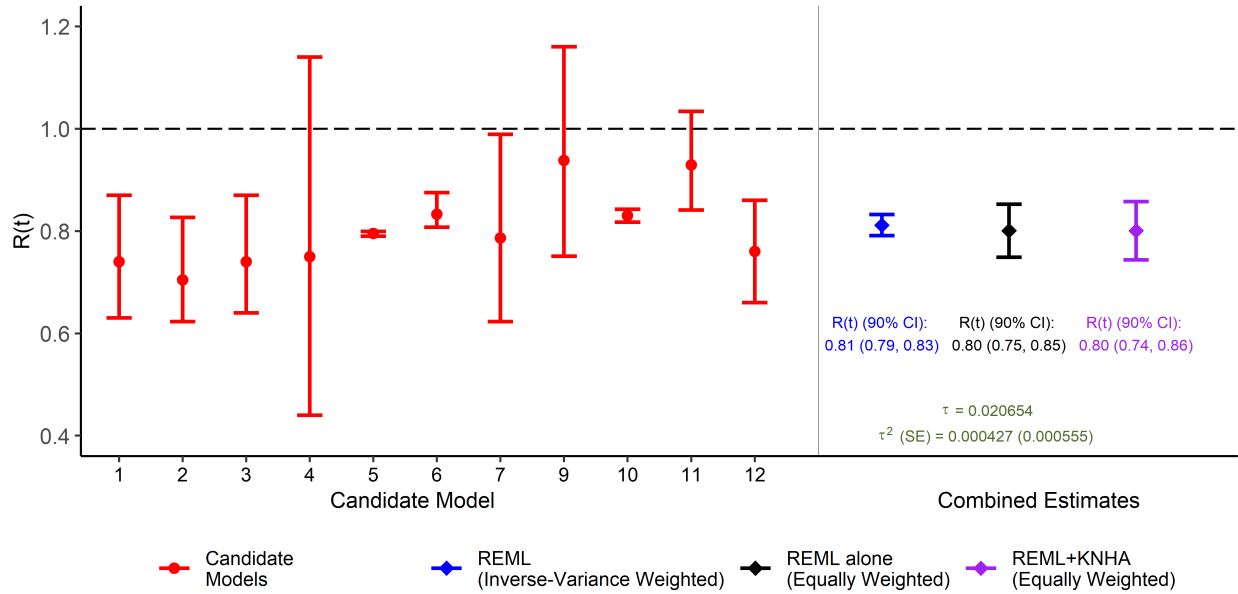

Figure 1: $R(t)$ estimates from the candidate models for anonymised nation/region 10, together with calculated combined estimates using: an *inverse-variance* weighted approach with Wald-type CIs; an equally weighted approach with Wald-type CIs (*REML alone*); and an equally weighted approach with KNHA CIs (*REML+KNHA*). The error bars illustrate the 90% CIs.

The combined estimate obtained is 0.81 for *inverse-variance* weighted approach, and 0.80 for each of the equally weighted approaches, with 90% CIs ranging from 0.79 to 0.86 indicating that we can be reasonably sure the true $R(t)$ for this particular region at time t is below 1. As mentioned above, estimates in this setting are derived using model predictions, and a model with wider 90% intervals could in fact be more representative of the situation when there is inherent uncertainty throughout multiple data collection and modelling streams than a model with narrower 90% intervals using fewer data streams. The results shown in Figure 1 show that the *inverse-variance* weighted approach produced narrower 90% CIs compared to either of the equally weighted approaches. As τ^2 is very small, the standard error of the estimate dominates the inverse variance weighting, and so this narrow 90% interval is primarily driven

by the estimates from candidate models 5 and 10, which had narrower 90% intervals compared to the other candidate models. Conversely, candidate model 4 contributed little information to the combined *inverse-variance* weighted estimate due to the wider 90% intervals provided. This example highlights a key advantage of the equally weighted approach in this particular setting; the ability to avoid potential up-weighting of models providing estimates with lower levels of uncertainty that are not fully accounting for inherent uncertainties. Both the *REML alone* and *REML+KNHA* equally weighted approaches provided similar results in this worked example. However, a more in-depth look at the differences between the results obtained from these two methods is explored in the Results section, below.

4   Results

A full set of results for $R(t)$ and $r(t)$ for the 12 anonymised candidate models is provided across 12 anonymised UK nations/regions below. The estimate for τ^2 for each outcome measure and region is provided in the Appendix.

