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Inconsistencies in handling missing data across stages of prediction modelling: a review of methods used

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Abstract:	Objective: No clear guidance exists on handling missing data at each stage of developing, validating and implementing a clinical prediction model (CPM). We aimed to review the approaches to handling missing data that underly the CPMs currently recommended for use in UK healthcare. Study design and Setting: A methods review to identify CPMs recommended by the National Institute for Health and Care Excellence (NICE), which summarized how missing data is handled across their pipelines. Results: 23 CPMs were included. Six missing data strategies were identified: complete case analysis (CCA), multiple imputation, imputation of mean values, k-nearest neighbours imputation, using an additional category for missingness, considering missing values as risk-factor-absent. 52% of the development articles and 48% of the validation articles did not report how missing data were handled. CCA was the most common approach used for development (40%) and validation (44%). At implementation, 57% of the CPMs required complete data entry, whilst 43% allowed missing values. 3 CPMs had consistent paths in their pipelines. Conclusion: A broad variety of methods for handling missing data underly the CPMs currently recommended for use in UK healthcare. Missing data handling strategies were generally inconsistent. Better quality assurance of CPMs needs greater clarity and consistency in handling of missing data.
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Inconsistencies in handling missing data across stages of prediction modelling: a review of methods used

Authors: Tsvetanova et al.

Dear Editor,

Thank you for the opportunity to submit the above titled manuscript for consideration of publication in the *Journal of Clinical Epidemiology*.

Our paper is a review of methods used to handle missing data across the pipeline of a clinical prediction model (CPM). Commonly, CPMs are increasingly developed and validated using routinely collected data, such as electronic health records, where missing data are present and need careful handling. Whilst methods for handling missing data have received considerable attention at the development stage of CPMs, we feel that this has been under-explored in the external validation and implementation stages. In turn, this lack of guidance has potentially resulted in inconsistency between imputation methods used across the stages of development, validation, and implementation of a CPM. Notably, the extent to which these methods are inconsistent is currently unclear.

In the paper we review twenty three CPMs that are currently recommended for use in the UK healthcare and summarise the methods used to handle missing data at the development, external validation and implementation stages. This paper will be of a value to those, facing the issue of missing data in prediction modelling.

We have uploaded our manuscript and supplemental material.

There are no conflicts of interest.

This manuscript arises from original research; has not been published elsewhere; and is not currently under submission elsewhere.

As corresponding author, I have had full access to all the data and have had final responsibility for the decision to submit the manuscript for publication. On behalf of my co-authors, I hope that you will find our paper of sufficient interest and quality for publication in the *Journal of Clinical Epidemiology.*

Yours sincerely,

Antonia Tsvetanova, BSc (Hons) MRes
PhD candidate
University of Manchester

What is New?

Key findings

- To date, missing data has been well-addressed at the development stage of a CPM, whilst it has been under-explored in the stages of external validation and implementation.
- Missing data has been generally handled inconsistently across the pipeline of CPMs used in the UK healthcare.
- Missing data and their handling has been poorly reported and accounted for.

What this adds to what was known

- No examples in which missing data were allowed in practice and where missing data were handled consistently between validation and implementation stages was found.

What is the implication and what should change now?

- A framework for handling missing data is needed to quality assure CPM pipelines.

Inconsistencies in handling missing data across stages of prediction modelling: a review of methods used

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Abstract

Objective: No clear guidance exists on handling missing data at each stage of developing, validating and implementing a clinical prediction model (CPM). We aimed to review the approaches to handling missing data that underly the CPMs currently recommended for use in UK healthcare.

Study design and Setting: A methods review to identify CPMs recommended by the National Institute for Health and Care Excellence (NICE), which summarized how missing data is handled across their pipelines.

