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# OPEN-SOURCE SUB-SAHARAN AFRICAN PBPK POPULATION:

## INTEGRATING ANATOMICAL, PHYSIOLOGICAL, AND ENZYMATIC VARIABILITY



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OSP Conference 2027, Beerse, Belgium

Raphaëlle Lesage (ESQlabs)

# Sub-Saharan African populations and genetic diversity

## Why African-specific pharmacokinetic data matter

**67%**
of the global HIV burden is in Sub-Saharan Africa

**> 80%**
of tuberculosis-related deaths worldwide

**~1.5 bn**
people — 2nd most populous continent after Asia

Africa remains underrepresented in pharmacokinetic studies and most data come from non-African populations

## African-specific PK studies: why does it matter?

- Different physiology
- Large genetic diversity (polymorphism)
- Allele frequencies differ from Asian & European populations

UNAIDS. Global HIV & AIDS statistics — Fact sheet. UNAIDS; 2023.

Twesigomwe D, Mazhindu TA, Nagy M, Agesa G, Scholefield J, Masimirembwa C. Pharmacogenomics in Africa: A Potential Catalyst for Precision Medicine in Genetically Diverse Populations. Annu Rev Genomics Hum Genet. 2025;26(1):321–349. doi:10.1146/annurev-genom-121323-104008.

# Sub-Saharan African populations and genetic diversity

## Inter-ethnicity heterogeneity

| Variant | Freq. | population | source |
|---|---|---|---|
| CYP2D6 *29/*29 | 2 - 30% | African | 3,5,6,8 |
| | 0.63% (4/635) | African (Zimbabwe) | Current study* |
| | 17% | Zimbabwean (Shona) | 5,6,33,36 |
| | 30% | Igbo (Nigeria) | 5,6,33,36 |
| | ~0% | Asian/European | 5,6,33,36 |
| CYP2D6 *17/*17 | 19% | Zimbabwean (whole) | 6,32–35 |
| | 34% | Zimbabwean (Shona) | 6,32–35 |
| | 0-0.5% | Asian | 6,32–35 |

- African genome carries 25%  more polymorphism than the non-African genomes
- Heterogeneity coming from distinct evolutionary trajectories
- Some allele variant only found in African
- Continental-level classification doesn't capture regional diversity (Lootens et al. (2025)
- Data gap

* Marasanapalle, V.P et al. (2024), Investigation of the Differences in the Pharmacokinetics of CYP2D6 Substrates, Desipramine, and Dextromethorphan in Healthy African Subjects Carrying the Allelic Variants CYP2D6*17 and CYP2D6*29, When Compared with Normal Metabolizers. J Clin Pharm, 64: 578-589. https://doi.org/10.1002/jcph.2366

# Project scope and objectives

*Development of a **physiologically based pharmacokinetic (PBPK) population model specifically for** Sub-Saharan African **populations**, starting with Zimbabwe and South Africa*

✓ Open-source resource in PK-Sim



**African Institute of Biomedical Science and Technology (AiBST)**
- Project Management
- Data Management

**Advisory Committee**

**Wits (SBIMB)/AiBST**
- ❑ Integrated PGx Database
- ❑ Tissue Biobanking

➢ Human genetics

**Wits (WDGMC)/AiBST**
- ❑ Liver tissue collection
- ❑ Population parameter collection

➢ Tissue & population data collection

**AiBST & Dundee**
- ❑ Genotyping
- ❑ Enzyme Quantification
- ❑ Enzyme activity

➢ Wet lab analyses

**AiBST, Makarere Uni & ESQlabs**
- ❑ Data Integration
- ❑ Model development

➢ Modelling & Validation work

# Agenda

1. Project data flow
2. SSA population data collection and processing
3. Accounting for genetic variability (polymorphism)
4. Testing population with probe drugs
    1. CYP2D6-specific (Dextromethorphan)
    2. CYP2B6-specific (Efavirenz)
5. Considerations for building a new built-in PK-Sim population
6. Conclusion & take-away

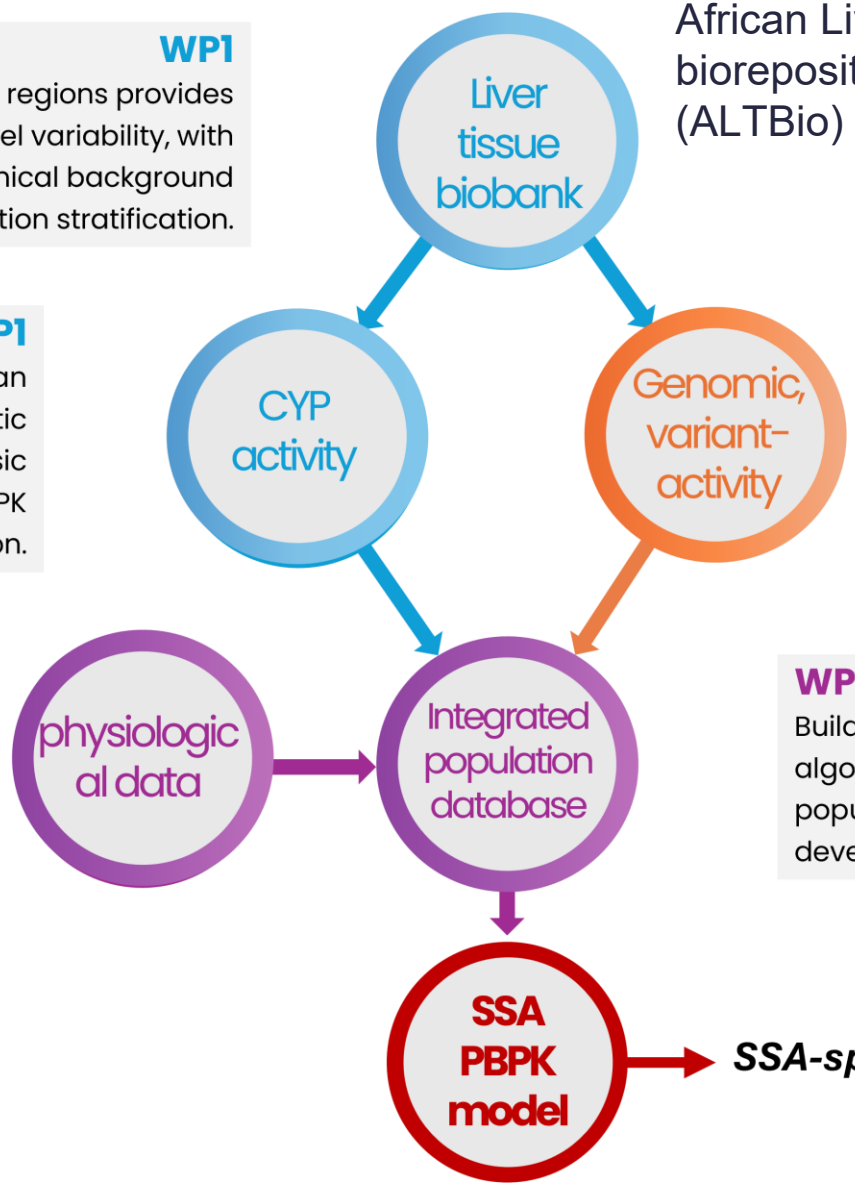


# Project overview: data flow

**WP1**
Liver tissue collected across African regions provides direct measurements and donor level variability, with metadata on age, sex, region and clinical background for population stratification.

**WP1**
Measures CYP and UGT activity in African liver tissue. These data establish realistic metabolic capacity and intrinsic clearance for the Sub Saharan PBPK population.

**WP3**
Age and sex distributions, anthropometric measurements and core physiological data including blood flows, organ volumes, biochemical markers and functional ranges..



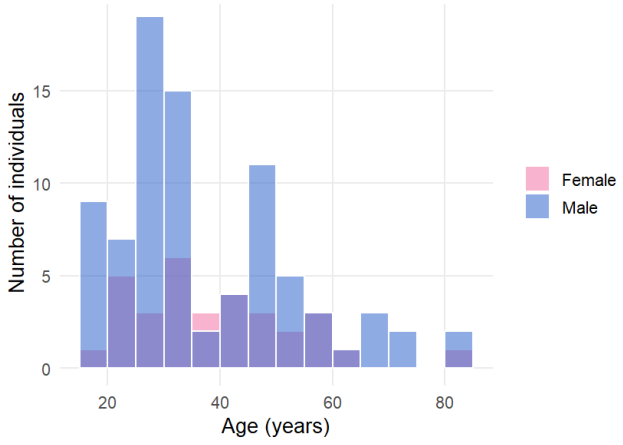

**WP2**
Curates whole genome and exome data and links genotypes to drug metabolism phenotypes for CYPs (CYP Genotype–phenotype relationships).

**WP3**
Builds the integrated African database and algorithms that link genotypes, phenotypes and population parameters for PBPK model development.

