

Estimating Therapeutic Exposure of Extended-Release Methylphenidate in Youths With ADHD Using Imputed Body Weight and Pharmacokinetic Modeling

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Objective

To investigate the feasibility of using imputed weight to predict concentration of methylphenidate extended-release (MTP-ER) in youths with attention deficit-hyperactivity disorder (ADHD) using a published PK model.

Methods

Study Cohort: Youths aged 5-17 years who had prescription records of MTP-ER in 2020 and an ADHD diagnosis within the 6 months prior to their first observed MTP-ER prescription.

Data Source: The IQVIA PharMetrics® Plus Closed Health Plan claims database.

Statistical Analysis:

- Daily MTP-ER dosage was calculated using the unit milligram dose of distinct prescriptions on the index date, defined by the first MTP-ER.
- Individual body weights were imputed by randomly sampling from age- and sex-specific normal distributions derived from the CDC growth chart.
- A previously published pharmacokinetic model for MTP-ER was applied to estimate individual therapeutic concentration using imputed weights, assuming a bioavailability of 16% [Teuscher, 2018]

$$CL_i = 1.3L/h * Imputed Weight^{0.75} \quad \text{where } CL_i \text{ the clearance for individual } i$$

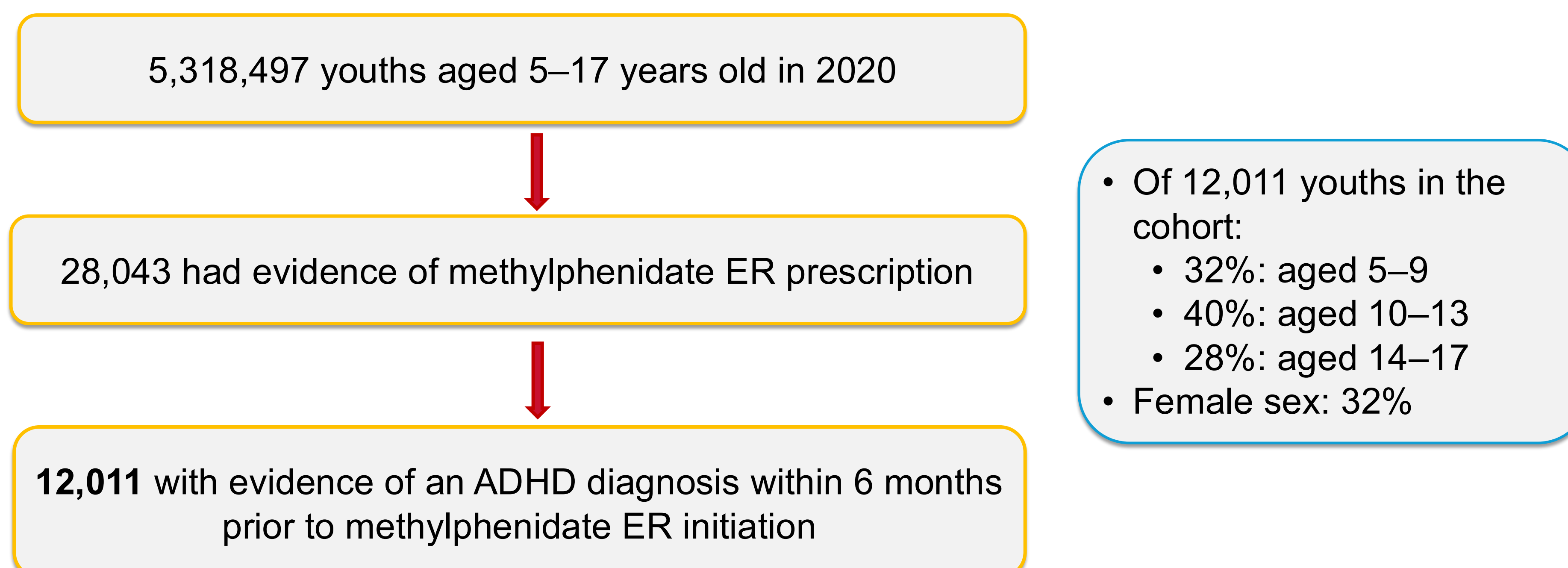
Therapeutic concentration, C, at steady state using CL_i from the above formula:

$$C \text{ (ng/ml)} = \frac{F \text{ (bioavailability)} * Dose}{CL_i * Dosing \text{ interval}} = \frac{F \text{ (bioavailability)} * Dose * 10^6}{1.3 * 1000 * Imputed Weight^{0.75} * 24h}$$

- The observed dose and concentration was examined by age and sex.