Results: 23 CPMs were included. Six missing data strategies were identified: complete case analysis (CCA), multiple imputation, imputation of mean values, k-nearest neighbours imputation, using an additional category for missingness, considering missing values as risk-factor-absent. 52% of the development articles and 48% of the validation articles did not report how missing data were handled. CCA was the most common approach used for development (40%) and validation (44%). At implementation, 57% of the CPMs required complete data entry, whilst 43% allowed missing values. 3 CPMs had consistent paths in their pipelines.

Conclusion: A broad variety of methods for handling missing data underly the CPMs currently recommended for use in UK healthcare. Missing data handling strategies were generally inconsistent. Better quality assurance of CPMs needs greater clarity and consistency in handling of missing data.

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Statistical models; Prognosis; Predictive medicine; Missing data; Imputation.

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1. Introduction

Clinical prediction models (CPMs) are statistical models or algorithms that use a set of predictor variables to calculate an individual's chance of developing or having a certain condition, and thus aid clinicians with the associated clinical reasoning and decision-making[1]. Three major phases can be identified in the CPM pipeline: (i) developing and internally validating a CPM; (ii) validating the model on new independent cohorts of patients (external validation), potentially adjusting or updating the model as needed; and (iii) implementing the model in clinical practice while monitoring its impacts[2].

CPMs are increasingly developed and validated using routinely collected data, such as electronic health records, where missing data are common and need careful handling in the CPM pipeline[3,4]. A simple, but inefficient (and potentially biased), approach is complete case analysis (CCA), where all patients with missing values are excluded. This method is only valid in situations where the data are missing completely at random and where there is sufficient sample size after missing case deletion to enable robust inference[5–7]. On the other hand, multiple imputation (MI) is often seen as the gold standard as it allows all data to be used, makes the *weaker* missing (*not completely*) at random assumption, and appropriately accounts for uncertainty in the missing data[8,9]. MI, however, is not easily used in clinical contexts, because we are dealing with one patient at the time and it often requires knowledge about the outcome that is not yet available[10–12].

Whilst methods for handling missing data have received considerable attention at the development stage of CPMs, there is a lack of research exploring handling missing data in external validation and implementation stages. In turn, this lack of guidance has potentially resulted in inconsistency between imputation methods used across the stages of development, validation, and implementation of a CPM. However, the extent to which missing data handling methods are consistent, or otherwise, across the CPM pipeline is currently unclear. Hoogland *et al* claimed that they have not been able to find an example, in which missing data were allowed in practice and where missing data were handled in a consistent way across validation and implementation[13]. Notably, any lack of consistency might lead to overly optimistic (or pessimistic) assessments of model performance estimated at development and validation stages of a CPM, compared with performance at time of implementation[14,15]. For example, suppose a CPM is developed and validated using CCA, then at implementation it is applied to all patients with missing data handled using mean imputation – that would be inconsistent because the natural variability of the data will be compromised if all the missing values are imputed by the mean of those, which are available.

Consistency of imputation methods across the stages of the CPM pipeline would help ensure that the predictive performance reported from external validation studies is based upon consistent methods (in terms of handling missing data) with those to be applied when the model is implemented.

The aim of this study was to review CPMs recommended for use in UK healthcare and to summarise the methods used to address missing data across the models' (i) development, (ii) external validation and (iii) implementation stages – the CPM pipeline.

2. Methods

We sought to identify and describe existing clinical prediction models used in UK clinical practice, with respect to missing data handling across their CPM pipeline. We only included models that are recommended by the National Institute for Health and Care Intelligence (NICE), which has a role in weighing the evidence around CPMs. We chose this approach, to ensure coverage of the whole CPM pipeline, noting that many models are developed but not validated or implemented[16]. We asked NICE for a list of CPMs they recommend. To widen the search, we added further CPMs identified in our earlier research and, we reached-out to the scientific community on Twitter. The tweet by AT on March 25th 2020 was seen 11,286 times, receiving 8 replies and 13 re-tweets – of these, we only included any CPMs that NICE recommends but had not mention in their list. A final list of CPMs was established and data were summarized in an information extraction table.