4.1   Combined *R(t)* Estimates

The $R(t)$ estimates by region for the candidate models are shown in Figure 2. The upper 90% CIs were lower than 1 for all individual regions indicating that that we can be reasonably sure that $R(t)$ for all individuals regions at time t was below 1. On visual inspection, the difference in 90% CI for $R(t)$ between equally weighted models using *REML alone* versus *REML+KNHA* approaches was minimal. On closer inspection of the combined estimates to additional decimal places (data not shown), in seven of the 12 regions the *REML+KNHA* approach provided a wider and more conservative 90% CI than the *REML alone* approach, compared to five instances where the *REML alone* approach provided a wider 90% CI than the *REML+KNHA* approach. Looking at models across different regions, candidate model 4 consistently had wider 90% intervals compared to the other candidate models, whilst candidate models 5 and 10 consistently had narrower 90% intervals. The τ^2 estimates for all regions were again very small (see Table 2 in the Appendix), indicating that the standard error of the estimate dominates the inverse variance weighting, which, coupled with the large disparity in uncertainty for estimates in each region, highlights the appropriateness of applying equal weighting to the models in this setting. Moreover, the equal weighted approaches provided wider 90% CIs compared to the *inverse-variance* weighting approach for all regions (Table 2).
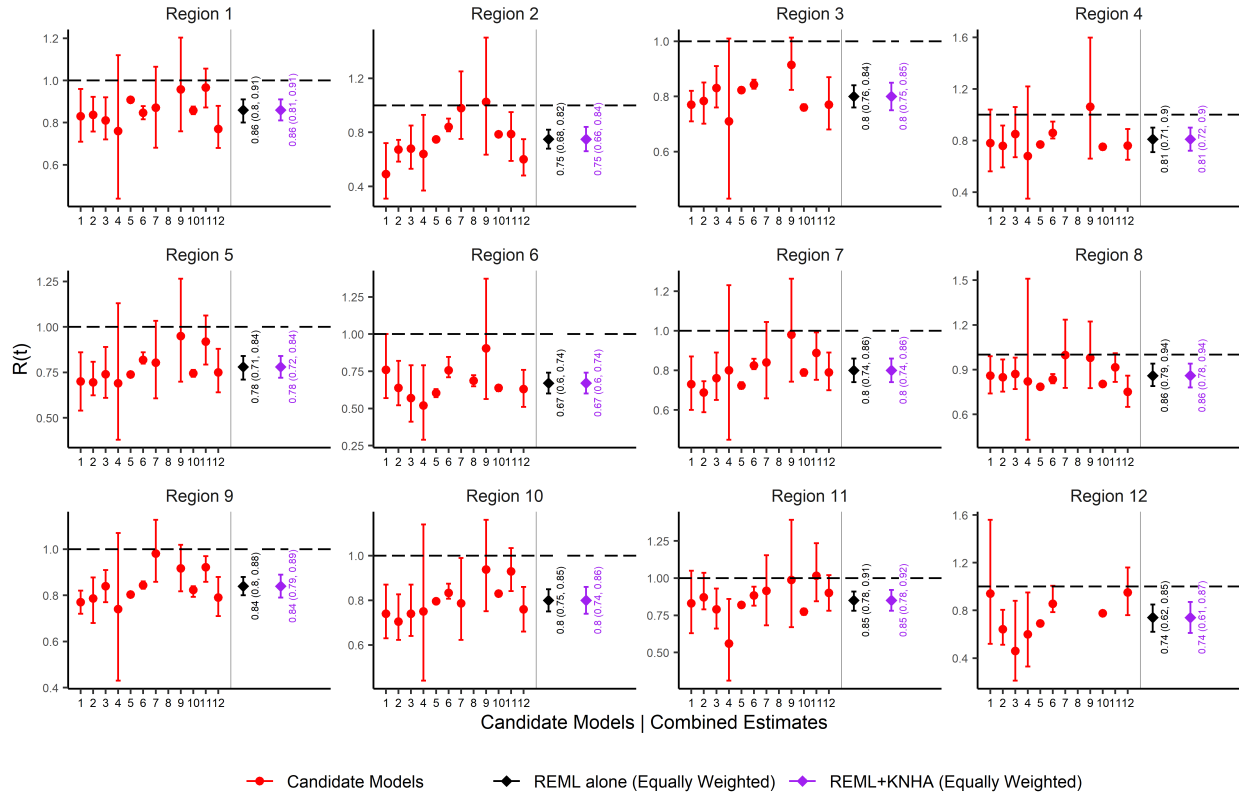
Figure 2: $R(t)$ estimates from the candidate models by anonymised nation/regions, together with calculated combined estimates using equally weighted models, with *REML alone* or *REML+KNHA* approaches for the 90% CIs. The error bars illustrate the 90% CIs.