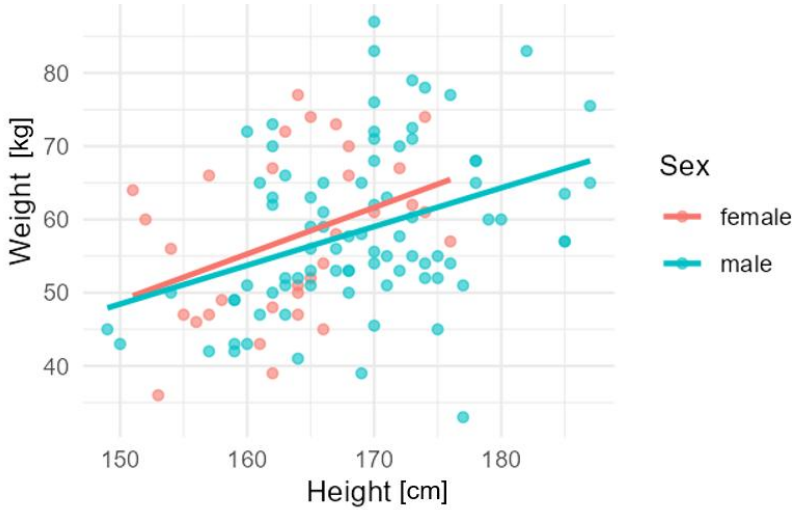
# Zambian individual data Mubbunu et al. (2018)

- Zambian necropsy study
- n = 83 M / 32 F
- Demography: Age, sex
- Anthropometry: Height, weight, organ weight

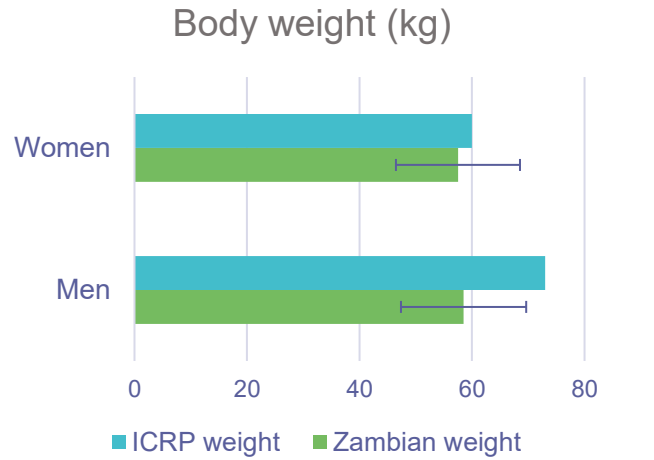
## Age distribution by sex

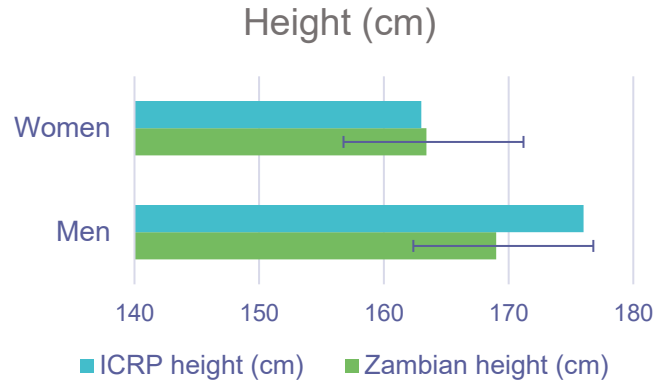



## Weight vs. Height by sex




## Compared to the European population:



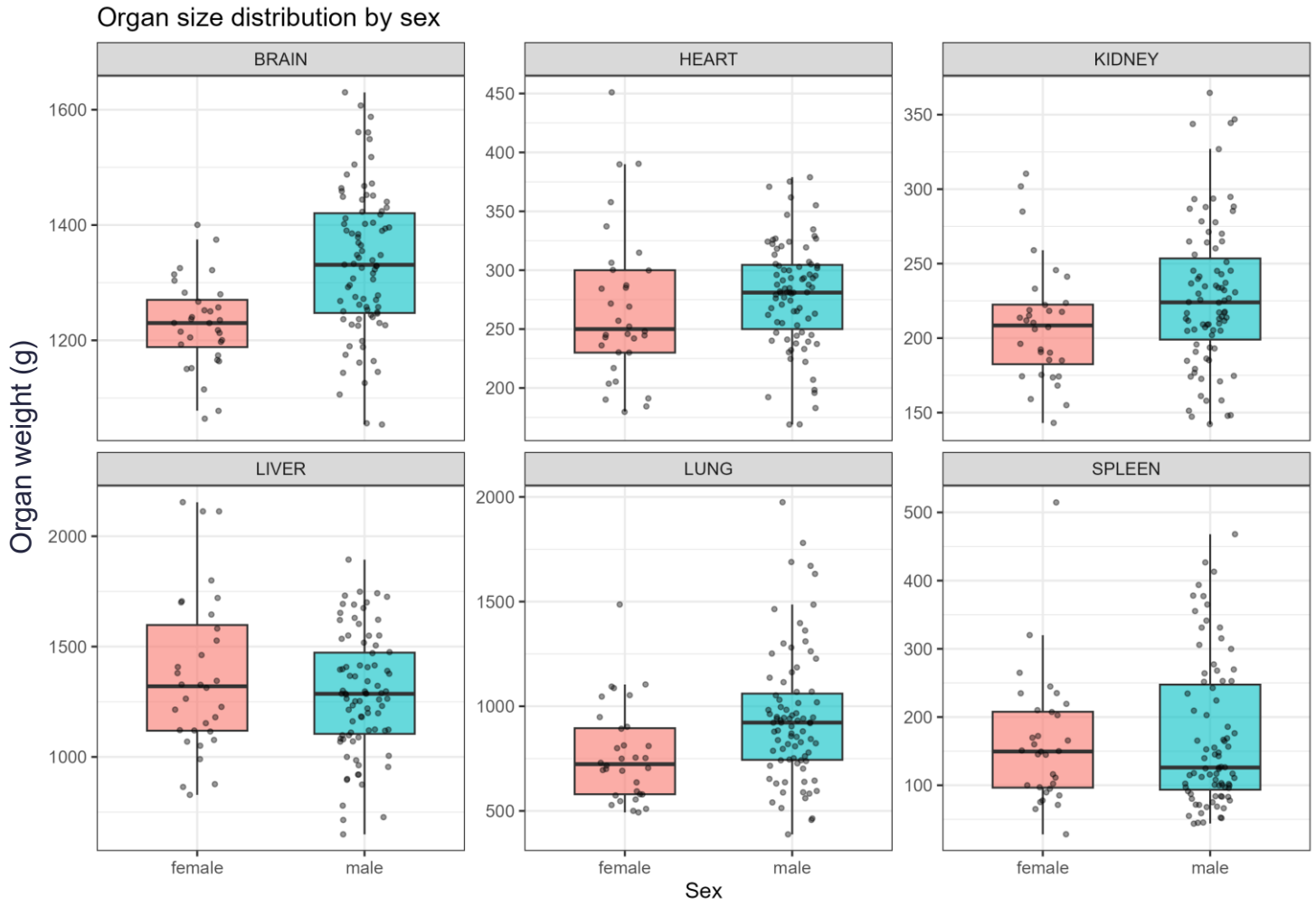





1. Mubbunu, L. et al, *Correlation of Internal Organ Weights with Body Weight and Body Height in Normal Adult Zambians: A Case Study of Ndola Teaching Hospital*, *Anatomy Research International*, 2018, 4687538, 5 pages, 2018. https://doi.org/10.1155/2018/4687538
2. *ICRP, 2002. Basic Anatomical and Physiological Data for Use in Radiological Protection Reference Values. ICRP Publication 89. Ann. ICRP 32 (3-4).*

# Zambian individual data Mubbunu et al. (2018)

## Organ weight




1) Convert to volume with a density of 1g/ml
2) Add blood volume

Mubbunu, L. et al, *Correlation of Internal Organ Weights with Body Weight and Body Height in Normal Adult Zambians: A Case Study of Ndola Teaching Hospital*, *Anatomy Research International*, 2018, 4687538, 5 pages, 2018. https://doi.org/10.1155/2018/4687538

# Benchmarking the Mubbunu Liver weight against literature data

| Series | Sex | Liver (dry) weight (g) |
|---|---|---|
| **Peddle & Kirk, Cape Town - Black South African only** | M | 1,300 ± 257 |
| | F | 1,268 ± 271 |
| **Mubbunu (n=115)** | M | 1,285.3 ± 270.1 |
| | F | 1,367.9 ± 357.2 |
| **Govender, KZN (n = 500)** | Mixte | 1,376.6 ± 435.4 |
| **Obiajulu, Lagos, pathology removed (n = 19), mixte population** | Mixte | 1,571 ± 410 |