2.1. Search Strategy and selection criteria

We used Google Scholar to search for the original development papers, and papers that aimed to externally validate the CPMs. The search for the original development papers included synonyms for [development] combined with [prognostic/predictive/prediction model], and [developer's name], with the latter being identified by using MDCalc free online medical reference source[17]. The search for external validation papers was performed using forward citations from each of the original development papers, followed by *search within citing articles* option. This option assures that all the validation articles for the specific CPM, have cited the original derivation article of the CPM. The search terms for validation papers included [name of the CPM] – both abbreviated and extended. As a pragmatic approach to maintain a viable number of papers to screen, we selected the top ten most cited (according to Google scholar as-of 18/09/20) validation papers for each CPM. For validation papers, articles were included if they: (i) performed independent external validation of the CPMs; or (ii) reported a comparison between the CPM of interest and another CPM(s) within independent data. Articles that had a primary purpose of developing a new prediction model and comparing it with the CPM of

interest were excluded. We preferred to get information on the implementation stage for each CPM from documentation provided by the CPMs' developers. If this was not available, we obtained the information from the online tools of the model (e.g., stand-alone online calculator website or part of MDCalc). Each tool was tested to assess 1) if it is possible to obtain a prediction with missing information or not, and 2) if so, how the missing data were being handled by the CPM. The information extraction for all stages was completed on 22/09/20.

2.2. Data extraction and synthesis

Data extraction of included articles was completed by one author (AT). Additionally, 10% of the data extraction was independently undertaken by a second author (GPM). We categorised the eligible articles into two groups: development articles and external validation articles. The following details for each paper were extracted:

(i) For both development and validation studies, general information such as: author, year of publication and paper title.

(ii) For both development and validation studies, data surrounding the source of data used (e.g., cohort, case-control, registry), the sample size and the outcome of interest.

(iii) For development studies: the modelling method used (e.g., logistic, survival), and software used for analysis.

(iv) For both development and validation studies, missing data handling approach (e.g., complete case analysis, imputation methods, other or none reported).

(v) For both development and validation studies, model performance, reported strengths and limitations of the studies and any stated assumptions made.

Information on the implementation stage of each CPM was extracted from the original online calculator of the CPM, or from MDCalc.

The Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement has been applied to all the articles included in this review – items 9, 13a and 13b[18].

When extracting information on missing data, studies that have reported that missing data is present, but have not described how it was handled, were put in the category 'unclear'. This was used for item 13b. Studies where no information on the presence of missing data or any handling method was reported, were categorised as 'not reported'.

2.3. Definition of consistency across CPM pipeline

We define 'consistency' as where the missing data handling method used at *validation* is compatible with the method to be used *at* the *implementation* stage. (Note that no reference made to development approach). *Compatibility* means that the validation approach will accurately reflect the performance at implementation under identical missingness mechanisms (e.g. in our case, only permitting MAR). The following cases can be considered consistent:

(i) Where the same method is used at both validation and implementation stages (noting this excludes *CCA – all data required*, as this requires MCAR, but includes *MI – MI*, although this is never observed in practice.)

(ii) *MI at validation – all data required* at implementation, since MI is designed to reflect this appropriately under MAR.

For a CPM pipeline to be considered as having compatible missing data handling methods across its development, validation and implementation stages, all combinations of methods must comply with the above definition.

3. Results

The search strategy identified 23 clinical prediction models that met the eligibility criteria, as shown on Figure 1. (The original list of all CPMs could be found in Appendix A) Description of each CPM and its corresponding external validation papers are summarised in Table 1.

In total, information from 233 articles was extracted. Development articles were available for 23 out of 24 CPMs. There was one development article (Waterlow Score), for which access to the published paper could not be obtained, therefore, we did not consider this model further. A total of 210 external validation articles were included in this study. For six out of 23 CPMs, there were less than 10 validation papers available, when the search criteria were applied (QRISK, Thoracoscore, The Leicester practice risk score, FRAX, BOADICEA and NEWS2).