4.2 Combined *r* Estimates

In terms of $r(t)$ (Figure 3), initial visual inspection yielded a similar conclusion to the combined estimates for $R(t)$. The 90% CIs were equal to or lower than zero for all individual regions indicating that that we can be reasonably sure that $r(t)$ for all individuals regions was not increasing. Only slight differences were found in the 90% CI estimates between the two approaches. However, in this case, closer inspection of the estimates indicated that in eight of the 12 regions the *REML alone* approach provided a wider 90% CI than the *REML+KNHA* approach, compared to four instances where the *REML+KNHA* approach provided a wider 90% CI than the *REML alone* approach. Looking at models across regions, it is first important to note that there were only half of the candidate models for which estimates were available for $r(t)$ compared to estimates for $R(t)$, particularly evident for region 12, in which only three candidate models were included. In terms of variability, candidate models 5 and 10 once again consistently had narrower 90% intervals across regions, whilst candidate model 9 consistently had wider 90% intervals. Although the τ^2 estimates for all regions were again small for $r(t)$, showing low inter-model variability, the equally weighted approaches provided moderately wider 90% CIs compared to the *inverse-variance* weighting approach for all regions (see Table 3 in the Appendix), which is preferable where there is the potential that uncertainty is arising outside of the scope of some modelling approaches.
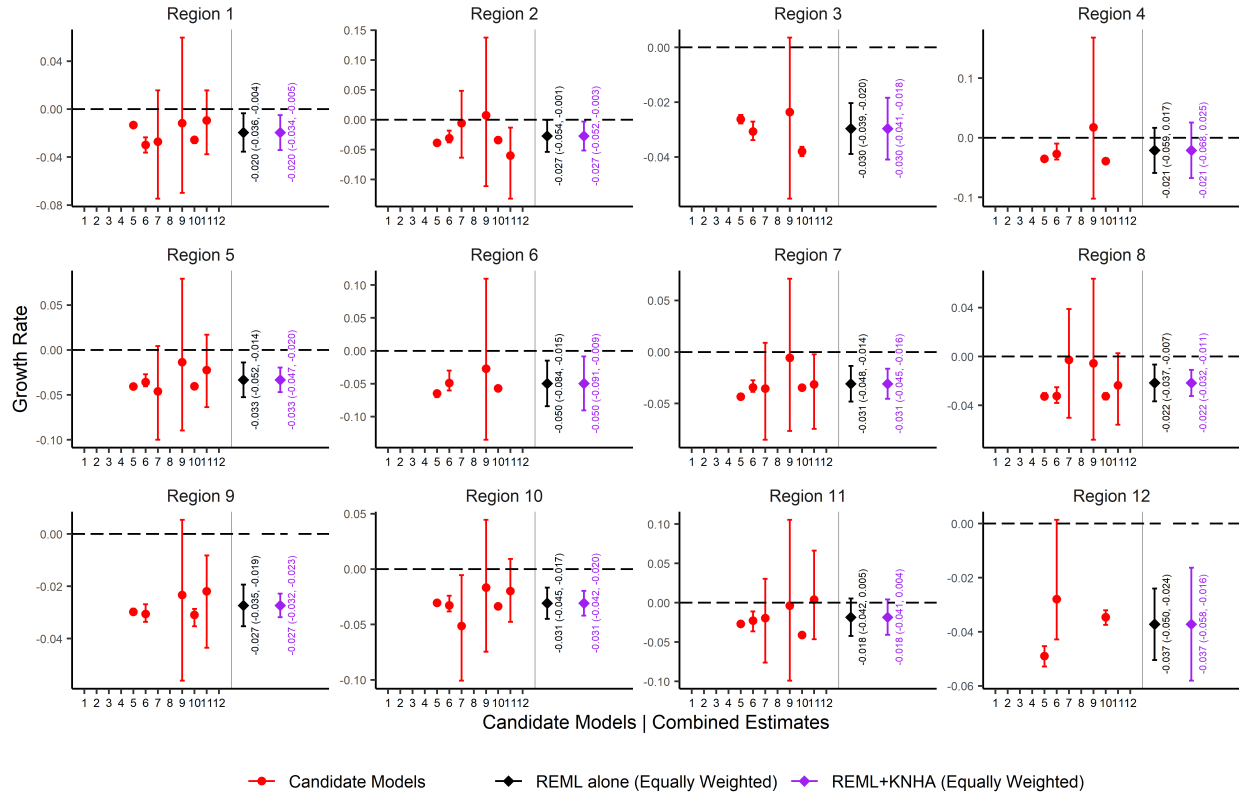
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Figure 3: $r(t)$ estimates from the candidate models by anonymised nation/regions, together with calculated combined estimates using equally weighted models, with *REML alone* or *REML+KNHA* approaches for the 90% CIs. The error bars illustrate the 90% CIs.

5 Discussion

When comparing the results of the *REML alone* and *REML+KNHA* approaches, both provided almost identical results for $R(t)$, and very similar results for $r(t)$. In addition, both approaches provided more conservative CIs around the combined estimate compared to the standard *inverse-variance* weighting approach.

There are a number of possible extensions to the methodology presented. For example, y_i are assumed to be unbiased and normally-distributed estimates of the corresponding true effect[43], and alternative approaches to approximate y_i and se_i may be used. However, as noted in the Cochrane Handbook for Systematic Reviews of Interventions, a median will be very similar to the mean when the distribution of the data is symmetrical[44]. Moreover, the use of the square-root of the variance from the optimisation process to approximate se_i enables a larger estimate to be provided, and thus a more conservative degree of uncertainty. Alternative methods to calculate the standard deviation (to be used for an approximation of se_i) such as those outlined by Bland[45] and Wan *et al*[46] are not possible due to the lack of availability of the sample size, minimum and maximum in this setting. Wan *et al*[46] notes the use of $Q_i(75) - Q_i(25)/1.35$ taken from the Cochrane Handbook[44], however as noted in the Cochrane Handbook, this approximation is for instances with large sample sizes. In addition, Figure 4 shows the normal distributions generated using mean of y_i^* and standard deviation of se_i^* from Equations (6) and (7) for $R(t)$ estimates from the candidate models for anonymised nation/region 10. This provides a visual confirmation of the fit of the candidate model percentiles against the drawn distributions (with the exception of Model 5 which is marked as skewed as per the result obtained using the skewness calculation in Equation (8)). Finally, and of key importance, it has been shown that the performance of statistical methods, such as REML for a meta-analysis, are robust, even in the case of extreme non-normal

distributions[34,35].

