

Age-related changes in plasma proteins, haematocrit, and CYP3A4 activity for physiologically based pharmacokinetic model implementation in older adults

Cleo Demeester^{a,b}, Pieter Annaert^{b,c}, Patrick Augustijns^b, Jan Schlender^d, André Dallmann^{e,*}, Thomas Wendl^{a,*}

^a Bayer AG, Research & Development, Pharmaceuticals, Model-Informed Drug Development, Building B106, 51368 Leverkusen, Germany; ^b Drug Delivery and Disposition, KU Leuven, Gasthuisberg O&N II, Herestraat 49—Box 921, 3000 Leuven, Belgium; ^c BioNotus, Galileilaan 15, 2485 Niel, Belgium; ^d Novartis Institute of Biomedical Research, Basel, Switzerland; ^e Bayer HealthCare SAS, Lille, France, on behalf of: Research & Development, Pharmaceuticals, Model-Informed Drug Development, Bayer AG, Leverkusen, Germany; * These authors share last authorship

KU LEUVEN



1 BACKGROUND

- The older population is underrepresented in clinical trials [1].
- A useful alternative for investigating pharmacokinetics (PK) in older people is physiologically based pharmacokinetic (PBPK) modelling.
- Previously, a huge effort has been made to inform the older adults in the open-source PBPK software PK-Sim® [2].
- This study investigates the age-related changes in plasma protein concentrations, haematocrit values, and cytochrome P450 (CYP) 3A4 activity and test whether the implementation of these changes enhances the performance of PBPK models for the older population.

2 MATERIALS & METHODS

- Human serum albumin concentrations and haematocrit values were derived from the National Health and Nutrition Examination Survey (NHANES) [3].
- Values for alpha-1-acid glycoprotein (AAG), free fatty acids, liver blood flow and liver weight were sourced from literature data.
- Various functions were fitted to predict their relationship to age.
- The CYP3A4 ontogeny was derived by calculating the intrinsic unbound clearance from published plasma clearance data for the CYP3A4 probe compounds midazolam and alfentanil using the well-stirred model [4] depicted in Figure 1.
- The senescence functions were integrated into existing PBPK models for midazolam (middle ER) and nimodipine (high ER) to simulate the PK in older adults using PK-Sim® [5].

