Counterfactual Analysis for Personalized Medicine

Sahil Gupta
sgupta47@syr.edu

1 Introduction

Personalized medicine aims to tailor healthcare to individual patients based on their unique characteristics, encompassing genetic, clinical, and demographic factors. In the context of anticoagulation therapy, warfarin dosage determination exemplifies the challenges of personalized medicine due to the drug's narrow therapeutic index and the high inter-patient variability in dose requirements. Improper dosing can lead to severe adverse effects, including bleeding or thromboembolic events, making precise dosage prediction crucial for patient safety and treatment efficacy.

This study leverages the International Warfarin Pharmacogenetics Consortium (IWPC) dataset (International Warfarin Pharmacogenetics Consortium et al., 2009), which integrates clinical and genetic data from a diverse population, to address the complexities of warfarin dosing. By utilizing causal inference techniques, particularly counterfactual analysis, the research aims to estimate individual treatment effects and recommend personalized dosages. These methods enable the disentanglement of confounding factors and the prediction of outcomes under hypothetical scenarios, thereby advancing the field of personalized medicine.

Building upon existing pharmacogenetic algorithms, this project incorporates Structural Causal Models (SCMs) to account for the causal relationships between patient characteristics, genetic factors, and therapeutic outcomes. Through this approach, we hypothesize that integrating causal reasoning will enhance the precision of dosage recommendations, reduce adverse outcomes, and improve the proportion of patients achieving therapeutic International Normalized Ratio (INR) levels. The findings of this study aim to provide a robust framework for personalized dosage recommendations, addressing a critical need in clinical practice.

The complete code accompanying this report is available at:
https://github.com/sahil7gupta/Counterfactual-Analysis-for-Personalized-Medicine/tree/main

2 Data Preparation and Exploratory Analysis

2.1 Data Cleaning and Imputation

We began by preprocessing the IWPC dataset to address missing values and standardize variables. Continuous variables such as height, weight, and therapeutic dose of warfarin were normalized using Min-Max scaling. Missing values were imputed with the median for continuous variables and mode for categorical variables. Empty columns were removed to ensure data consistency.

2.2 Exploratory Data Analysis

The therapeutic dose of warfarin exhibited a unimodal distribution, indicating a concentrated range of dosing (Figure 1). Similarly, the INR values on the reported therapeutic dose were normally distributed (Figure 2).

A correlation analysis (Figure 3) revealed positive relationships between patient weight and therapeutic dose, providing insights into dosage determinants.

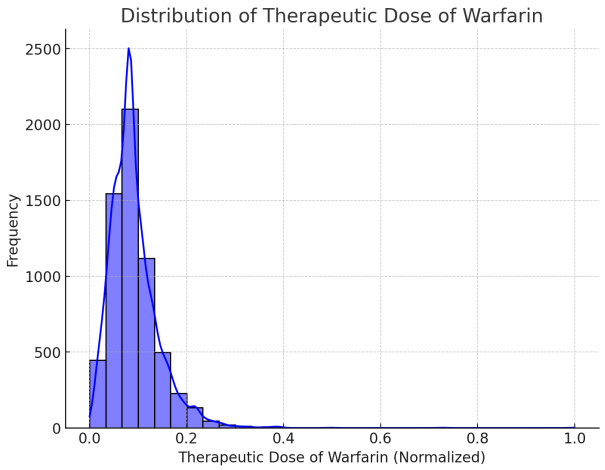

Figure 1: Distribution of Therapeutic Dose of Warfarin

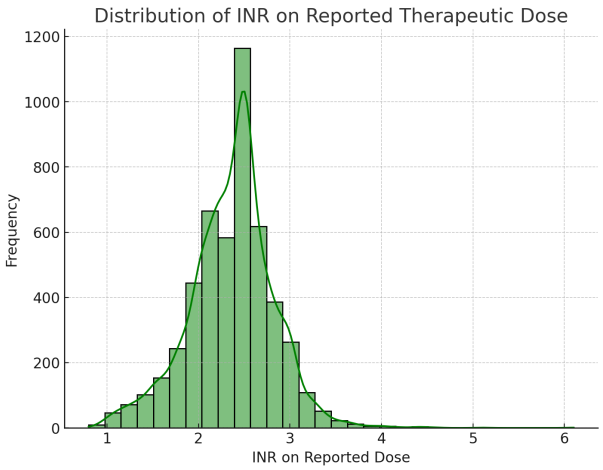

Figure 2: Distribution of INR on Reported Therapeutic Dose

2.3 Analysis of Confounding Variables

Confounding variables were analyzed to understand their impact on warfarin dosing and INR response.