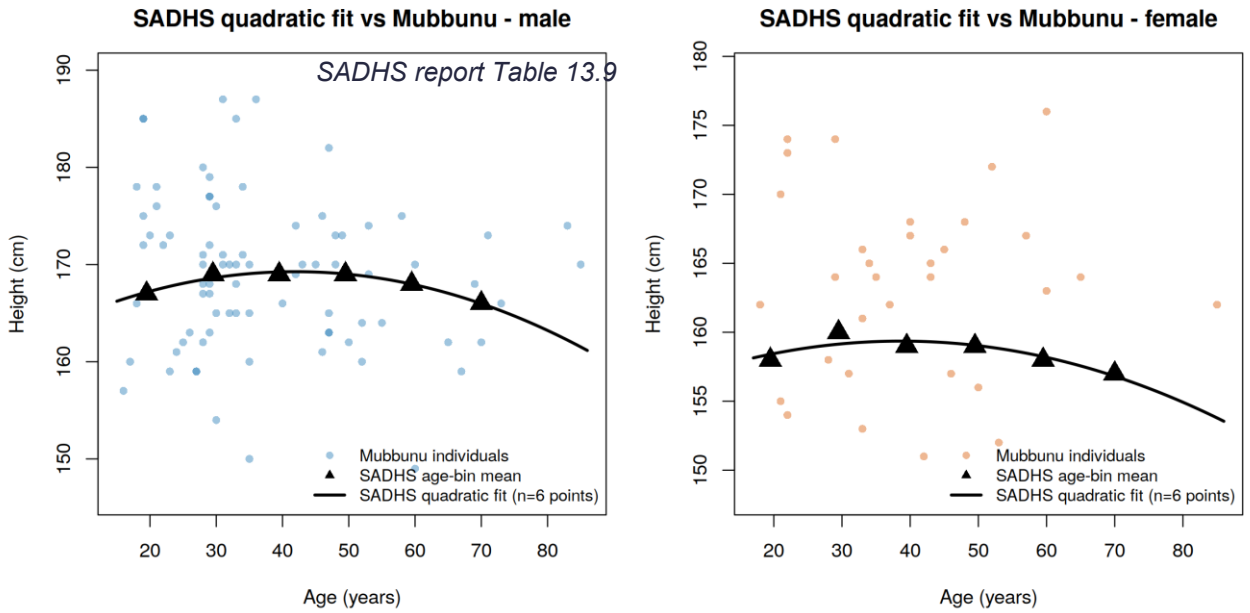
- The Mubbunu study is the only one with paired organ weight, body height, and body weight data
- Other studies only report the average liver weight, without matched body weight/height

➔ The Mubbunu mean liver weight is consistent with other literature values, assuming the same average body weight

# Benchmarking the Mubbunu data against the South African demographic report 2023 (summary statistics)

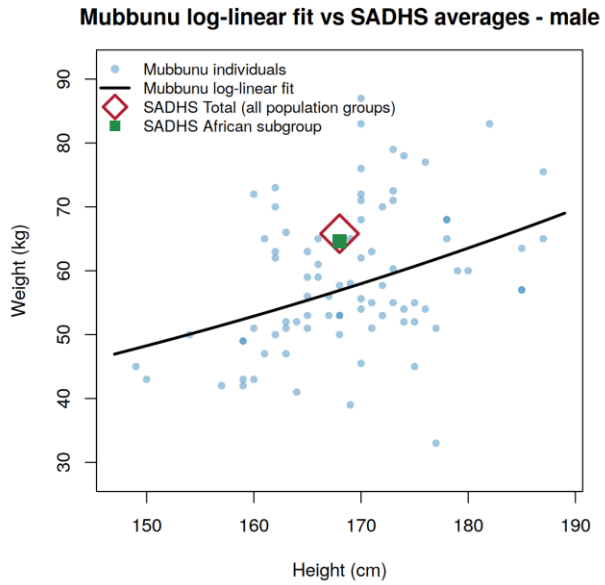
South African Medical Research Council. South Africa Demographic and Health Survey 2003. Available from: http://www.mrc.ac.za/bod/sadhs.htm

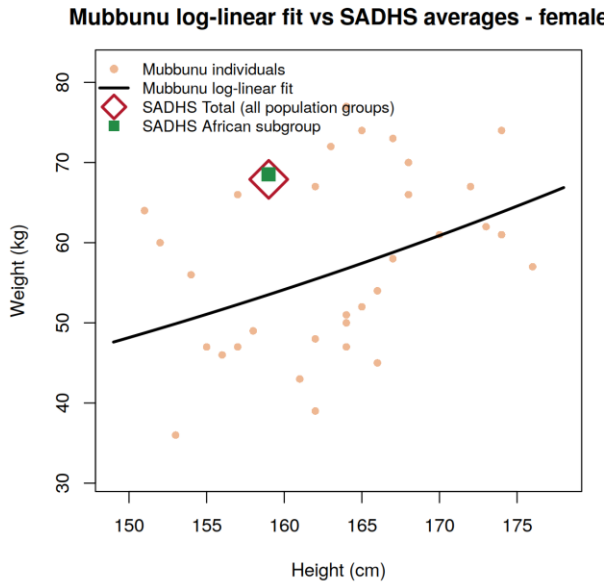
✓ Contains data from all SA (all ethnicities) per age groups as well as data for the African sub-group (African ancestry)







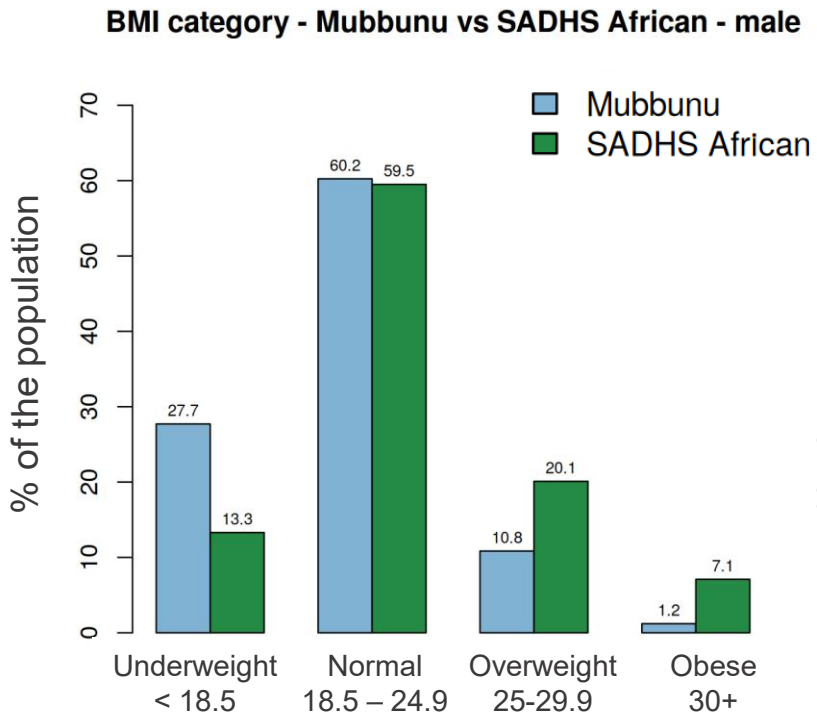


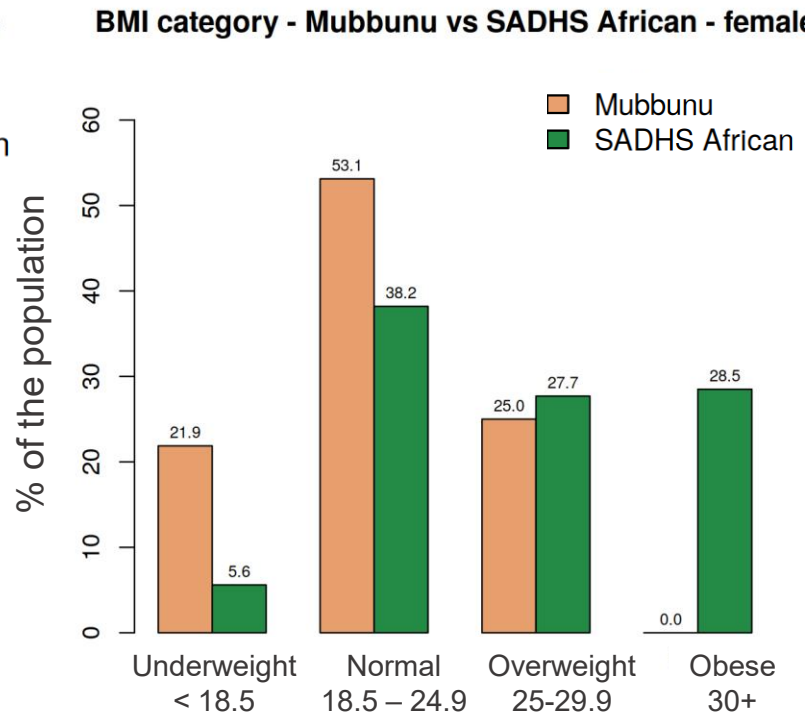




➔ The height of Mubbunu individuals is comparable to that of the South African male population. Mubbunu females tend to be taller.

➔No strict relation between height and weight, SADHS population is heavier. Females are more susceptible to overweight than males in the SA cohort.

# Benchmarking the Mubbunu data against the South African demographic report 2023




- ➔ Larger proportion of females tend to be overweighted compared to males, in both populations.
- ➔ Gender difference is observed in the SA
- ➔ The Mubbunu population shows females with lower BMI than SA overall.