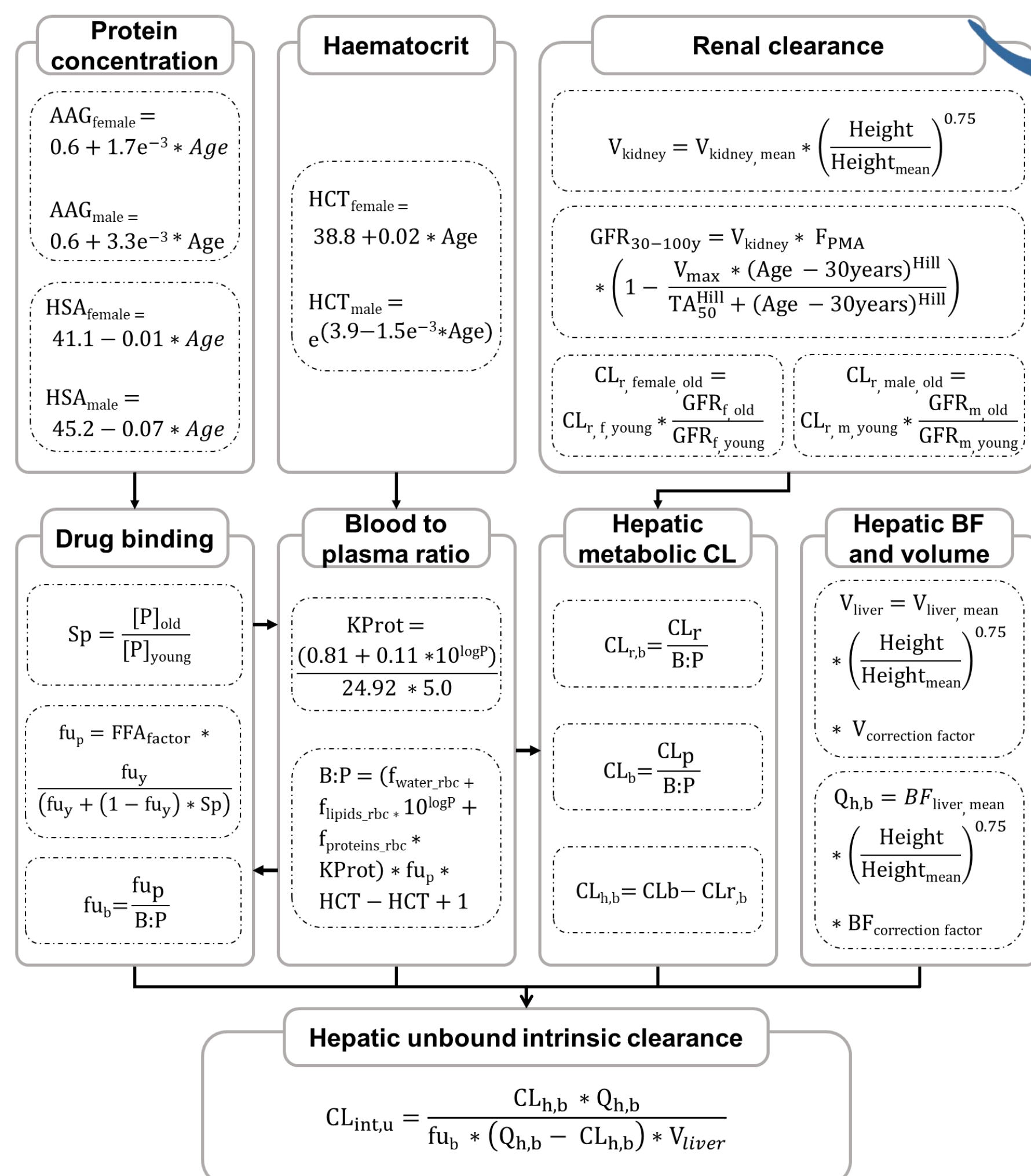


Figure 1. Workflow of calculating the hepatic unbound intrinsic clearance via the well-stirred model for older and younger adults