Results

Figure 1: Diagram of the cohort selection



Conclusion

Imputing individual body weight using CDC growth chart distributions enables estimation of therapeutic concentration through pharmacokinetic modeling in real-world claims data. This approach warrants further investigation in dose-exposure relationships and their associations with health outcomes in pediatric ADHD populations.

Results

Figure 2: Distribution of imputed weight by age and sex

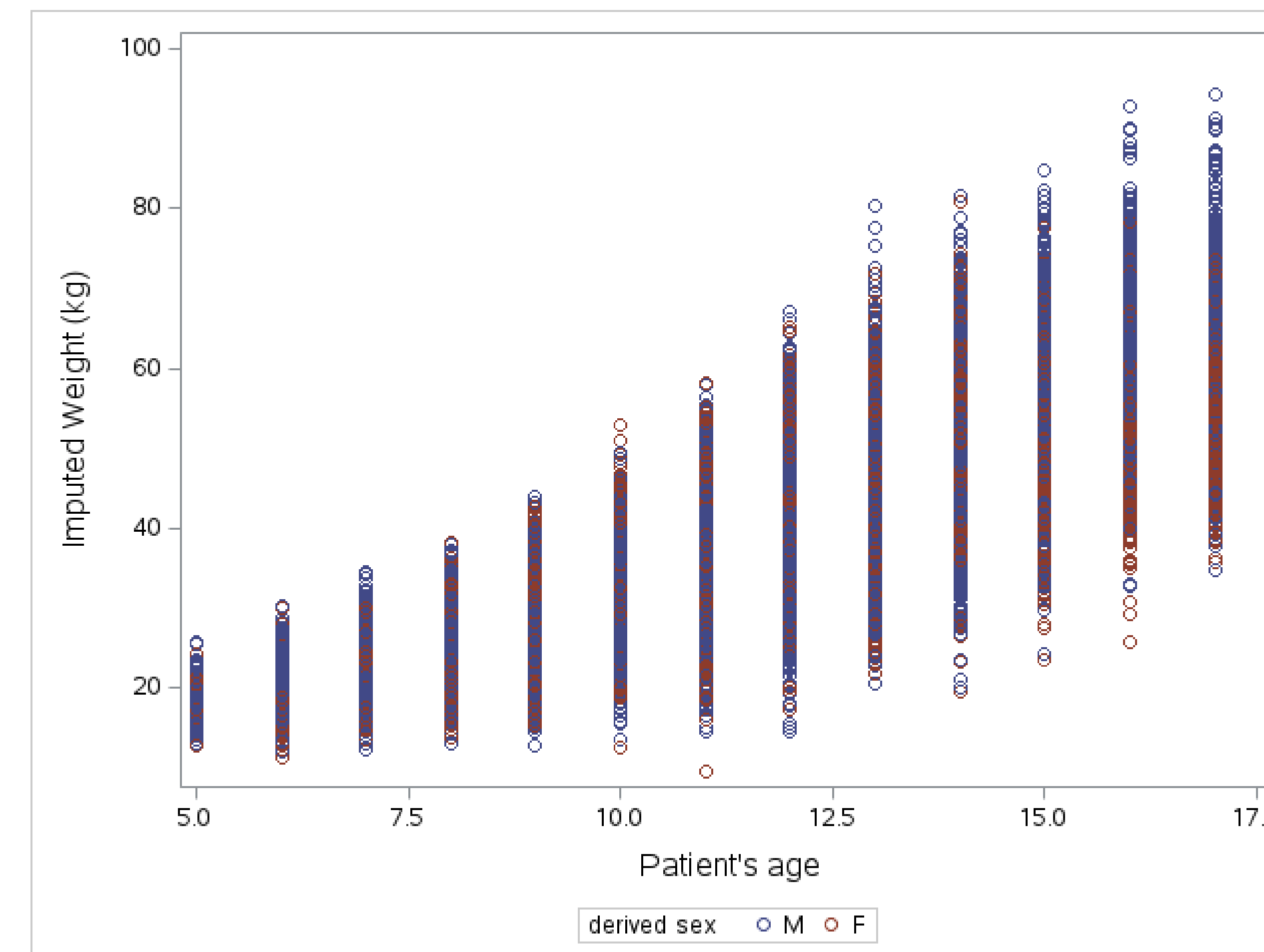


Figure 2:

- Imputed weights by age (95% confidence interval)
- 5 – 9 yrs: 25kg (15kg-35kg)
- 10 – 13 yrs: 39kg (21kg-58kg)
- 14 – 17 yrs: 56kg (34kg-77kg)

Figure 3:

- Daily MTP-ER dosage ranged from 8.6mg to 108mg
- 99.18% of youths received \leq 60mg/day.