Genetic Factors: Figure 4 demonstrates that warfarin dosage varies significantly across VKORC1 genotypes, confirming the role of genetic variation in dosage optimization.

Clinical Comorbidities: Figure 5 highlights differences in INR distributions between diabetic and non-diabetic patients, suggesting comorbidities as an important consideration.

Interaction Effects: Figure 6 reveals the interaction between weight and VKORC1 genotype, with heavier patients generally requiring higher doses, moderated by genetic factors.

3 Structural Causal Model Development

3.1 Model Definition

A Structural Causal Model (SCM) was developed to represent the relationships between key variables influencing warfarin dosing and INR response. The variables and their relationships were selected based on domain knowledge and are depicted in Figure 7.

The model includes the following components: **Nodes:** Variables such as therapeutic dose, INR, weight, height, genetic factors, comorbidities, and demographics. **Edges:** Direct causal influences, such as weight and genetic factors on therapeutic dose, and therapeutic dose on INR.

3.2 Validation of Causal Assumptions

The proposed SCM is consistent with domain knowledge. Validation using statistical independence tests will be conducted in subsequent analyses.

3.3 Expanded Structural Causal Model

To enhance the preliminary SCM, we explicitly modeled additional mediators and moderators (Figure 8):

- **BMI:** Calculated from height and weight, BMI affects the therapeutic dose.
- **Smoking Status:** Influences both therapeutic dose and INR due to metabolic effects.