3 RESULTS

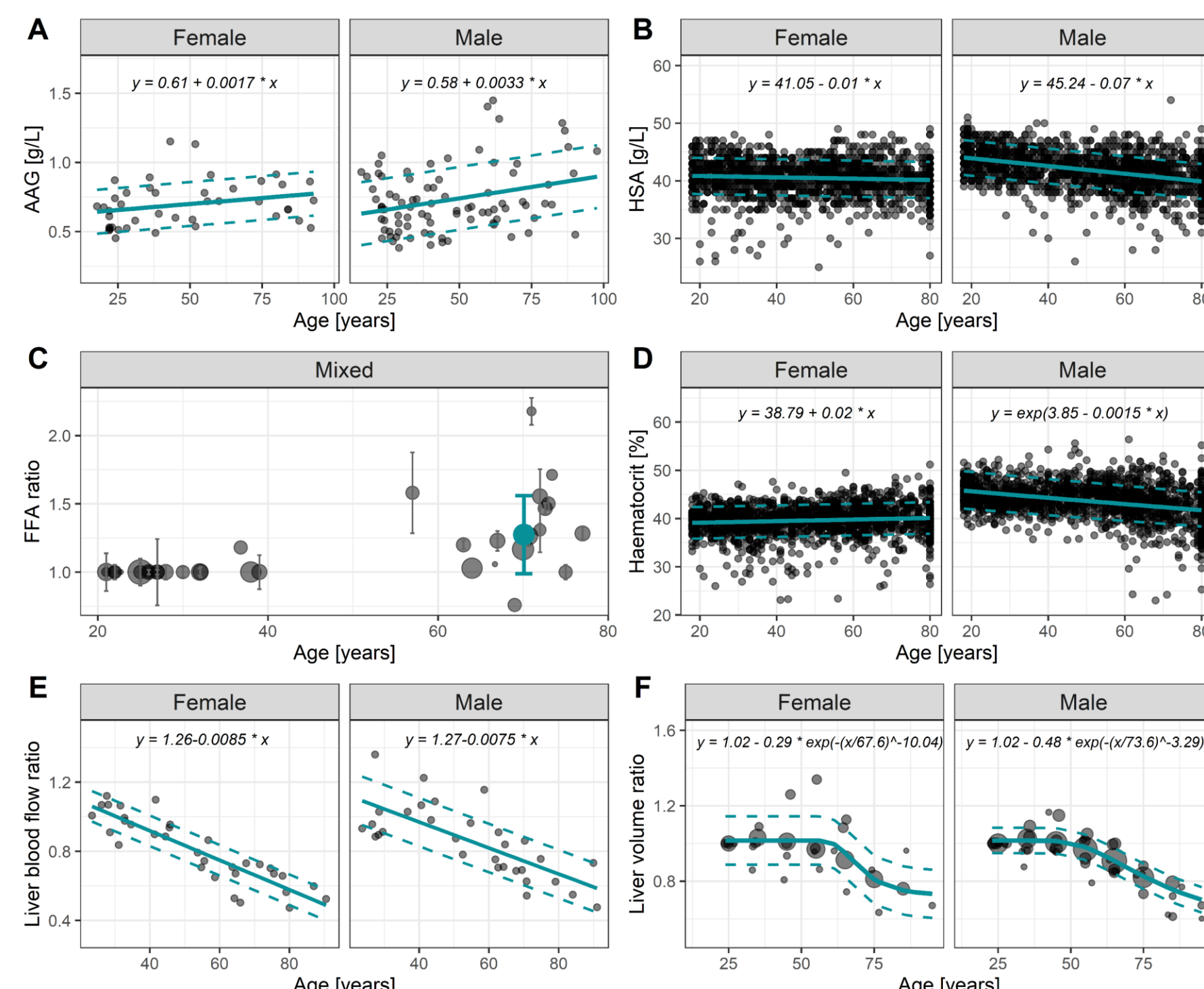


Figure 2. Correlations between age and alpha-1-acid glycoprotein (AAG) concentration (panel A), human serum albumin (HSA) concentration (panel B), haematocrit level (panel C), total free fatty acids (FFA) (panel D), liver blood flow (panel E) and liver volume (panel F), discretised by sex.

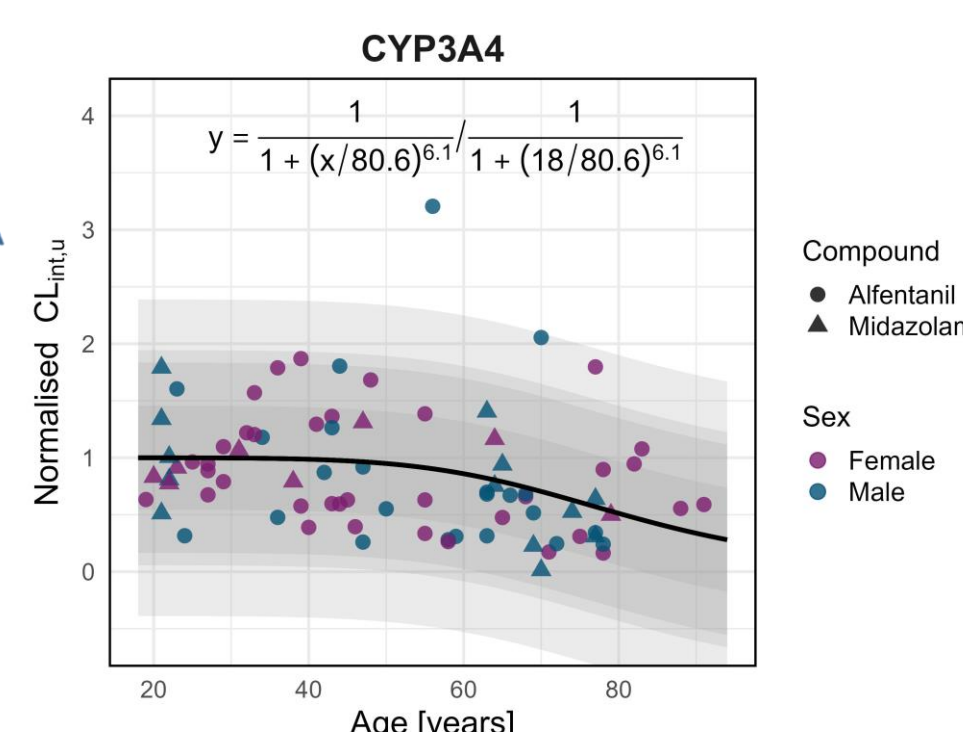


Figure 3. Calculated hepatic unbound intrinsic clearance ($CL_{int,u}$) over age normalised by sex and administered compound. The hill function given represents the best-fitted model and is also given as a solid line with its confidence intervals in grey.