South African Medical Research Council. South Africa Demographic and Health Survey 2003. Available from: http://www.mrc.ac.za/bod/sadhs.htm

# Translating individual level data into a PK-Sim ready population

For importing the population in PK-Sim:

1. Correct for blood content
2. Compute fat volume
3. Adjust Muscle and Fat content to absorb the residual of body weight (calculated vs. target observed BW)
4. Redefine CYP enzyme expression distribution

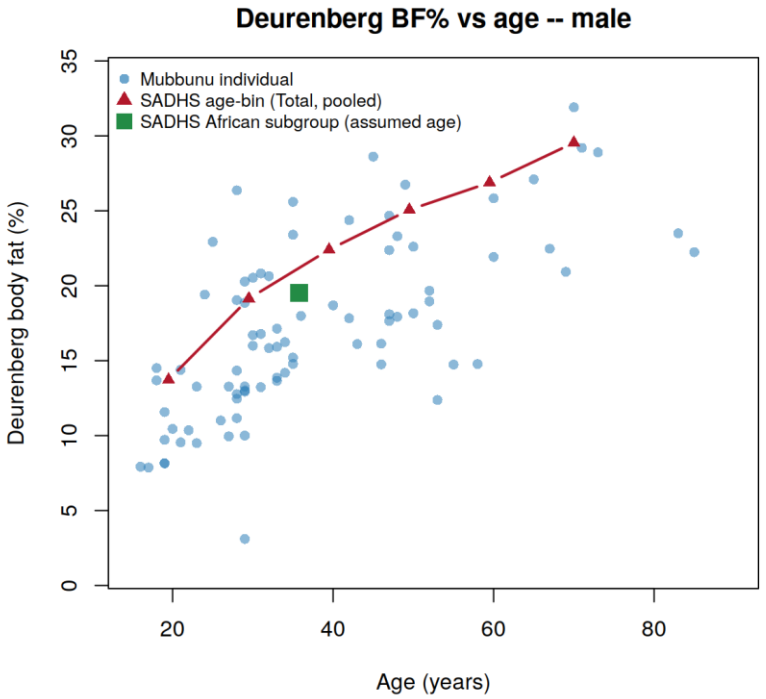
Method form (Willmann *et al.* 2007)
Blood volume per organ, given relative to the total blood volume provided by ICRP, 2002 report

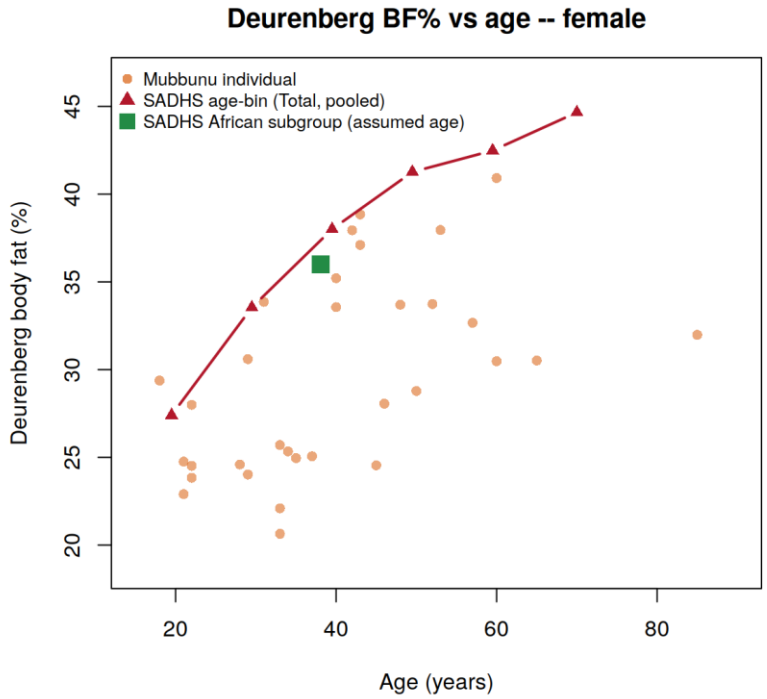
Willmann S, Höhn K, Edginton A, Sevestre M, Solodenko J, Weiss W, Lippert J, Schmitt W. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. J Pharmacokinet Pharmacodyn. 2007;34(3):401–431. doi:10.1007/s10928-007-9053-5.

# Adding body fat volume

## Calculate body fat volume: Deurenberg equation

$$BF\% = 1.20 \times BMI + 0.23 \times age - 10.8 \times sex - 5.4$$
$$(males = 1, females = 0)$$




Mubbunu individual
SADHS age-bin (Total, pooled)
SADHS African subgroup (assumed age)

| Mean body fat | SADHS | Mubbunu |
|---|---|---|
| Male | 19.5% | 17.1% |
| Female | 36% | 29.6% |

➔ Mubbunu mean Deurenberg BF% is significantly lower than SADHS African subgroup in both sexes (17.1% vs 19.5% male; 29.6% vs 36.0% female), consistent with the BMI gap.

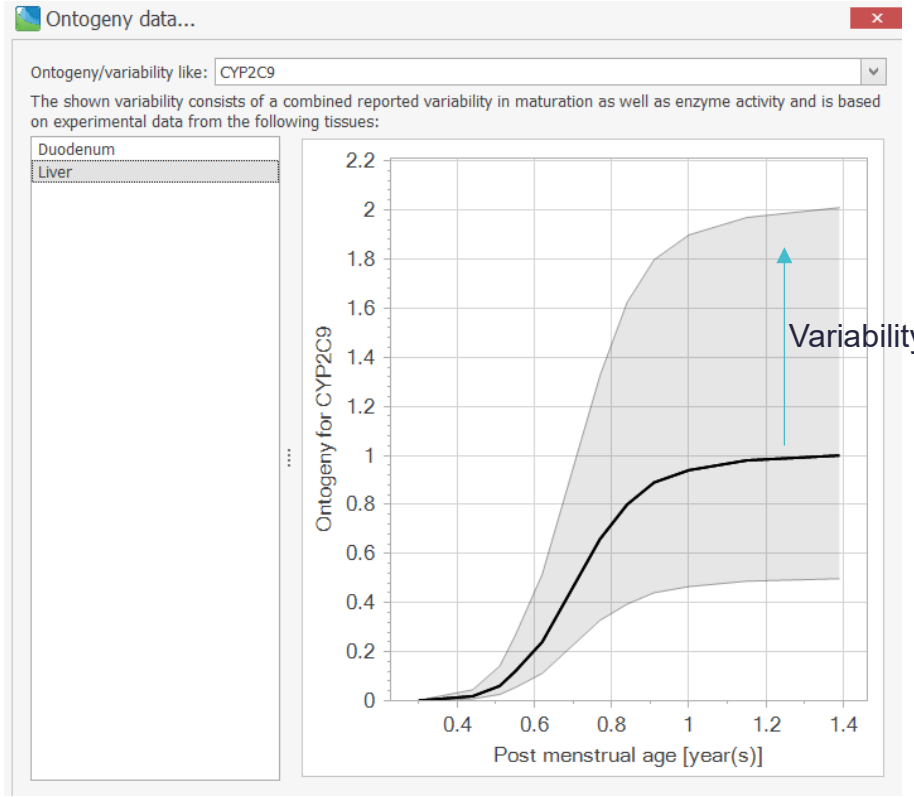
# CYP enzyme distribution and polymorphism

- Polymorphism:
  - Diverse alleles of the same gene can express a protein with normal, decreased to increased function (e.g. CYP2B6 1*/1*)
  - Via expression or i intrinsic activity

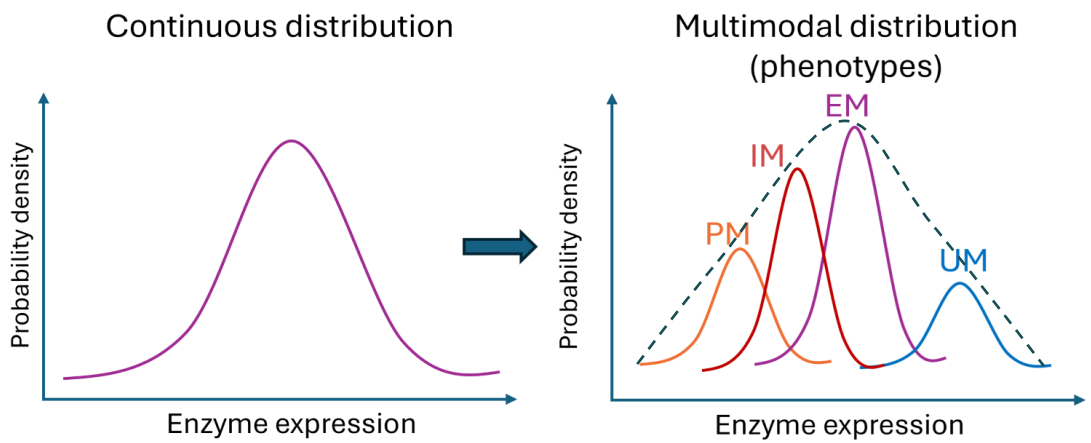
$$V = \frac{kcat \times E \times S}{K_m + S}$$