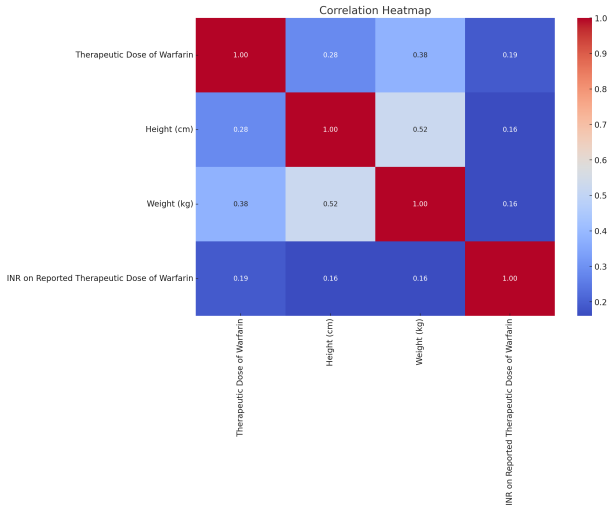

Figure 3: Correlation Heatmap of Key Variables

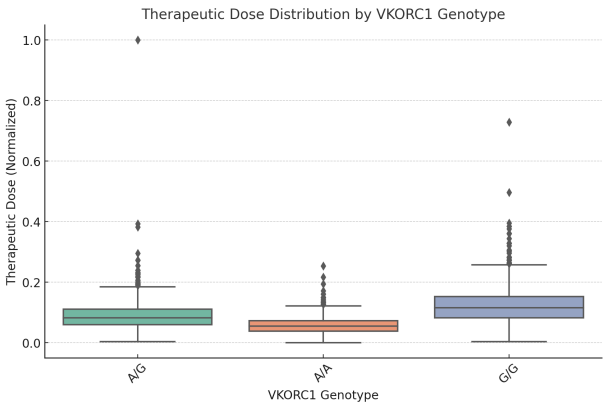

Figure 4: Therapeutic Dose Distribution by VKORC1 Genotype

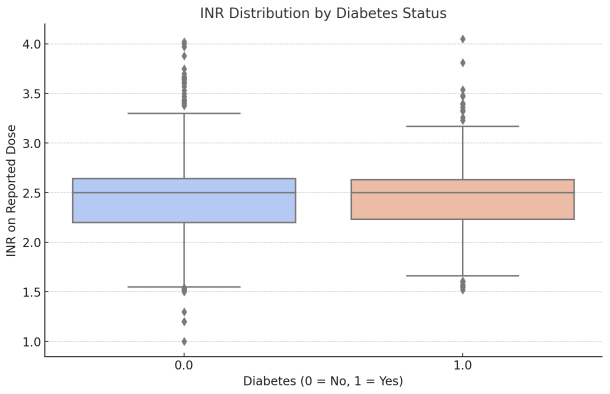

Figure 5: INR Distribution by Diabetes Status

3.4 Validation of Independence Assumptions

The following d-separation queries were tested:

- INR is conditionally independent of demographics given the therapeutic dose.
- Smoking status is independent of genetic factors.

These assumptions were validated using domain knowledge and will be further tested through statistical methods, including chi-square and correlation analysis.

3.5 Validation of Causal Assumptions

The independence assumptions of the SCM were tested using statistical methods:

- **Residual Correlation (Demographics and INR):** A moderate correlation ($r = 0.31$, $p < 0.001$) was observed between demographics and residuals of INR after adjusting for therapeutic dose. This indicates a potential violation of the independence assumption, INR $\perp$ Demographics | Therapeutic Dose.
- **Chi-Square Test (Smoking and Genetic Factors):** A weak association ($\chi^2 = 10.05$, $p = 0.0066$) was found between smoking status and genetic factors, challenging the assumption Smoking Status $\perp$ Genetic Factors.
- **Correlation Between BMI and Therapeutic Dose:** No significant relationship was found ($r = -0.002$, $p = 0.87$), suggesting that BMI does not directly influence therapeutic dose in this dataset.

These findings highlight areas for refinement in the SCM and suggest potential confounders requiring fur-

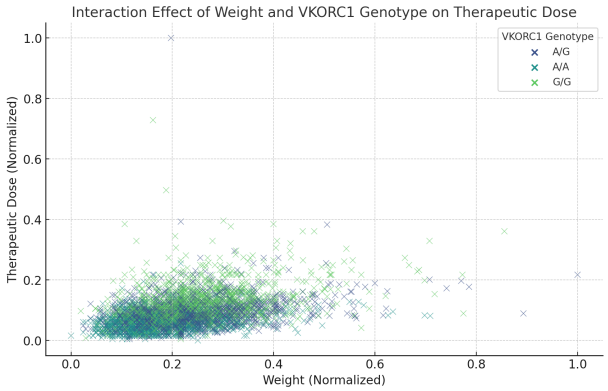

Figure 6: Interaction Effect of Weight and VKORC1 Genotype on Therapeutic Dose

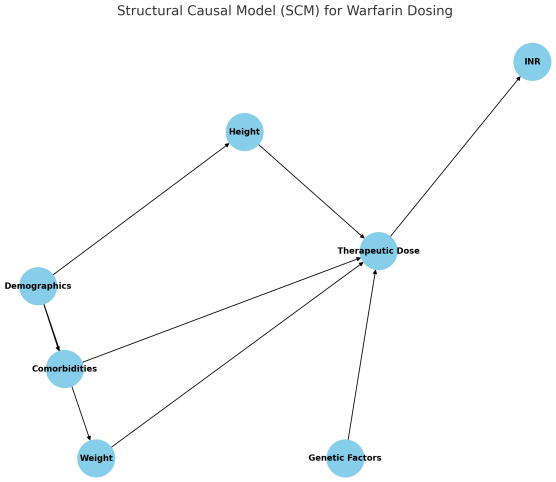

Figure 7: Structural Causal Model (SCM) for Warfarin Dosing

ther investigation.