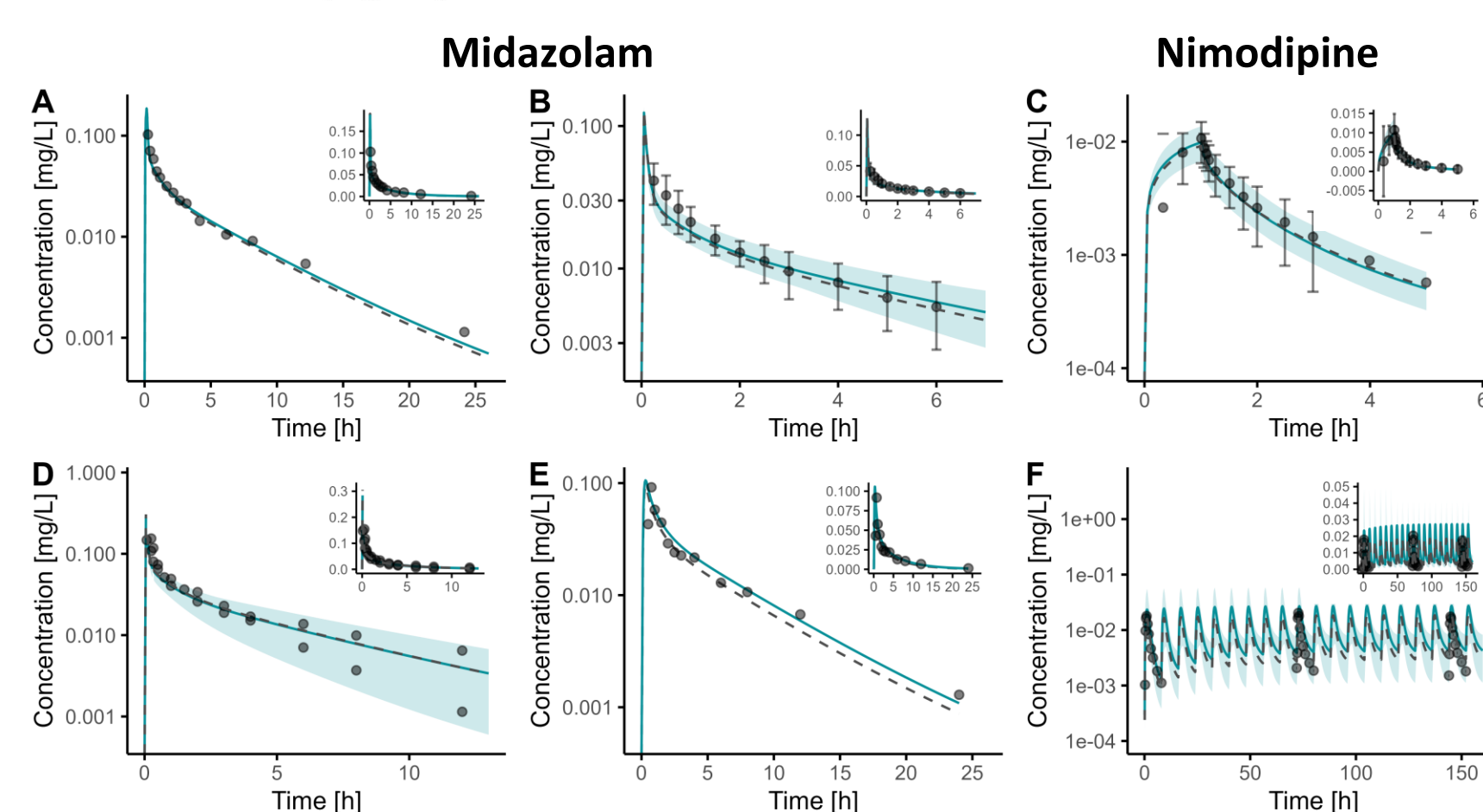


Figure 4 Observed (symbols) and predicted modified (blue line) and predicted original (dashed grey line) plasma concentration-time profiles of midazolam and nimodipine in older adults. Panel A: Midazolam 5 mg IV. Panel B: Midazolam 0.03 mg/kg IV. Panel C: Nimodipine 15 µg/kg IV. Panel D: Midazolam 0.07 mg/kg IV. Panel E: Midazolam 10 mg orally. Panel F: Nimodipine 30 mg TID orally.

4 CONCLUSION

- Age-specific changes in plasma proteins, FFA, haematocrit, liver blood flow and liver weight were observed and described.
- By taking these changes into account, the well-stirred model predicted a decrease in unbound intrinsic clearance at older age.
- The PBPK models incorporating the age-related changes performed well for midazolam and nimodipine; further studies with other probes are needed.
- This method could be applied to explore the ontogeny of other CYP enzymes.

Personal information – Cleo Demeester

cleo.demeester@kuleuven.be

KU Leuven – Drug Delivery and Disposition

LinkedIn