It should be noted that some models rely on similar data streams for their primary information, and there is likely a spatial relationship between regional estimates from the same group. In terms of similar data streams, the model structures are all different, and a large amount of variation is observed in the estimates. Consequently, the impact on the results is extremely limited. To illustrate this degree of impact, a sensitivity analyses on the $R(t)$ estimates was performed using the `rma.mv` call from the `metafor` package[43], which enables a model to be fitted for dependent effect sizes. An equally weighted model, using REML and Wald-type CIs, was formulated with model number fitted as the inner-most random effect, and data type fitted as the outer-most random effect in the model. The results were almost identical to the univariate equally weighted model (using REML and Wald-type CIs), with no differences observed larger than 0.01. It should be noted that at the time of writing, the `rma.mv` call does not have the ability to incorporate the *REML+KNHA* approach and so this comparison was not possible. In terms of any dependence between regional estimates from the same group, any correlation assumptions are not consistent between models and as a result, this is outside of the scope of this paper. However, the authors acknowledge that future work in this area might be worth exploring. A final remark in terms of possible correlations between the metrics of interest should also be made here. However, although $R(t)$ and $r(t)$ are probably correlated, not all groups provide both sets of estimates for these, and more importantly, not all candidate models are modelled in the same way between groups and the degree in which $R(t)$ and $r(t)$ are correlated will vary i.e., they may have differing correlation structures, etc. As a result, it is not possible to accurately carry this out without making further untestable assumptions regarding the different correlation structures.

The assumption that all candidate models are valid/plausible is important to note, however each model uses different ways to estimate $R(t)$, which are all equally valid and each provides insight into the current value. Inclusion of a variety of approaches is crucially important as any subgroup of models could lead to potential up-weighting of models providing estimates with lower levels of uncertainty that are not fully accounting for inherent uncertainties. For these reasons, the incorporation of equal weighting has been chosen. The use of equal weighting in meta analyses is not novel and as noted by Borenstein *et al*[28], its application has actually been recommended in some papers[42,47,48]. The purpose of this paper is not to advocate the use of the approach in general meta analyses settings, but for this particular setting. It is also important to note that $R(t)$ is in effect impossible to measure as it would require perfect knowledge of all individuals through time, and there are therefore no 'gold-standards' to compare the individual (and combined) estimates to. There are, however, real world assessments of these data which align, but have potential natural sampling bias (and are therefore not a gold standard), for example: the Office for National Statistics (ONS) survey which covers estimates for England, Wales, Scotland and Northern Ireland[49]; the CoMix study which consists of a survey of UK adults[50]; and the REACT (REal-time Assessment of Community Transmission) study which incorporates a series of studies using home testing on people across England[51]. When the model estimates are combined therefore, and despite potential natural sampling bias, informal comparisons can be made against these survey estimates to help provide approximate feasibility checks on the results.

The authors also acknowledge that, whilst meta analyses in this setting was chosen as it is well established and able to provide rapid results which are easy to interpret, there are other methods that could be applied to combine estimates, such as various ensemble modelling approaches[9–11], expert elicitation[13], the use of a supra Bayesian approach[15,16].

Another possible extension is in regards to the use of combining estimates for an entire region, i.e. not splitting the regions into urban versus rural areas, or not taking into account the number of care homes, etc. Indeed, by definition $R(t)$ is an average over a population. However, if the population in question is very heterogeneous in space or the models used to estimate $R(t)$ become unreliable due to very low case numbers (in this situation case numbers are stochastic and not well approximated by exponential models) then $R(t)$ may not be an appropriate measure. However, in order to address this and ensure that any combination is representative, a basic reliability score is also calculated for use when interpreting these results for a specific region. The reliability score uses estimated case numbers in the modelled region and the heterogeneity in space of the numbers of cases (e.g. a dense urban outbreak compared to rural areas with no cases)[52]. It should also be noted that each model provides estimates for each region individually, i.e. estimates for all English regions were not combined to get an overall estimate for England. The use of a reliability score for each region when presenting the results enables for a more measured conclusion to be drawn from the combined estimates for each region. Further investigation into the reliability score and combining estimates for smaller spatial

regions is likely to form part of future work in this area.

Finally, many of the candidate models provide estimates of $R(t)$ over specific time periods, thus providing estimates of $R(t)$ at a specific date. We would therefore like to explore predicting $R(t)$ as a time series, as opposed to at a specific time point, which is particularly important if $R(t)$ changes rapidly over time. Further to this, we would like to explore predicting the probably that $R(t)$ is changing and how rapidly it is changing, using historical combined estimates of $R(t)$ as a prior.

6 Summary

This paper describes appropriate statistical methodology to provide a combined estimate of effective reproduction number, $R(t)$, and the daily rate of exponential growth, $r(t)$, of COVID-19 in the UK from an agreed set of expert academic models. The methods proposed use an equally weighted random effects model, with the REML approach to estimate τ^2, and incorporating either the Wald-type or KNHA approaches for estimating the CIs, to combine estimates from a series of candidate models.

A meta-analysis using a random effects model as opposed to a fixed effects model is chosen to account for the varying modelling approaches and/or underlying assumptions between candidate models. Moreover, an equally weighted method is adopted in preference to an *inverse-variance* method, as we are combining individual model predictions where additional uncertainty does not necessarily imply imprecision, but is just a reflection of the data being modelled.

The choice of using the well-established REML to estimate τ^2 is recommended as it has been shown to be robust against deviations from normality - many epidemiological models can, at times, produce skewed output distributions for the parameters of interest. Both the Wald and KNHA approaches for calculating the CIs perform well, particularly in the case of KNHA, when only a limited number of models are available for comparison[29,34,35].