Figure 3: Distribution of methylphenidate MTP-ER dose by age and sex

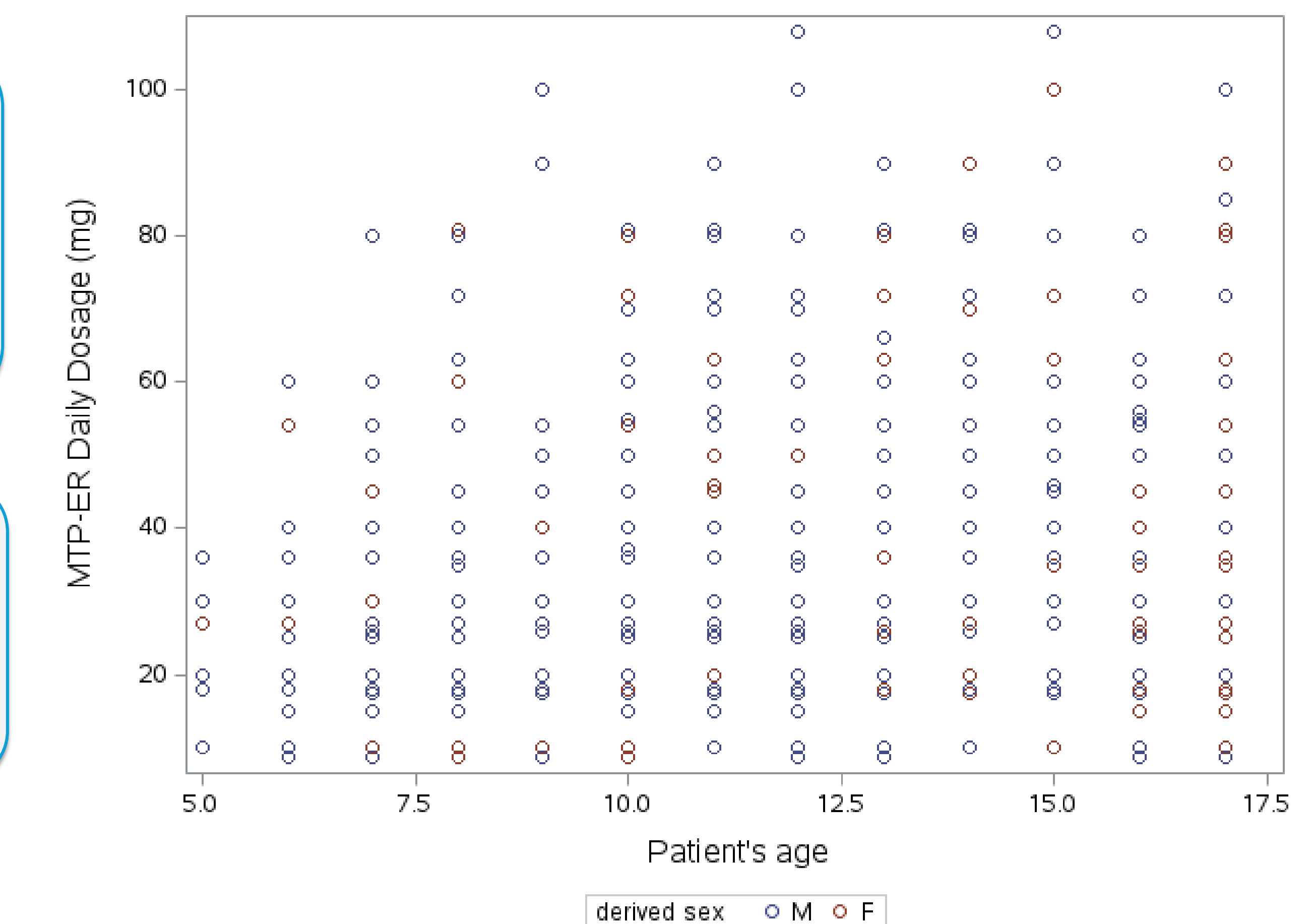


Figure 4: Distribution of estimated therapeutic concentration of MTP-ER with bioavailability of 16% at steady state by age and sex