  - Result in Poor, Intermediary, Extensive and Ultra metabolizer phenotypes

- In PK-Sim:
  - Standard deviation from the mean available in the ontogeny function (per age)



# Accounting for CYP enzyme polymorphism




$$X \sim \sum_i p_i \,.\, logNormal(\mu_i, \sigma)$$

$\mu_i$ = scaled mean (via activity factor*)
$\sigma$ =same variability
$p_i$ = frequency of phenotype

Each phenotype has:
- its **own distribution** (same GSD, shifted GM)
- its **own probability** (frequency)

CPIC® Clinical Pharmacogenetics Implementation Consortium

**GENE: CYP2C9**

| Allele 1 | Allele 2 | Activity Score | Phenotype |
|---|---|---|---|
| Normal | Normal | 2.0 | CYP2C9 Normal Metabolizer |
| Normal | Decreased | 1.5 | CYP2C9 Intermediate Metabolizer |
| Normal | No function | 1.0 | CYP2C9 Intermediate Metabolizer |
| Decreased | Decreased | 1.0 | CYP2C9 Intermediate Metabolizer |
| Decreased | No function | 0.5 | CYP2C9 Poor Metabolizer |
| No function | No function | 0.0 | CYP2C9 Poor Metabolizer |

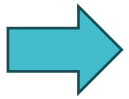
**Frequencies of CYP2C9 phenotypes in biogeographical groups**

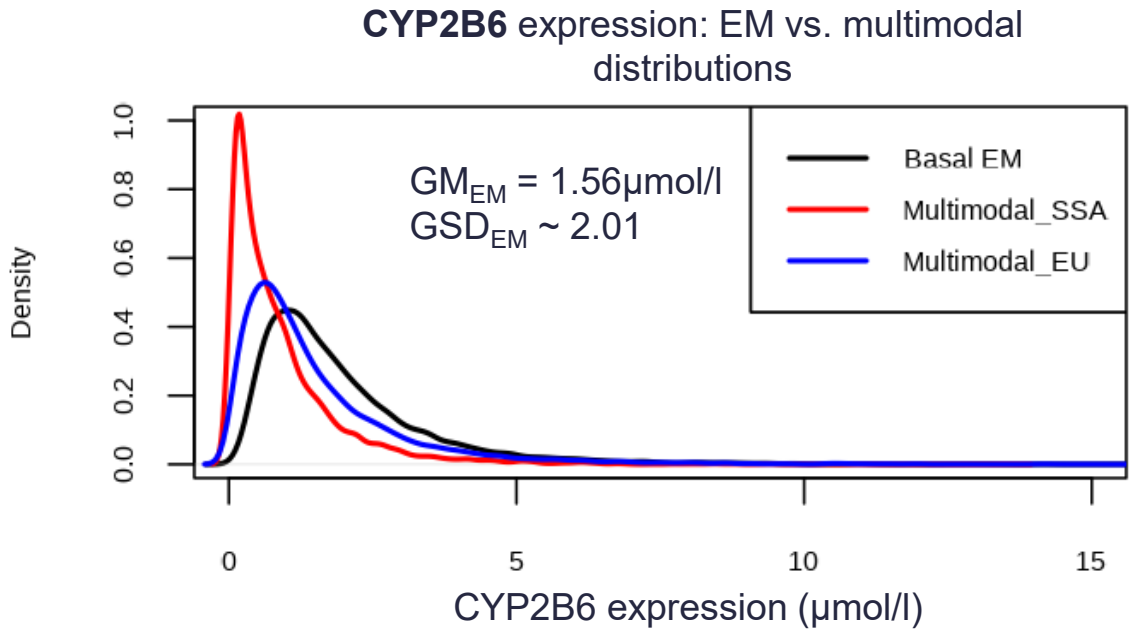
| AS | European | Sub-Saharan African |
|---|---|---|
| 2 | 0.63 | 0.731 |
| 1.5 | 0.21 | 0.214 |
| 1 | 0.14 | 0.050 |
| 0.5 | 0.02 | 0.005 |
| 0 | 0.01 | 0.000 |

- Km kept constant over the whole range of modeled activity/enzyme abundance

# Example: implementing a multimodal distribution for CYP2B6

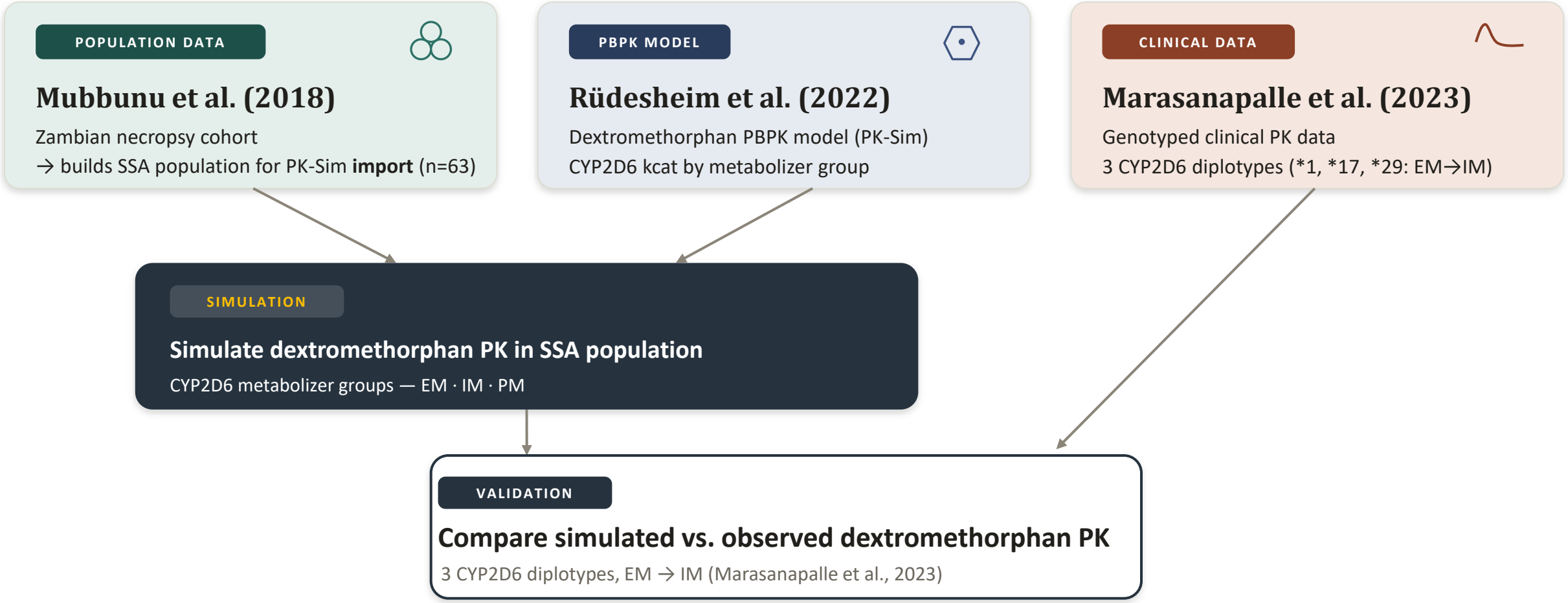
| Phenotype (diplotype) | Sub-Saharan African freq. | European freq. | Scaling factor |
|---|---|---|---|
| Ultra rapid | 0 | 0.056 | 2 |
| Extensive | 0.143 | 0.430 | 1 |
| Intermediate | 0.368 | 0.380 | 0.5 |
| Poor | 0.237 | 0.074 | 0.1 |
| None | 0.000 | 0 | 0 |






- The resulting CYP enzyme expression distribution is skewed towards lower levels compared to the basal expression
- Not built-in, requires post-hoc modification the population generated by PK-Sim

# SSA PBPK Population - Dextromethorphan (CYP2D6) Validation





Mubbunu et al. (2018) — Zambian necropsy cohort.
Rüdesheim et al. (2022) — CPT Pharmacomet Syst Pharmacol. 11:494–511 · Open-Systems-Pharmacology/Dextromethorphan-Model (GitHub).
Marasanapalle et al. (2023) — J Clin Pharmacol. (CYP2D6*17/*29 vs. normal metabolizers).

# Testing the population with Dextromethorphan (CYP2D6)

## 1. Clinical data cohort:

**Table 1.** Demographics

| Characteristics | NM<br>*CYP2D6*1/*2* diplotype[a]<br>n = 12 | IM<br>*CYP2D6*17*17*<br>n = 12 | IM<br>*CYP2D6*29*29*<br>n = 4 |
|---|---|---|---|
| Age (years) | 22.5 (18-25) | 23.0 (20-40) | 22.5 (19-23) |
| Male/female | 12 (100)/0 | 10 (83.3)/2 (16.7) | 4 (100)/0 |
| BMI (kg/m$^2$) | 20.7 (18.8-23.9) | 20.6 (17.8-24.1) | 21.5 (20.3-22.6) |

Values for age and body mass index (BMI) are median (range). Number (%) is reported for male/female subjects.
[a]The *CYP2D6*1/*2* diplotypes include the subjects carrying genotypes **1/*1*, **1/*2*, and **2*2*.