Finally, in order to further protect against skew in the input distributions, an appropriate assessment of the skewed parameters is obtained via optimisation and passed to the `rma` call from the `metafor` package[43], together with the estimates from the fitted distributions of each candidate model. The REML method is applied to estimate the heterogeneity variance parameter, and using either the standard Wald-type or KNHA approach for the calculation of the CIs thus enables for an appropriate combined estimates to be formulated.

7 Acknowledgements

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8 Appendix

8.1 List of SPI-M Modellers/Modelling Groups

- Dr Paul Birrell (National Infection Service, Public Health England, London, UK)

- Dr Jonathan Carruthers (National Infection Service, Public Health England, London, UK)

- Dr André Charlett (Centre for Infectious Disease Surveillance and Control, Public Health England, UK)

- Prof Daniela DeAngelis (Medical Research Council Biostatistics Unit, School of Clinical Medicine, University of Cambridge, UK)

- Joshua Blake (Medical Research Council Biostatistics Unit, School of Clinical Medicine, University of Cambridge, UK)

- Prof Matt Keeling (Department of Biological Sciences and Mathematics Institute, University of Warwick, UK)

- Dr Louise Dyson (School of Life Sciences and Mathematics Institute, University of Warwick, UK)

- Dr Sebastian Funk (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Dr Sam Abbott (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Nikos Bosse (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Joel Hellewell (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Sophie Meakin (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- James Munday (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Katharine Sherratt (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Dr Robin Thompson (Mathematical Institute, University of Oxford, UK)

- Prof John Edmunds (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Dr Nicholas Davies (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Dr Christopher Jarvis (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Amy Gimma (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Kevin Van Zandvoort (Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, UK)

- Prof Neil Ferguson (Medical Research Council Centre for Outbreak Analysis and Modelling, Imperial College London, UK)

- Dr Marc Baguelin (Medical Research Council Centre for Outbreak Analysis and Modelling, Imperial College London, UK)

- Dr Lorenzo Pellis (Department of Mathematics, University of Manchester, UK)

- Dr Thomas House (Department of Mathematics, University of Manchester, UK)

- Dr Christopher Overton (Department of Mathematics, University of Manchester, UK)

- Joshua Burton (Department of Mathematics, University of Manchester, UK)

- Filippo Pagani (Department of Mathematics, University of Manchester, UK)

- Prof Katrina Lythgoe (Big Data Institute, University of Oxford, UK)

- Dr Francesca Scarabel (LIAM, Department of Mathematics and Statistics, York University, Canada)

- Dr Jonathon Read (Centre for Health Informatics, Computing, and Statistics, Lancaster University, UK)

- Dr Chris Jewell (Lancaster Medical School, Lancaster University, UK)

- Dr Leon Danon (College of Engineering and Mathematical Sciences, University of Exeter, UK)

- Dr Robert Challen (College of Engineering and Mathematical Sciences, University of Exeter, UK)

- Dr Ellen Brooks-Pollock (Population Health Sciences, University of Bristol, Bristol, UK)

- Dr Nabeil Salama (Marine Scotland Science, Aberdeen, UK)

8.2   Model Descriptions

Detailed information on the models are available from the Royal Society pre-print[2]. However, the following provides a brief summary of the models obtained from the Department of Health and Social Care[52]:

- The University of Cambridge MRC Biostatistics Unit and Public Health England (PHE) use a deterministic age-structured compartmental model, incorporating data from the number of daily deaths and serology data (primary inputs), combined with school attendance and mobility data.

- The University of Warwick use a deterministic age-structured compartmental model, with model parameters fitted to epidemiological data including hospital admissions and bed occupancy, intensive care unit admissions, number of daily deaths, serological data and, for some model configurations, the proportion of Pillar 2 tests that are positive.

- The London School of Hygiene and Tropical Medicine (LSHTM) jointly estimates the trajectory of infections and reproduction number using a renewal equation model and observed delays, with the model fitted to different data streams (in particular: cases and hospitalisations) separately.

- The MRC Centre for Global Infectious Disease Analysis at Imperial College London uses a stochastic age-structured compartmental model, which includes transmission in care homes. Model parameters are fitted to epidemiological data, including hospital admissions and bed occupancy, intensive care unit admissions, number of daily deaths, Pillar 2 testing, together with REACT community survey and blood donor serological data.

- The University of Manchester uses a deterministic compartmental model, incorporating data from hospital admissions, hospital and intensive care unit bed occupancy, and hospital deaths.

- The Scottish Government uses a hierarchical Bayesian mechanistic model developed by Imperial College London, including the bespoke package Epidemia, to estimate the reproduction number. The model incorporates data including the number of daily deaths and contact patterns.

- Lancaster University uses two approaches to estimate reproduction numbers; the first is an application of the renewal equation method using the EpiEstim library and using data on cases (England, Scotland) and hospital admissions (Northern Ireland, Wales); and the second approach is a meta-population transmission model of infection within and between local authorities incorporating movement data and fitted to case data.

- The University of Exeter and University of Bristol use a renewal equation model produced using the EpiEstim library. The model uses data on cases and hospital admissions.