3.1. Missing Data

Six missing data approaches were identified through the literature search within the development and validation papers, summarised in table 2.

3.1.1. Missing data handling at Development stage of a CPM

From the 23 development papers, 12 (52%) did not report how the analysis handled missing data. The most common method for missing data handling was CCA, used in ten (44%) articled. MI was used in only one development article (4%).

3.1.2. Missing data handling at Validation stage of a CPM

From the 210 external validation articles, the approach to handling missing data was not reported in 100 studies (48%). As with the development studies, CCA was the most common method used in the validation articles (n=85, 40%). Multiple imputation was used in thirteen (6%) of the 210 studies. Twelve studies (6%) used 'other methods' such as single imputation, k-nearest neighbour (KNN) imputation, additional category for missing values (missing indicator method) or missing values considered as normal (e.g., if a comorbidity is not recorded, it is assumed to be absent).

3.1.3. Missing data handling at the Implementation stage of a CPM

When applied to an individual patient during the CPM's (iii) implementation stage, only one (4%) of the 23 CPMs (QRISK[254]) used mean imputation for a measure of deprivation when geographical region is unknown, conditional mean imputation based on ethnicity, age and sex, if there are missing values of Cholesterol/HDL ratio, blood pressure and BMI, and it uses zero imputation when the SD of the last two blood pressure readings is missing[254]. Eight CPMs (35%) make the assumption for missing values to be the lowest/normal – ABCD2[255], TIMI[256], CRB65[257], EuroScore[258], FRAX[259], CHADVASC[260], DG-ROMA[261], NEWS2[262]. Overall, thirteen CPMs (57%) require that all data is present when making a prediction at implementation stage; these models were Thoracoscore[263], NPI[264], Leicester Risk Score[265], PREDICT[266], Blatchford[267], HAS-BLED[268], GRACE[269], Framingham[270], Gleason[271], Braden Scale[272], APACHE[273], APGAR[274], MTS[76]. The remaining CPM – BOADICEA[275], (4%) has a category 'unknown' for non-continuous variables, however it is unclear what assumptions have been made in relation to missing data handling.

3.2. Consistency of missing data handling across the pipeline of a CPM

Overall, results showed that missing data were generally handled in an inconsistent way across the pipeline of a CPM, according to our definitions of 'consistency' as pictured on Figure 2. Consistent 'paths' (MI at validation – All data required at implementation) were observed for only three CPMs: Thoracoscore, Manchester Triage system, APGAR score (see Supplementary material).

3.3. TRIPOD statement

Across all the development and external validation articles included, 27 studies (12%) stated that potential bias and inconsistency in the results might have occurred owing to missing data. Of the development studies, 11 (48%) have followed checklist item 9 from the TRIPOD statement, which is to describe how missing data are handled. Similarly, from the 210 external validation studies, 112 (53%) have followed checklist item 9. All the development and

validation articles have described the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time (checklist item 13a from the TRIPOD statement). Of the development studies 12 (52%) have described the characteristics of the participants, including the number of participants with missing data (checklist item 13b). 126 (60%) of the validation studies have followed this point.

4. Discussion

In this review of CPMs recommended for use by NICE, we showed that there are inconsistencies across the CPMs pipeline with regards to missing data handling approaches. We found that only three CPMs met one of the two definitions for consistency in handling missing data that we have proposed. Indeed, Thoracoscore, Manchester Triage System and APGAR score had consistent paths (MI at validation – All data required at implementation). We considered this consistent, since MI is designed to reflect this appropriately under the weaker MAR assumption for missingness. We did not find any consistency paths where the same approach of handling missing data, is used in validation and implementation stages (MI – MI). This case has not been observed in practice, perhaps since it is challenging to use MI at implementation stage, where extra information and potentially other data is needed. Although, CCA – All data required might be also considered as 'consistent' by some, since it uses the same approach throughout the pipeline, we have excluded it has a possible 'consistent' path option, because it requires the missingness mechanism to be MCAR, which is rarely the case. Finally, we did not find any cases where missing data were allowed in practice, which is in line with the statement made by Hoogland *et al*[13]. It is less clear what the prediction made by the CPM will be if we allow missing data to occur at implementation, because the missing mechanism is likely to be different from the one at development and external validation stages[276].