## 2. CYP2D6 kcat values from the published PBPK model:

### S4.1 Population $k_{cat}$ Values

**Table S4.1.1:** Dextromethorphan population CYP2D6 $k_{cat}$ values for CYP2D6 activity scores (ASs)

| Activity Score | Projected Phenotype | $k_{cat} \rightarrow$ dxt [1/min] | $k_{cat}$ Percentage of Reference (AS = 2) [%] |
|---|---|---|---|
| 0 | PM | 0.0 | 0 |
| 0.25 | IM | 5.3 | 2 |
| 0.5 | | 32.9 | 14 |
| 1 | | 96.6 | 40 |
| 1.25 | NM | 115.2 | 48 |
| 1.5 | | 151.8 | 63 |
| 2 | | 242.5 | 100 |
| 3 | UM | 413.2 | 170 |

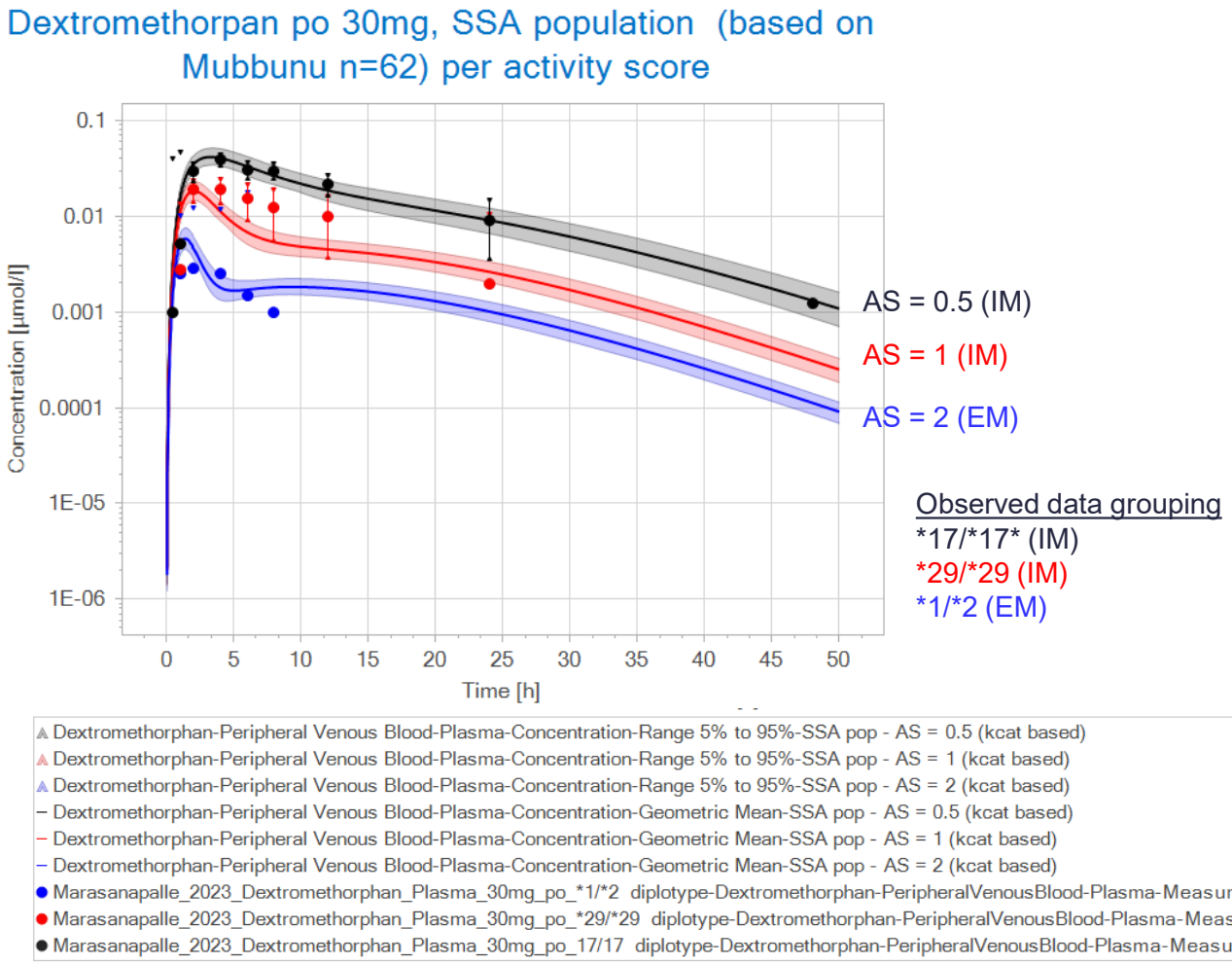
AS: CYP2D6 activity score, CYP2D6: Cytochrome P450 2D6, IM: intermediate metabolizer, $k_{cat}$: catalytic rate constant, NM: normal metabolizer, PM: poor metabolizer, UM: ultrarapid metabolizer.

$$V = \frac{kcat \times E \times S}{K_m + S}$$

## 3. Virtual SSA population:

- Corresponds to Mubbunu individuals
- Size= 62 (limited to bmi >19.5 by PK-Sim)

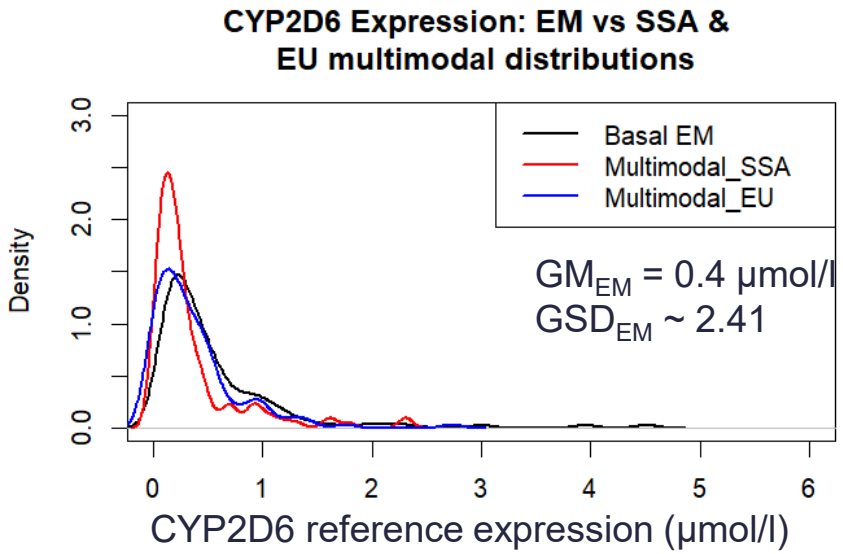
# Validating the SSA population with Dextromethorphan (CYP2D6)