8.3 Combined Estimates of *R(t)*

	Region 1	Region 2	Region 3	Region 4	Region 5	Region 6	Region 7	Region 8	Region 9	Region 10	Region 11	Region 12
Model 1	0.83 (0.71, 0.96)	0.49 (0.31, 0.72)	0.77 (0.71, 0.82)	0.78 (0.56, 1.04)	0.70 (0.54, 0.86)	0.76 (0.57, 1.00)	0.73 (0.60, 0.87)	0.86 (0.74, 0.99)	0.77 (0.72, 0.82)	0.74 (0.63, 0.87)	0.83 (0.63, 1.05)	0.94 (0.52, 1.56)
Model 2	0.84 (0.76, 0.92)	0.67 (0.58, 0.74)	0.78 (0.70, 0.85)	0.76 (0.59, 0.92)	0.69 (0.62, 0.81)	0.64 (0.52, 0.82)	0.69 (0.59, 0.75)	0.85 (0.75, 0.97)	0.79 (0.68, 0.88)	0.70 (0.62, 0.83)	0.87 (0.79, 1.04)	0.64 (0.51, 0.80)
Model 3	0.81 (0.72, 0.92)	0.68 (0.53, 0.85)	0.83 (0.76, 0.91)	0.85 (0.67, 1.06)	0.74 (0.61, 0.89)	0.57 (0.41, 0.79)	0.76 (0.65, 0.89)	0.87 (0.77, 0.98)	0.84 (0.77, 0.91)	0.74 (0.64, 0.87)	0.79 (0.66, 0.93)	0.46 (0.21, 0.88)
Model 4	0.76 (0.44, 1.12)	0.64 (0.37, 0.93)	0.71 (0.43, 1.01)	0.68 (0.35, 1.22)	0.69 (0.38, 1.13)	0.52 (0.29, 0.79)	0.80 (0.45, 1.23)	0.82 (0.43, 1.51)	0.74 (0.43, 1.07)	0.75 (0.44, 1.14)	0.56 (0.31, 0.86)	0.60 (0.33, 0.95)
Model 5	0.91 (0.90, 0.92)	0.75 (0.73, 0.77)	0.82 (0.81, 0.83)	0.77 (0.76, 0.78)	0.74 (0.73, 0.75)	0.60 (0.58, 0.63)	0.72 (0.71, 0.74)	0.78 (0.77, 0.80)	0.80 (0.80, 0.81)	0.80 (0.79, 0.80)†	0.82 (0.80, 0.84)	0.69 (0.67, 0.71)
Model 6	0.85 (0.82, 0.88)	0.84 (0.81, 0.90)	0.84 (0.83, 0.86)	0.86 (0.82, 0.95)	0.82 (0.80, 0.86)	0.76 (0.71, 0.85)	0.82 (0.81, 0.86)	0.83 (0.81, 0.87)	0.84 (0.83, 0.86)	0.83 (0.81, 0.87)	0.88 (0.81, 0.94)	0.86 (0.79, 1.01)
Model 7	0.87 (0.68, 1.07)	0.98 (0.75, 1.25)	NA	NA	0.80 (0.61, 1.03)	NA	0.84 (0.66, 1.04)	1.00 (0.78, 1.23)	0.98 (0.86, 1.13)	0.79 (0.62, 0.99)	0.91 (0.68, 1.15)	NA
Model 8	NA	NA	NA	NA	NA	0.69 (0.65, 0.72)	NA	NA	NA	NA	NA	NA
Model 9	0.96 (0.76, 1.20)	1.03 (0.63, 1.50)	0.91 (0.82, 1.01)	1.06 (0.66, 1.60)	0.95 (0.70, 1.26)	0.90 (0.56, 1.37)	0.98 (0.74, 1.26)	0.98 (0.77, 1.22)	0.92 (0.82, 1.02)	0.94 (0.75, 1.16)	0.99 (0.67, 1.39)	NA
Model 10	0.86 (0.84, 0.88)	0.78 (0.77, 0.80)	0.76 (0.75, 0.77)	0.75 (0.73, 0.77)	0.74 (0.73, 0.76)	0.64 (0.62, 0.66)	0.79 (0.77, 0.80)	0.80 (0.79, 0.82)	0.82 (0.79, 0.84)	0.83 (0.82, 0.84)	0.77 (0.75, 0.79)	0.78 (0.76, 0.79)
Model 11	0.97 (0.87, 1.06)	0.79 (0.59, 0.95)	NA	NA	0.92 (0.79, 1.06)	NA	0.89 (0.75, 0.99)	0.92 (0.82, 1.01)	0.92 (0.86, 0.97)	0.93 (0.84, 1.03)	1.01 (0.84, 1.24)	NA
Model 12	0.77 (0.68, 0.88)	0.60 (0.48, 0.75)	0.77 (0.68, 0.87)	0.76 (0.65, 0.89)	0.75 (0.64, 0.88)	0.63 (0.51, 0.76)	0.79 (0.70, 0.89)	0.75 (0.65, 0.86)	0.79 (0.71, 0.88)	0.76 (0.66, 0.86)	0.90 (0.78, 1.02)	0.95 (0.76, 1.16)
Inverse-variance Weighted REML alone $\hat{\theta}$ *(95%CI)*	0.87 (0.84, 0.89)	0.75 (0.70, 0.79)	0.81 (0.78, 0.83)	0.77 (0.75, 0.78)	0.76 (0.73, 0.79)	0.65 (0.62, 0.69)	0.78 (0.74, 0.81)	0.82 (0.79, 0.84)	0.83 (0.81, 0.85)	0.81 (0.79, 0.83)	0.83 (0.79, 0.86)	0.74 (0.69, 0.80)
Equally Weighted REML alone $\hat{\theta}$ *(95%CI)*	0.86 (0.80, 0.91)	0.75 (0.68, 0.82)	0.80 (0.76, 0.84)	0.81 (0.71, 0.90)	0.78 (0.71, 0.84)	0.67 (0.60, 0.74)	0.80 (0.74, 0.86)	0.86 (0.79, 0.94)	0.84 (0.80, 0.88)	0.80 (0.75, 0.85)	0.85 (0.78, 0.91)	0.74 (0.62, 0.85)
Equally Weighted REML+KNHA $\hat{\theta}$ *(95%CI)*	0.86 (0.81, 0.91)	0.75 (0.66, 0.84)	0.80 (0.75, 0.85)	0.81 (0.72, 0.90)	0.78 (0.72, 0.84)	0.67 (0.60, 0.74)	0.80 (0.74, 0.86)	0.86 (0.78, 0.94)	0.84 (0.79, 0.89)	0.80 (0.74, 0.86)	0.85 (0.78, 0.92)	0.74 (0.61, 0.87)
τ^2 *(SE)*	0.000915 (0.000982)	0.002856 (0.002833)	0.001222 (0.001078)	0.000004 (0.000177)	0.001020 (0.001180)	0.001391 (0.001574)	0.001677 (0.001643)	0.000598 (0.000765)	0.000984 (0.000893)	0.000427 (0.000555)	0.001534 (0.001861)	0.003216 (0.004129)