CCA was the commonest approach for handling missing data at derivation and external validation of a CPM. Almost half of the studies did not report how missing data were handled. Furthermore, with exception of a few studies, no assumptions were made *explicit* in regard to the mechanisms of missingness. Overall, only half of the studies have adhered to the items from the TRIPOD statement that describe how missing data should be reported[277]. This could be because most of the articles were published before the TRIPOD was published in 2015.

When implementing CPMs in practice, methods for dealing with missing values are often driven by practical constraints. Issues with the applicability of multiple imputation (MI) methods

arise when the researcher only has access to published parameter estimates (for the CPM). For example, during the external validation and implementation stages, to make predictions for a new individual with missing data, one would need extra information, such as the imputation models and potentially other data. In most cases, this is impractical (for prediction models) in real world settings, although a recent work from Nijman et al suggest how this can be avoided[278]. Furthermore, there are alternative to MI methods emerging, such as the pattern sub-model, where one fits a pattern mixture model for every missing data pattern, using only data from that pattern[4].

The issue not well addressed in the literature, however, remains the extent to which these methods affect CPM performance. We currently do not know whether there is an effect in using different missing data approaches are used across the pipeline, although some of the articles suggested that potential bias in the results might have occurred due to missing data. One study has stated that ROC, D and R^2 statistics were not similar between patients with complete data when compared to the results obtained using multiply imputed data set[28]. Another study has stated that the presence of a specific variable could have changed the coefficients in the remaining variables[32]. Furthermore, it has been also pointed out that missing data impeded the categorization of some of the patients, which, in turn impaired the ability to validate the CPMs more definitively[121,251]. Many studies have stated that missing data could have affected their findings[51,54,77,95,238]. We propose that the way missing data are handled during validation should be compatible to that which will be used when the CPM is implemented. Future work should explore the effect of incompatibility in terms of reported/estimated predictive performance.

4.1. Strengths and limitations

To our knowledge, this is the first review of how missing data have been handled across the development, external validation and implementation pipeline of CPMs recommended for use in UK clinical practice. Although our search for CPMs did not involve a systematic review of literature, we used standard reporting guidelines, such as TRIPOD, to evaluate each included model.

Our review has certain limitations that are worth mentioning. First, we did not have a systematic way to search for CPMs within the NICE guidelines. Therefore, we asked NICE directly to provide us with a list of CPM they recommend, the scientific community on Twitter, and our research group – of the latter two, we filtered only those CPMs that are recommended in the NICE guidelines, in case they were not mentioned by NICE themselves. Therefore, our study might suffer lack of generalizability, since other CPMs might be recommended for use

in other healthcare settings and our review clearly could not cover all the existing CPMs. However, the included models cover a broad spectrum of clinical areas. Second, the external validation studies criteria included only the top ten most cited articles for each CPM as a pragmatic approach to maintain a viable number of papers to screen. Although there are some models, for which the total number of validation studies was less than or equal to 10 (n=7 CPMs), for the majority of the CPMs, especially those developed before 2010, this inclusion criteria would have excluded some validations. Thus, other validation studies might have applied alternative imputation strategies to those covered here.

5. Conclusion

We found considerable diversity, inconsistency and lack of reported detail in how missing data are handled across the development, external validation, and implementation stages of 23 CPMs currently recommended for use in UK healthcare. A framework for handling missing data is needed to quality assure CPM pipelines.

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TABLE TITLES

Table 1. List of CPMs included in this study.

Table 2. Identified missing data handling methods.