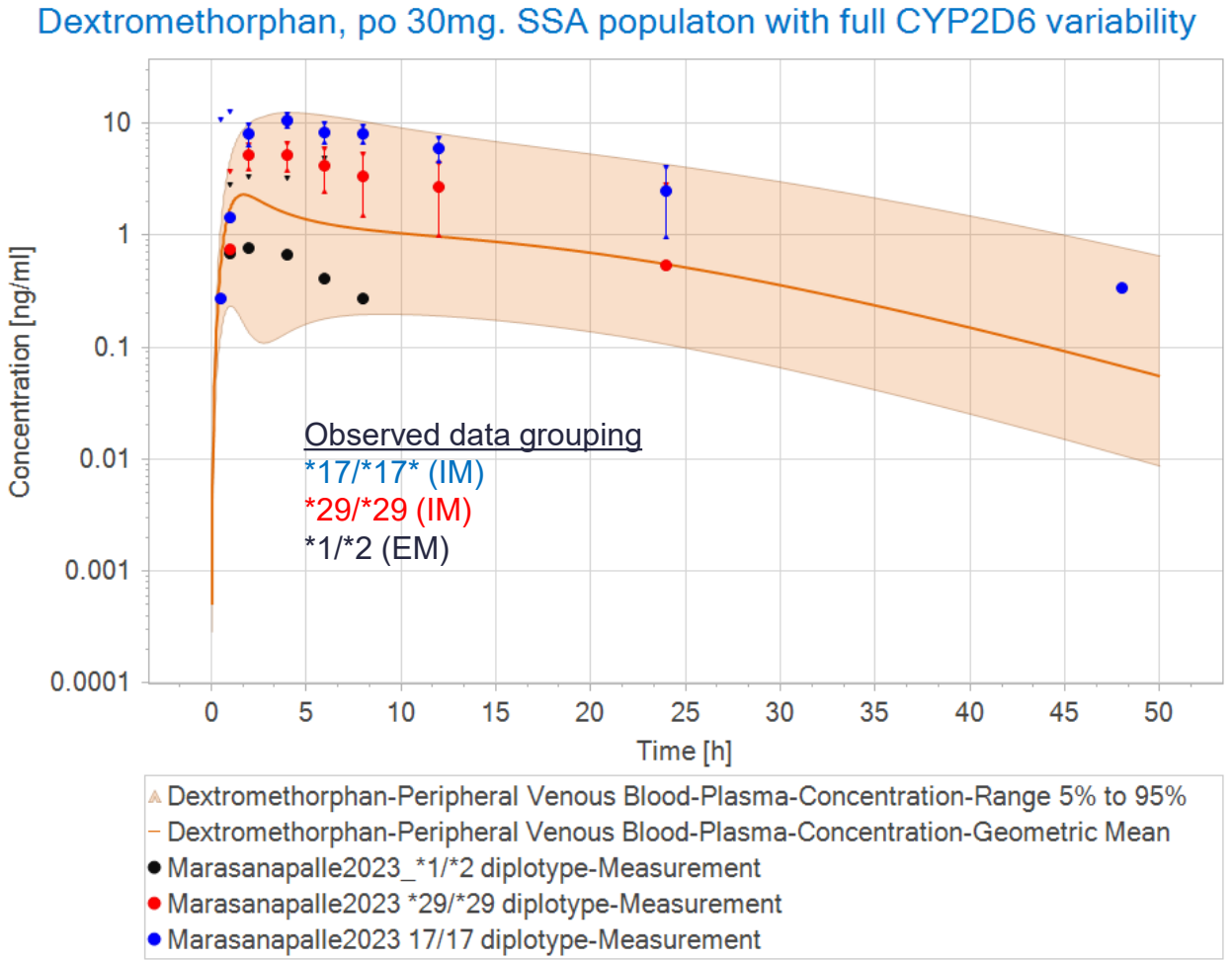

- Applying the published scaling of kcat values/ expression levels allowed replicating the observed profiles for the different diplotype groups with the Mubbunu-derived SSA population

# Dextromethorphan in the SSA population with a multimodal CYP2D6 distribution

- CPIC regional-specific phenotype frequencies
- Expression mean and GSD from PK-Sim ontogeny




- The resulting CYP enzyme expression distribution is skewed towards lower levels compared to the basal expression



# SSA PBPK Population - Efavirenz (CYP2B6) Validation

POPULATION DATA

## Mubbunu et al. (2018)

Zambian necropsy cohort
62 individuals · 37.8 ± 14.2 years · 65.4 ± 9.1 kg
32% female / 68% male (20 / 42)
→ builds SSA population for PK-Sim **import**

PBPK MODEL

## OSP Model Library

https://www.open-systems-pharmacology.org/OSP-PBPK-Model-Library/Efavirenz/

CLINICAL DATA

## Mukonzo et al. (2009)

SNPs clinical PK data
30 CYP2B6 SNPs
121 individuals · 26.5 ± 8.2 years · 57.5 ± 5.9 kg
57% female / 43% male

SIMULATION

**Simulate Efavirenz PK in SSA population**

CYP2B6 metabolizer groups — EM · IM · PM

VALIDATION

**Compare simulated vs. observed Efavirenz PK**

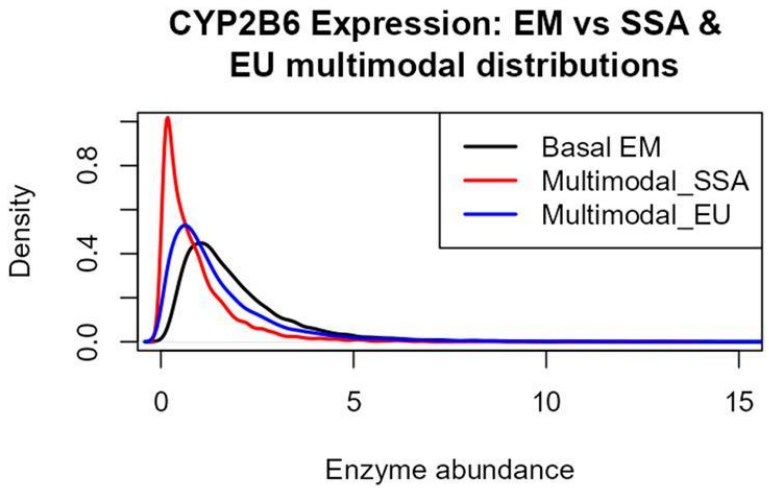
3 CYP2B6 diplotypes → Population (Mukonzo et al., 2009)

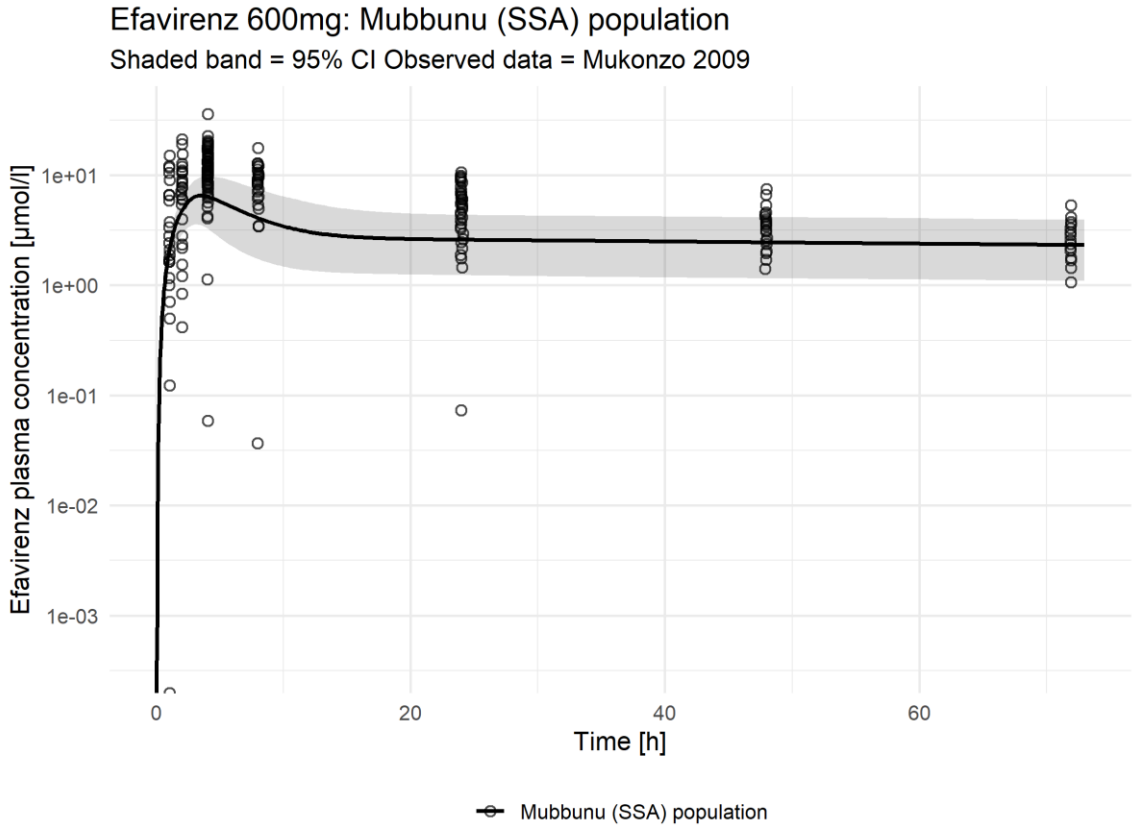
Mubbunu, *et al.* (2018), Anatomy Research International, 2018, 4687538. https://doi.org/10.1155/2018/4687538

Mukonzo, *et al.* (2009), British Journal of Clinical Pharmacology, 68: 690-699. https://doi.org/10.1111/j.1365-2125.2009.03516.x

# Efavirenz in the SSA population with a multimodal CYP2D6 distribution

| Phenotype (diplotype) | Sub-Saharan African freq. | European freq. | Scaling factor |
|---|---|---|---|
| Ultra rapid | 0 | 0.056 | 2 |
| Extensive | 0.143 | 0.430 | 1 |
| Intermediate | 0.368 | 0.380 | 0.5 |
| Poor | 0.237 | 0.074 | 0.1 |
| None | 0.000 | 0 | 0 |




- ➔ The Mubbunu-based population predicts the observed clinical data (slightly underpredicts Cmax)
- ➔ Population demographics differ.
- ➔ Matching population can be achieved with a PK-Sim built-in population database and the virtual population generation algorithm

# PK-sim database structure & population generation algorithm

## Age-dependent distributed parameters

| container | parameter | dimension | kernel_unit | population | gender | age | GA | distribution | mean_value | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| ArterialBlood | Volume | Volume | l | European_ICRP_2002 | FEMALE | 0 | 40 | Normal | 0,023269877 | 0,001163494 |
| ArterialBlood | Volume | Volume | l | European_ICRP_2002 | FEMALE | 1 | 40 | Normal | 0,041495489 | 0,002074774 |
| ArterialBlood | Volume | Volume | l | European_ICRP_2002 | FEMALE | 5 | 40 | Normal | 0,115657601 | 0,00578288 |
| ArterialBlood | Volume | Volume | l | European_ICRP_2002 | FEMALE | 10 | 40 | Normal | 0,196284487 | 0,009814224 |
| ArterialBlood | Volume | Volume | l | European_ICRP_2002 | FEMALE | 15 | 40 | Normal | 0,264482273 | 0,013224114 |
| ArterialBlood | Volume | Volume | l | European_ICRP_2002 | FEMALE | 30 | 40 | Normal | 0,320409048 | 0,016020452 |

- Lookup table
- Parameter are defined as a mean and a distribution for a given: **{age, gender, population}**

- The organ SDs in the database are *not total population variability*, but **residual variability after removing the height effect**

**Height-driven organ scaling:**

$$V_{mean} = V_{mean} * \left(\frac{H_{target}}{H_{mean}}\right)^{allometricScaleFactor}$$

$$V_{Deviation} = V_{Deviation} * \left(\frac{H_{target}}{H_m}\right)^{allometricScaleFactor}$$

**Correction to apply for new populations:**

$$CV_{organ} = \sqrt{(CV_{total}^2 - (0.75 \cdot CV_{height})^2)}$$

*Eq. (4), Willmann et al. 2007 — organ-volume CV corrected for relative body-height variability*

Willmann S, Höhn K, Edginton A, Sevestre M, Solodenko J, Weiss W, Lippert J, Schmitt W. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. J Pharmacokinet Pharmacodyn. 2007;34(3):401–431. doi:10.1007/s10928-007-9053-5.