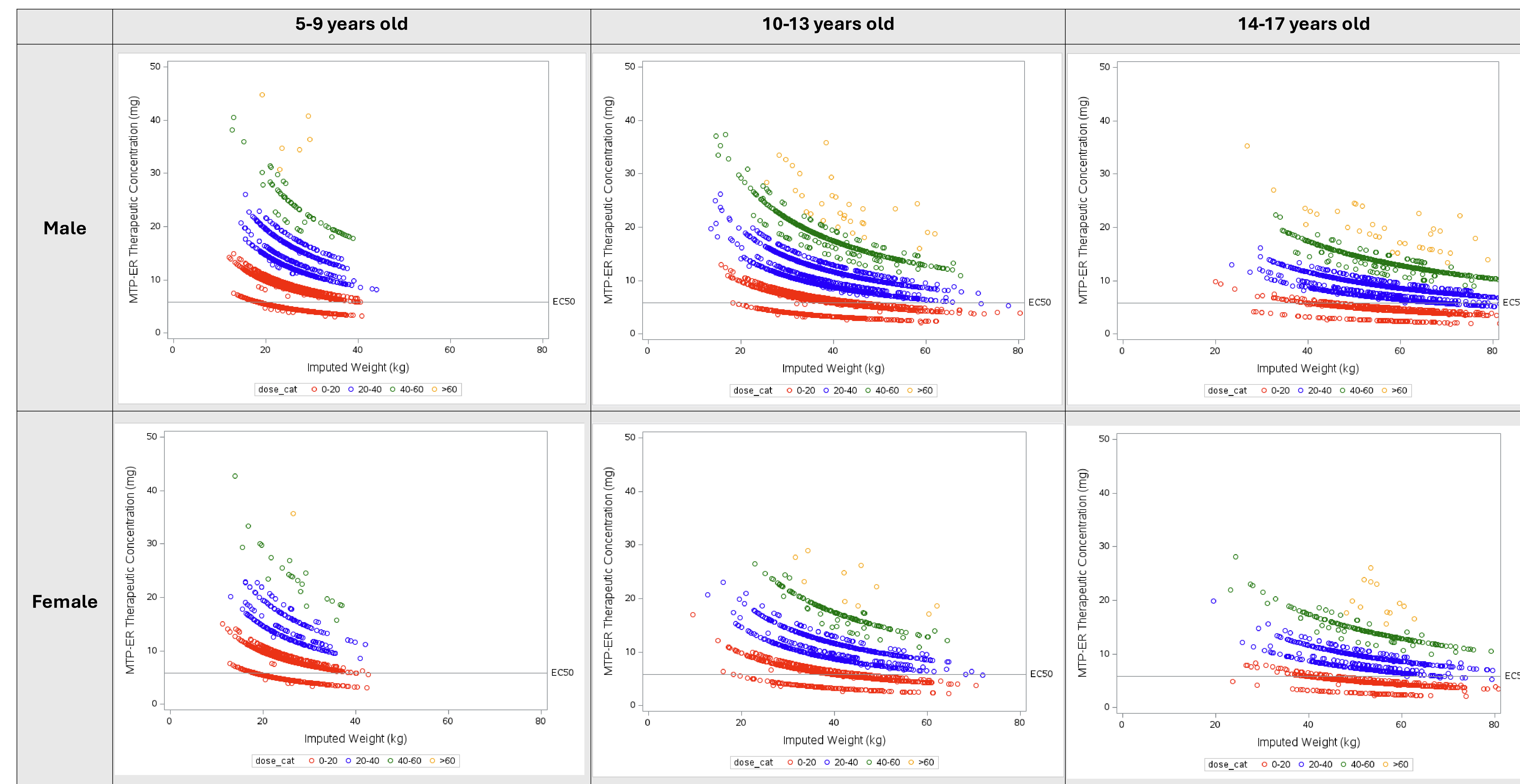


Figure 4:

- A substantial proportion of youths receiving daily dosages below 20mg were estimated to have the therapeutic concentration below the half-maximal effective concentration for MTP-ER, with this pattern becoming more pronounced with increasing age