FIGURE TITLES AND DESCRIPTION

Figure 1. CPMs Eligibility criteria.

Figure 2. Missing data handling across the pipeline of a CPM. A Sankey diagram, showing different 'paths' of handling missing data across the three stages of a CPM's pipeline. The X axis shows the stages of a CPM's pipeline, whilst the Y axis shows the number possible combinations based on the number of validation papers (0 to 210)

SUPPLEMENTARY MATERIAL CAPTION

Full list of combinations of missing data handling methods across the pipelines of the CPMs included in this study showing consistent/inconsistent 'paths'.

Figure

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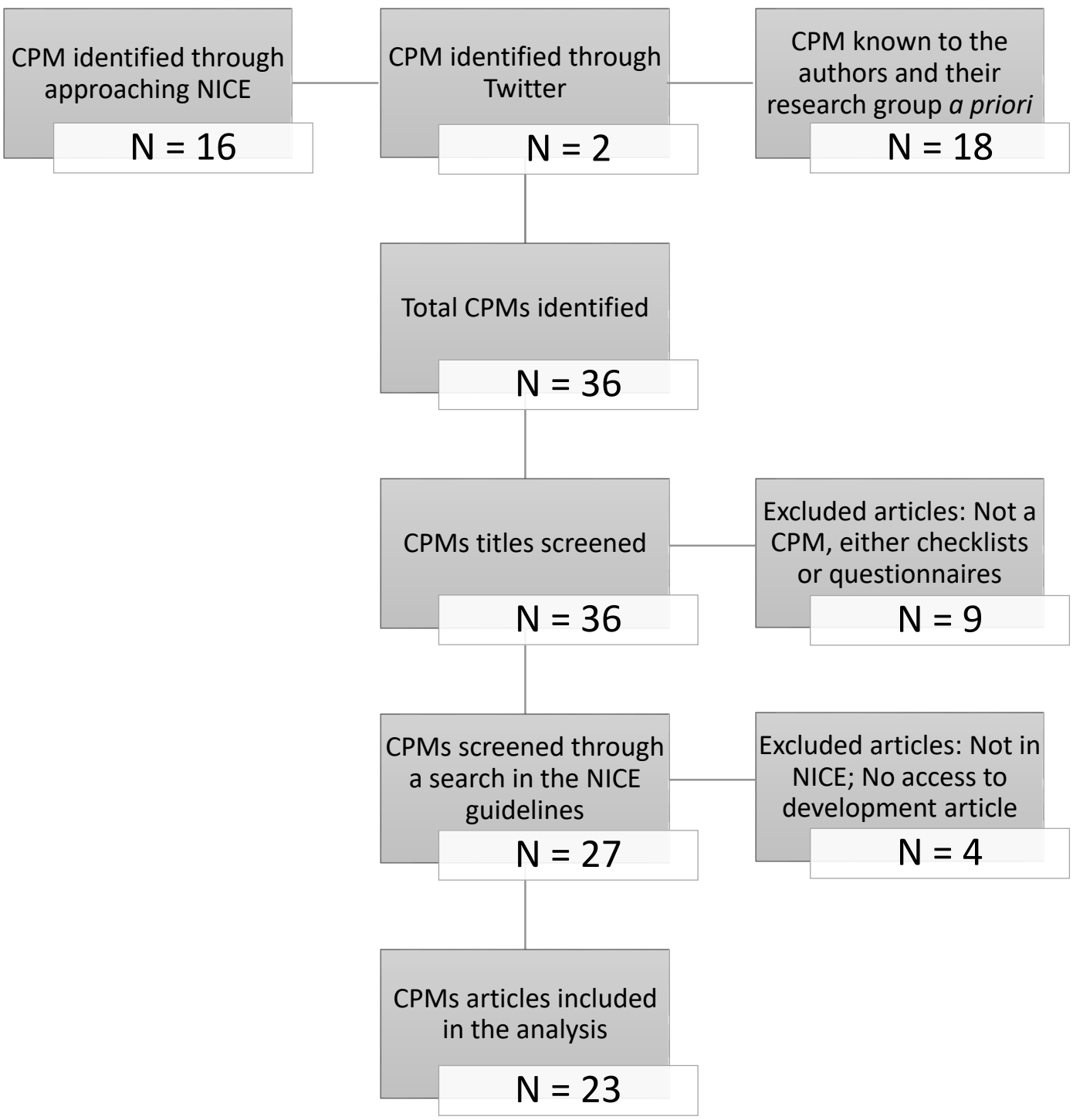
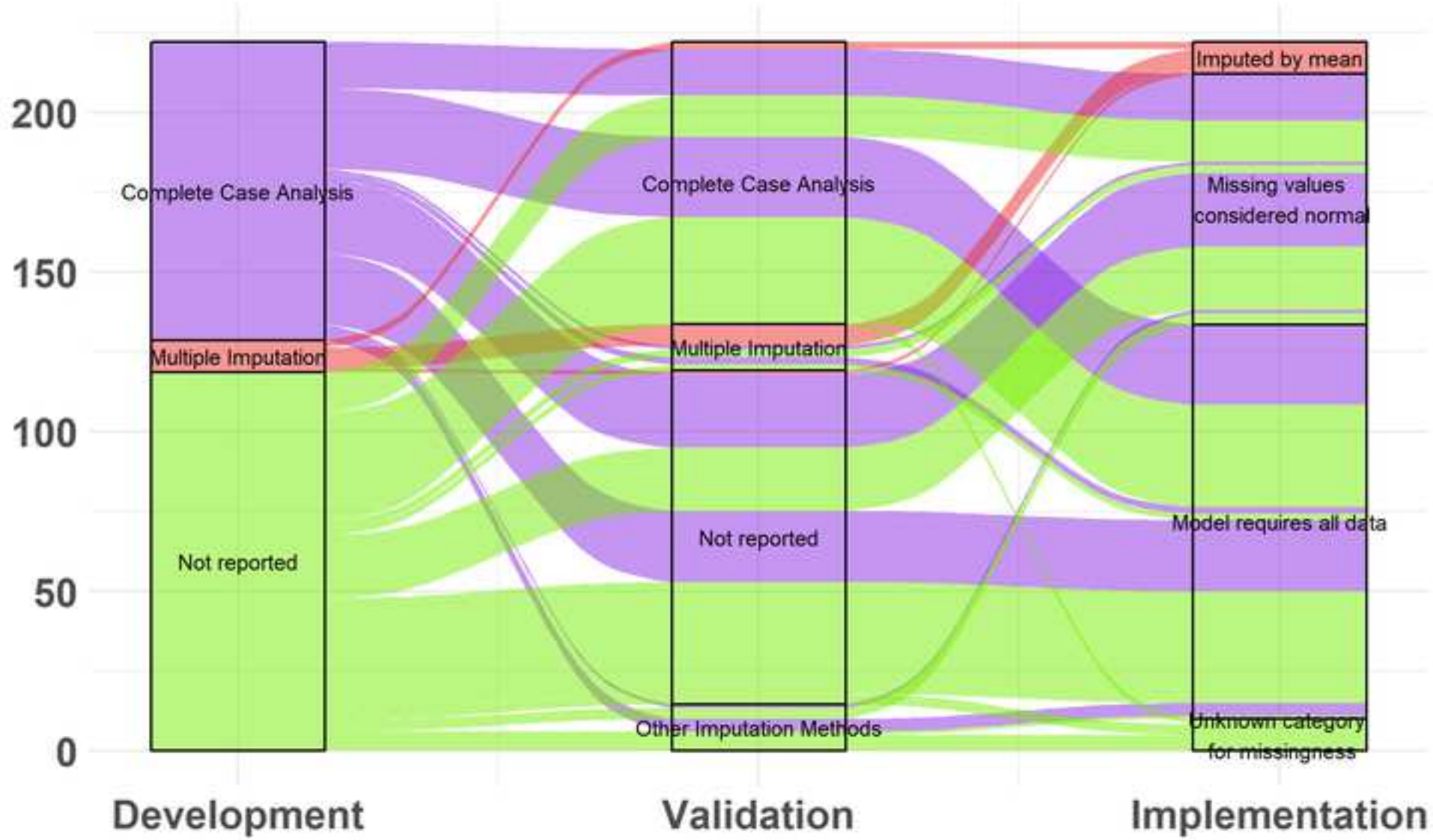