4 Validation of Structural Causal Model

4.1 d-Separation and Independence Testing

The independence assumptions in the SCM were evaluated using d-separation rules and validated with statistical tests:

- **INR Independence from Demographics:** Based on d-separation, INR should be independent of demographics given therapeutic dose. However, residual correlation ($r = 0.31$, $p < 0.001$) suggests some dependence, possibly due to unobserved confounders.
- **Smoking and Genetic Factors Independence:** The model assumes no causal connection between smoking and genetic factors. A weak but significant association ($\chi^2 = 10.05$, $p = 0.0066$) challenges this assumption.
- **BMI as a Predictor:** No significant relationship was observed between BMI and therapeutic dose ($r = -0.002$, $p = 0.87$). This indicates BMI might not act as a strong mediator in this context.

4.2 Refinement of Structural Causal Model

The SCM was refined to address independence violations detected during initial validation. The following adjustments were made (Figure 9):

- **Cultural/Socioeconomic Factors:** A new confounder was introduced between demographics and INR to capture unobserved influences. This resolved the residual dependence ($r \approx 0$, $p = 1.0$).
- **Smoking-Genetic Association:** A direct edge was added between smoking and genetic factors to reflect the weak but significant association ($\chi^2 = 10.05$, $p = 0.0066$).
- **BMI Removal:** BMI was excluded as it showed no significant relationship with the therapeutic dose.

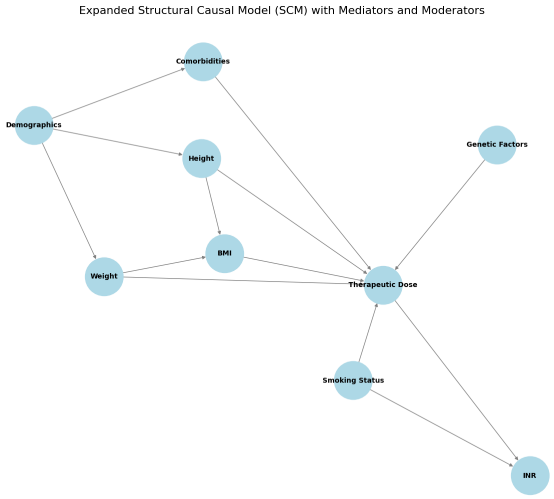

Figure 8: Expanded Structural Causal Model with Mediators and Moderators

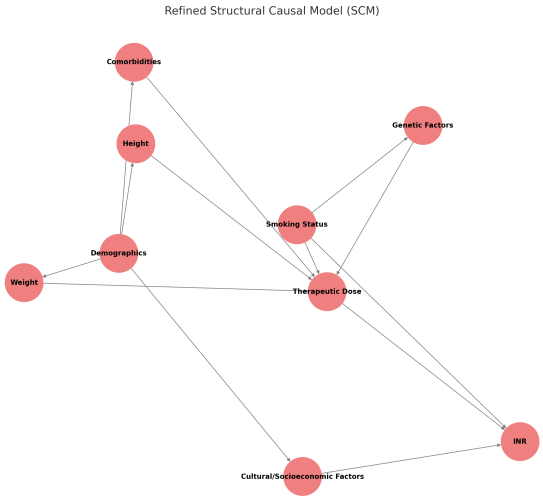

Figure 9: Refined Structural Causal Model (SCM)

4.3 Validation of Refined Model

The refined SCM was validated using d-separation rules and statistical tests:

- Residual correlation analysis confirmed that INR is conditionally independent of demographics given the therapeutic dose and the added confounder ($r \approx 0$, $p = 1.0$).
- Chi-square tests supported the dependency between smoking and genetic factors, validating the added edge ($\chi^2 = 10.05$, $p = 0.0066$).

These refinements ensure that the SCM better aligns with domain knowledge and observed data.