Table 2: *R(t)* estimates (90% CIs) for anonymised models 1 to 12 for all anonymised UK nation/regions, together with calculated combined estimates using: an *inverse-variance* weighted approach with Wald-type CIs; an equally weighted approach with Wald-type CIs (*REML alone*); and an equally weighted approach with KNHA CIs (*REML+KNHA*). All numbers displayed to two decimal places except τ^2(SE), displayed to six decimal places. Missing values indicate instances where estimates were not available for models for the specific nation/region. † Estimates found to be moderately to highly skewed.

8.4 Combined Estimates of *r(t)*

	Region 1	Region 2	Region 3	Region 4	Region 5	Region 6	Region 7	Region 8	Region 9	Region 10	Region 11	Region 12
Model 1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Model 2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Model 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Model 4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Model 5	-0.01 (-0.01, -0.01)	-0.04 (-0.04, -0.04)	-0.03 (-0.03, -0.02)	-0.04 (-0.04, -0.03)	-0.04 (-0.04, -0.04)	-0.06 (-0.07, -0.06)	-0.04 (-0.05, -0.04)	-0.03 (-0.03, -0.03)	-0.03 (-0.03, -0.03)	-0.03 (-0.03, -0.03)	-0.03 (-0.03, -0.02)	-0.05 (-0.05, -0.05)
Model 6	-0.03 (-0.04, -0.02)	-0.03 (-0.04, -0.02)	-0.03 (-0.03, -0.03)	-0.03 (-0.04, -0.01)	-0.04 (-0.04, -0.03)	-0.05 (-0.06, -0.03)	-0.03 (-0.04, -0.03)	-0.03 (-0.04, -0.03)	-0.03 (-0.03, -0.03)	-0.03 (-0.04, -0.02)	-0.02 (-0.04, -0.01)	-0.03 (-0.04, 0.00)
Model 7	-0.03 (-0.07, 0.02)	-0.01 (-0.06, 0.05)	NA	NA	-0.05 (-0.10, 0.00)	NA	-0.04 (-0.09, 0.01)	0.00 (-0.05, 0.04)	NA	-0.05 (-0.10, -0.01)	-0.02 (-0.08, 0.03)	NA
Model 8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Model 9	-0.01 (-0.07, 0.06)	0.01 (-0.11, 0.14)	-0.02 (-0.06, 0.00)	0.02 (-0.10, 0.17)	-0.01 (-0.09, 0.08)	-0.03 (-0.14, 0.11)	-0.01 (-0.08, 0.07)	-0.01 (-0.07, 0.06)	-0.02 (-0.06, 0.01)	-0.02 (-0.07, 0.04)	0.00 (-0.10, 0.11)	NA
Model 10	-0.03 (-0.03, -0.02)	-0.03 (-0.04, -0.03)	-0.04 (-0.04, -0.04)	-0.04 (-0.04, -0.04)	-0.04 (-0.04, -0.04)	-0.06 (-0.06, -0.05)	-0.03 (-0.04, -0.03)	-0.03 (-0.04, -0.03)	-0.03 (-0.04, -0.03)	-0.03 (-0.04, -0.03)	-0.04 (-0.04, -0.04)	-0.03 (-0.04, -0.03)
Model 11	-0.01 (-0.04, 0.02)	-0.06 (-0.13, -0.01)	NA	NA	-0.02 (-0.06, 0.02)	NA	-0.03 (-0.07, 0.00)	-0.02 (-0.06, 0.00)	-0.02 (-0.04, -0.01)	-0.02 (-0.05, 0.01)	0.00 (-0.05, 0.07)	NA
Model 12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Inverse-variance Weighted REML alone $\hat{\theta}$ *(95%CI)*	-0.02 (-0.03, -0.01)	-0.04 (-0.04, -0.03)	-0.03 (-0.04, -0.03)	-0.04 (-0.04, -0.03)	-0.04 (-0.04, -0.04)	-0.06 (-0.07, -0.05)	-0.04 (-0.04, -0.03)	-0.03 (-0.03, -0.03)	-0.03 (-0.03, -0.03)	-0.03 (-0.03, -0.03)	-0.03 (-0.04, -0.02)	-0.04 (-0.05, -0.03)
Equally Weighted REML alone $\hat{\theta}$ *(95%CI)*	-0.02 (-0.04, 0.00)	-0.03 (-0.05, 0.00)	-0.03 (-0.04, -0.02)	-0.02 (-0.06, 0.02)	-0.03 (-0.05, -0.01)	-0.05 (-0.08, -0.01)	-0.03 (-0.05, -0.01)	-0.02 (-0.04, -0.01)	-0.03 (-0.04, -0.02)	-0.03 (-0.04, -0.02)	-0.02 (-0.04, 0.01)	-0.04 (-0.05, -0.02)
Equally Weighted REML+KNHA $\hat{\theta}$ *(95%CI)*	-0.02 (-0.03, 0.00)	-0.03 (-0.05, 0.00)	-0.03 (-0.04, -0.02)	-0.02 (-0.07, 0.03)	-0.03 (-0.05, -0.02)	-0.05 (-0.09, -0.01)	-0.03 (-0.05, -0.02)	-0.02 (-0.03, -0.01)	-0.03 (-0.03, -0.02)	-0.03 (-0.04, -0.02)	-0.02 (-0.04, 0.00)	-0.04 (-0.06, -0.02)
τ^2 *(SE)*	0.000062 (0.000067)	0.000009 (0.000016)	0.000034 (0.000036)	0.000004 (0.000009)	0.000000 (0.000003)	0.000019 (0.000037)	0.000023 (0.000029)	0.000000 (0.000004)	0.000000 (0.000003)	0.000004 (0.000007)	0.000076 (0.000093)	0.000084 (0.000120)