Figure



Table

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CPM	Description	Validation articles
QRISK[18–20]	10-year risk of developing CVD	21–29
Thoracoscore[30]	NSCLC pre-operative risk of death	31–39
Nottingham Prognostic index[40]	Risk of recurrence and overall survival in breast cancer	41–50
The Leicester practice risk score[51]	Screening for undiagnosed T2DM	52,53
PREDICT[54]	Breast and prostate cancers	55–64
FRAX[65]	10-year risk of developing osteoporotic & hip fracture	66–74
Manchester Triage System[75]	Assign clinical priority to patients	76–85
CRB65[86]	Assessment of community acquired pneumonia	87–96
Blatchford[97]	Upper Gastrointestinal bleeding	98–107
APGAR[108]	Evaluate the prognosis of a newborn baby	109–118
ABCD2[119]	Stroke/Transient ischaemic attack	120–129
GRACE[130]	Adverse CVD outcomes	131–140
APACHE[141]	ICU scoring systems for predicting mortality	142–151
CHADVASC[152]	Atrial fibrillation stroke risk	153–162
DG-ROMA[163]	Risk of ovarian malignancy	164–173
TIMI[174]	Thrombolysis in myocardial infarction	175–183,
HAS-BLED[184]	Major Bleeding risk	185–194
BOADICEA[195]	Breast cancer risk prediction model	196–201
Gleason score[202]	Prostate cancer	203–212
Braden Scale[213]	Predicting pressure ulcer risk	214–223
EuroScore[224]	Short-term mortality after cardiac surgery	225–234

Framingham[235]	Risk of CVD over 10 years	236–245
NEWS2[246]	Identifying acutely ill patients	247–252

Table

Method	***Development***		***Validation***		***Implementation***	
	Pros	*Cons*	*Pros*	*Cons*	*Pros*	*Cons*
Complete Case Analysis	Simple	Loss of information	Simple	Selection bias	N/A Equivalent of CCA for Implementation: "Model requires all data"	N/A Equivalent of CCA for Implementation: "Model requires all data"
Mean Imputation	Short computation time	Only works for the average individual	Short computation time	Only works for the average individual	Computationally achievable	Only works for the average individual
Multiple Imputation	Original data/Conditional distribution	High computational cost; Large bias/trade-off for MNAR	Resembling a 'real-world' situation	High computational cost; Large bias/trade-off for MNAR	Original data/Conditional distribution	Cannot be applied to an individual patient; Outcome required
KNN imputation	Can be more accurate than mean/median imputation	High computational cost; Sensitive to outliers	Can be more accurate than mean/median imputation	High computational cost; Sensitive to outliers	N/A	N/A
Additional Category for Missingness	Simple	Known to be biased, even in MCAR	Simple	Unstable to changes in missingness mechanism	No loss of information	Unstable to changes in missingness mechanism
Missing values considered as Normal	None	Simple	Will be biased even in MCAR	simple Biased	Simple	Bias

Model requires all data	All information needed	N/A Only applicable to implementation stage	N/A Only applicable to implementation stage	N/A Only applicable to implementation stage	N/A Only applicable to implementation stage	No loss of information	Cannot be applied to individuals with missing values

CPM review Antonia Tsvetanova

Conflicts of interest: none to declare