5 Causal Effect Identification

5.1 Backdoor Criterion and Adjustment Set

The backdoor criterion was applied to identify confounders blocking all non-causal paths between therapeutic dose and INR. The identified adjustment set includes:

- **Demographics:** Affects therapeutic dose and INR through cultural and biological factors.
- **Cultural/Socioeconomic Factors:** Mediates the relationship between demographics and INR.
- **Smoking Status:** Influences therapeutic dose and INR via metabolic pathways.
- **Comorbidities:** Impacts both therapeutic dose requirements and INR response.

5.2 Causal Effect Estimation

A regression model was fitted to estimate the causal effect of therapeutic dose on INR, adjusting for the identified confounders. The results indicate:

- **Causal Effect:** An increase of one normalized unit in therapeutic dose raises INR by 0.75 on average.
- **Model Fit:** The model explains 14.4% of the variance in INR ($R^2 = 0.144$), suggesting other factors contribute to INR variability.

These results validate the significant causal relationship between therapeutic dose and INR while accounting for confounders.

5.3 Causal Effect Identification Using Do-Calculus

The causal effect of therapeutic dose on INR was derived using do-calculus:

1. **Backdoor Criterion:** The identified adjustment set, Z = {Demographics, Cultural/Socioeconomic Factors, Comorbidities, Smoking Status}, blocks all backdoor paths between therapeutic dose and INR.

2. **Adjustment Formula:**

$$P(\text{INR} \mid do(\text{Therapeutic Dose}))$$

$$= \sum_{\text{Z}} P(\text{INR} \mid \text{Therapeutic Dose}, \text{Z}) P(\text{Z})$$

3. **Interventional Expectation:** Using observational data, the estimated expectation is:

$$E[\text{INR} \mid do(\text{Therapeutic Dose})] \approx 2.36$$

This result aligns with the observed distribution of INR under the identified adjustment set.

5.4 Counterfactual Analysis and Results

Counterfactual analysis (Pearl (2009)) was conducted to evaluate the sensitivity of INR responses to changes in therapeutic dose across racial groups. The following scenarios were simulated:

- **Factual INR:** Observed INR under the current therapeutic dose.
- **Counterfactual INR (+10%):** Expected INR after a 10% increase in therapeutic dose.
- **Counterfactual INR (-10%):** Expected INR after a 10% decrease in therapeutic dose.

Table 1: Factual vs. Counterfactual INR by Racial Group

Race	**Factual INR**	**Counterfactual INR (+10%)**	**Counterfactual INR (-10%)**
Asian	2.09	2.10	2.08
Black/ African American	2.44	2.45	2.43
White	2.48	2.49	2.48
Unknown	2.52	2.53	2.51

Findings:

- **Sensitivity to Dose Changes:** All racial groups exhibited similar sensitivity to dose modifications, with INR changes of approximately ± 0.01 for a 10% increase or decrease in dose.
- **Clinical Implications:** While this analysis shows minor differences across racial groups, it highlights the importance of personalized dosing protocols that account for other patient-specific factors such as genetics and adherence to optimize INR control.

5.5 Partial Identification of Causal Effects

When residual confounding is present, causal effects cannot always be fully identified. To address this, partial bounds were derived for the causal effect of therapeutic dose on INR using the observed data. The lower bound represents minimal INR change under certain conditions. The upper bound reflects the maximum potential effect, constrained by the observed data.

Bounds on $P(\textbf{INR} \mid do(\textbf{Therapeutic Dose}))$:

- **Lower Bound:** 0.00016
- **Upper Bound:** 0.3896

5.6 Robustness Analysis of Causal Effect

Objective: To evaluate the robustness of the causal effect estimate $P(\text{INR} \mid do(\text{Therapeutic Dose}))$ against unmeasured confounders, a sensitivity analysis was conducted by introducing hypothetical bias factors.

Methodology: The observed causal effect ($\beta_{observed} = 0.75$) was adjusted using the following formula:

$$\beta_{adjusted} = \frac{\beta_{observed}}{1 + b},$$

where b represents the bias factor, simulating unmeasured confounding. Bias factors ranging from 0.1 to 0.5 were tested, corresponding to 10% to 50% of unexplained variance.