Table 3: *r(t)* estimates (90% CIs) for anonymised models 1 to 12 for all anonymised UK nation/regions, together with calculated combined estimates using: an *inverse-variance* weighted approach with Wald-type CIs; an equally weighted approach with Wald-type CIs (*REML alone*); and an equally weighted approach with KNHA CIs (*REML+KNHA*). All numbers displayed to two decimal places except τ^2(SE), displayed to six decimal places. Missing values indicate instances where estimates were not available for models for the specific nation/region.
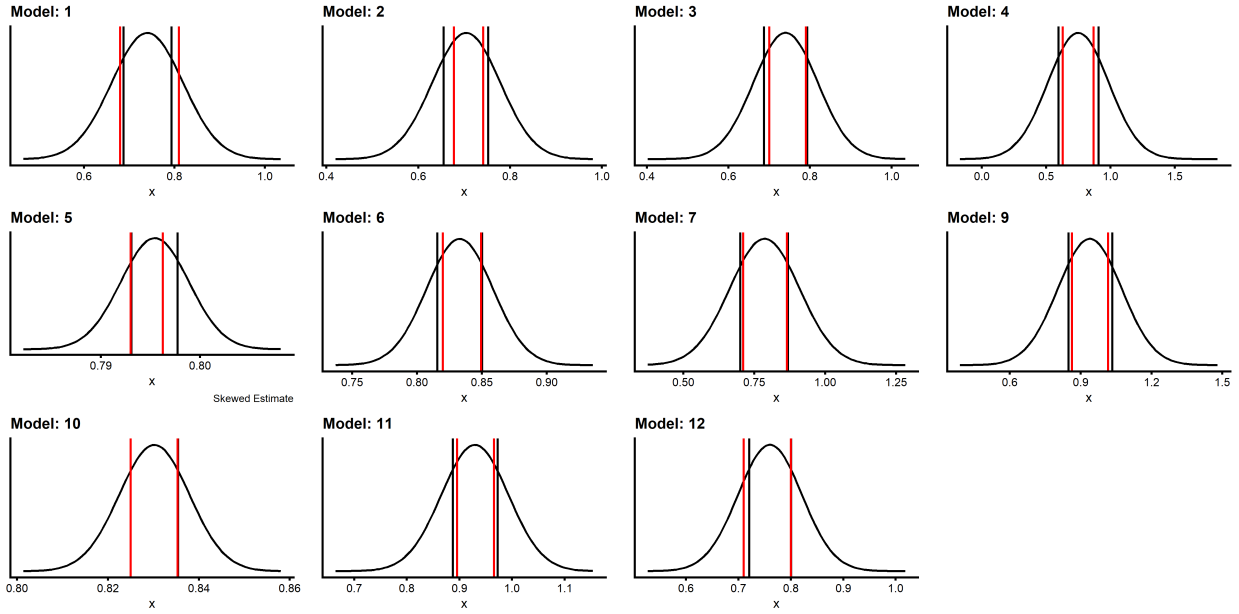
Figure 4: Normal distributions generated using mean of y_i^* and standard deviation of se_i^* from Equations (6) and (7) for $R(t)$ estimates from the candidate models for anonymised nation/region 10. Black vertical lines represent the 25th and 75th percentiles drawn from the generated normal distributions whilst the red vertical lines illustrate the 25th and 75th percentiles obtained directly from the candidate models. The plot for Model 5 is marked as skewed as per the result obtained using the skewness calculation in Equation (8).