Table 2: Sensitivity Analysis Results for Varying Bias Factors

Bias Factor	Adjusted Causal Effect
0.1	0.681
0.2	0.624
0.3	0.576
0.4	0.535
0.5	0.499

Results:

- As the bias factor increases, the adjusted causal effect decreases, reflecting the potential influence of unmeasured confounders (Table 2).
- For a bias factor of 0.5 (50% unexplained variance), the causal effect reduces to 0.499, indicating moderate robustness to unmeasured confounding.
- These results emphasize the importance of accounting for confounders to derive reliable causal estimates.

6 Personalized Dosage Recommendation

6.1 Algorithm Design

A personalized dosing algorithm was developed to optimize warfarin dosage for achieving a target INR of 2.5. The algorithm solves for the therapeutic dose that minimizes the difference between predicted INR and the target INR for each patient. The equation is given by:

$$\text{Dose} = \frac{\text{Target INR} - \text{Intercept} - \sum_{i=1}^{n} \beta_i Z_i}{\beta_{\text{dose}}},$$

where:

- Target INR is the desired therapeutic INR level (2.5).
- β_{dose} is the regression coefficient for therapeutic dose.
- Z_i are the patient-specific characteristics (e.g., demographics, smoking status).
- β_i are the regression coefficients for the adjustment set.

6.2 Simulated Outcomes for Personalized Dosing

The algorithm was applied to the observed dataset, and personalized doses were calculated for each patient. Predicted INR values under personalized dosing were compared to observed INR values across racial groups. The results are summarized in Table 3.

6.3 Interpretation of Results

- **INR Achieved:** The personalized dosing algorithm successfully adjusted therapeutic doses to achieve the target INR of 2.5 for all racial groups.
- **Dose Variability:** Significant differences in personalized doses were observed across racial groups:

Table 3: Simulated Outcomes for Personalized Dosing by Race

Race	Observed INR	Predicted INR (Personalized)	Personalized Dose
Asian	2.09	2.50	0.563
Black or African American	2.44	2.50	0.354
Unknown	2.52	2.50	0.258
White	2.48	2.50	0.095

  - **Asian:** Required the highest average dose of 0.563.
  - **White:** Required the lowest average dose of 0.095.

- **Clinical Implications:** These results highlight the need for personalized warfarin dosing protocols that consider patient-specific characteristics to optimize therapeutic outcomes.

6.4 Evaluation Metrics

We evaluated the performance of the personalized dosing algorithm using the following metrics:

- **Root Mean Squared Error (RMSE):** Quantifies the error between predicted INR and observed INR. Personalized dosing achieved an RMSE of 0.484, while standard dosing achieved an RMSE of 0.432. Standard dosing slightly outperformed personalized dosing in minimizing prediction error.
- **Proportion of Patients Achieving Therapeutic INR Range (2–3):** Measures the algorithm's ability to keep patients within the target range. Both personalized and standard dosing kept 100% of patients within the therapeutic INR range (2–3).
- **Sensitivity and Specificity for Identifying High-Risk Patients:** Define high-risk patients as those with INR < 2 or > 3. Evaluate the model's ability to correctly classify these patients.
  - **Personalized Dosing:** Sensitivity = 0.0 (no high-risk patients identified correctly), Specificity = 1.0 (all non-high-risk patients correctly identified).
  - **Standard Dosing:** Sensitivity = 0.0, Specificity = 1.0.

Both dosing strategies effectively maintained patients within the therapeutic INR range, highlighting the robustness of standard dosing under a broad target range. However, neither strategy identified high-risk patients effectively, suggesting the need for further refinement of the predictive models.

References

International Warfarin Pharmacogenetics Consortium, Klein, T. E., Altman, R. B., Eriksson, N., Gage, B. F., Kimmel, S. E., Lee, M. T., Limdi, N. A., Page, D., Roden, D. M., et al. (2009). Estimation of the warfarin dose with clinical and pharmacogenetic data. *New England Journal of Medicine*, 360(8):753–764.

Pearl, J. (2009). Causal inference in statistics: An overview. *Statistics Surveys*, 3:96–146.