# Conclusions & key take-aways

An open-source Sub-Saharan African PBPK population for PK-Sim: anatomy, physiology and enzymatic variability

### SSA population built from real cohort data

Zambian necropsy individuals (Mubbunu et al.) provide paired organ, height and weight data, benchmarked against South African survey statistics and completed with a Deurenberg-based fat volume.

*Next step: Hematocrit & albumin*

### Validated with CYP probe drugs

Dextromethorphan (CYP2D6) and efavirenz (CYP2B6) simulations give encouraging results compared to observed exposure in SSA clinical cohorts across phenotypes.

*Next step: + 1-2 probes*

### CYP enzyme polymorphism as mixtures

Genetic variability is captured by weighted mixtures distributions matched to regional phenotype frequencies (CYP2D6, CYP2B6)

### PK-sim Height-driven organ scaling

Organ volumes and their deviations scale allometrically with body height; database SDs are residual variability, so raw cohort data must be corrected before a PK-Sim import.

*Next step: database update*

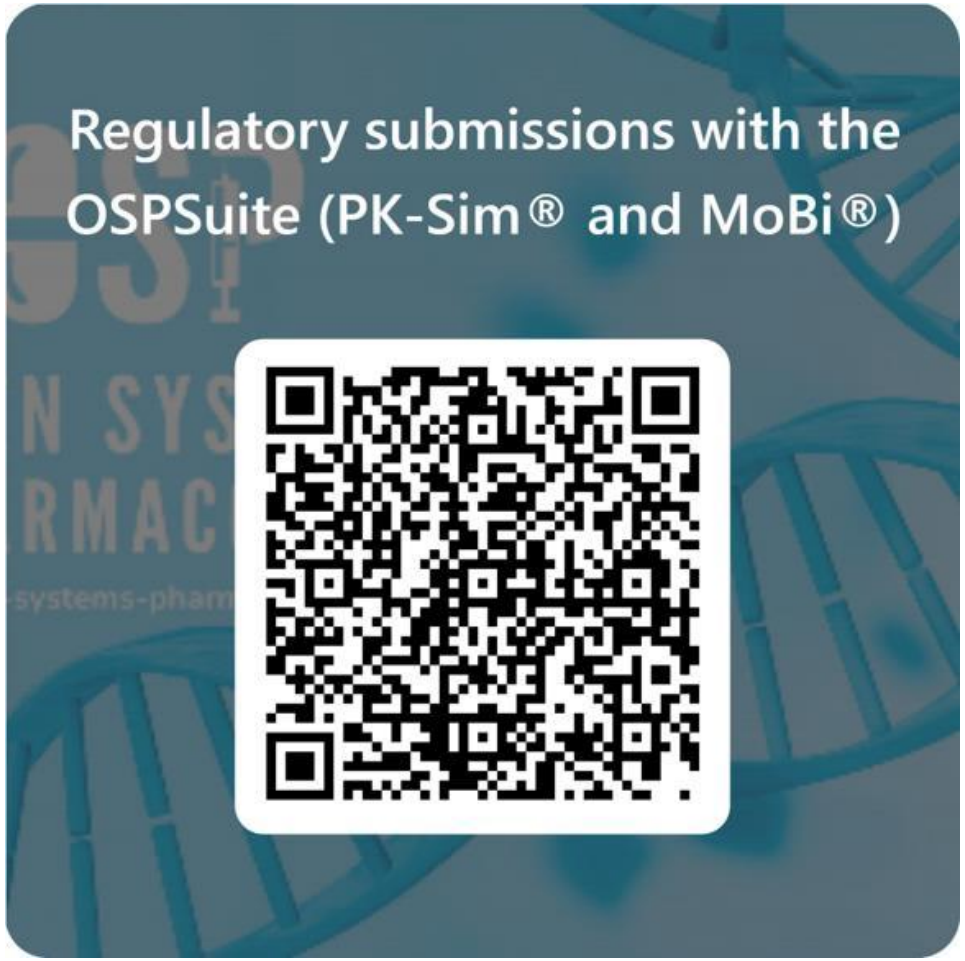
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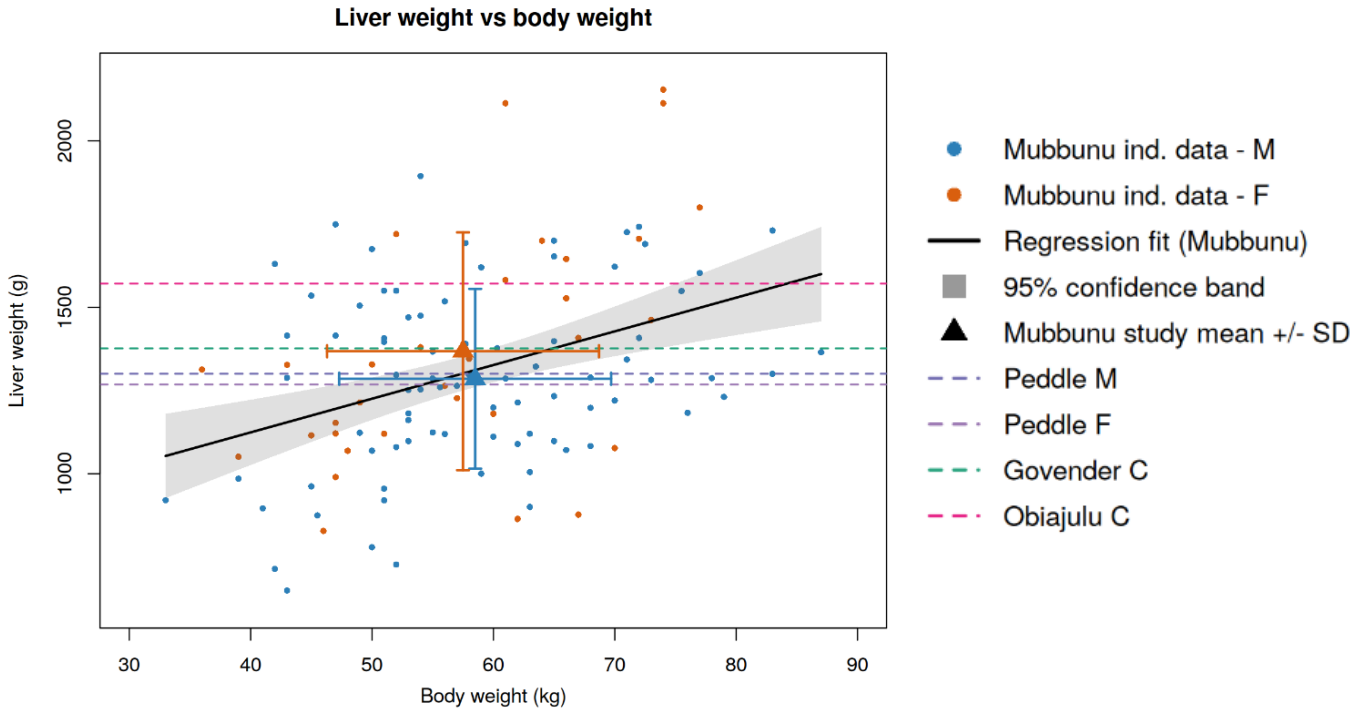
Acknowledgments: *This study is funded by the Gates Foundation (grant INV-089221) for the development of a* ***physiologically based pharmacokinetic (PBPK) population model specifically for*** S***ub-Saharan African populations****, starting with Zimbabwe and South Africa*

# The OSP community would like to hear about your experience



# Benchmarking the Mubbunu Liver weight against literature data

| Series | Sex | Liver (dry) weight (g) |
|---|---|---|
| Peddle & Kirk, Cape Town - Black South African only | M | 1,300 ± 257 |
| | F | 1,268 ± 271 |
| Mubbunu, Ndola (n=115) | M | 1,285.3 ± 270.1 |
| | F | 1,367.9 ± 357.2 |
| Govender, KZN (n = 500) | Mixte | 1,376.6 ± 435.4 |
| Obiajulu, Lagos, pathology removed (n = 19), mixte population | Mixte | 1,571 ± 410 |



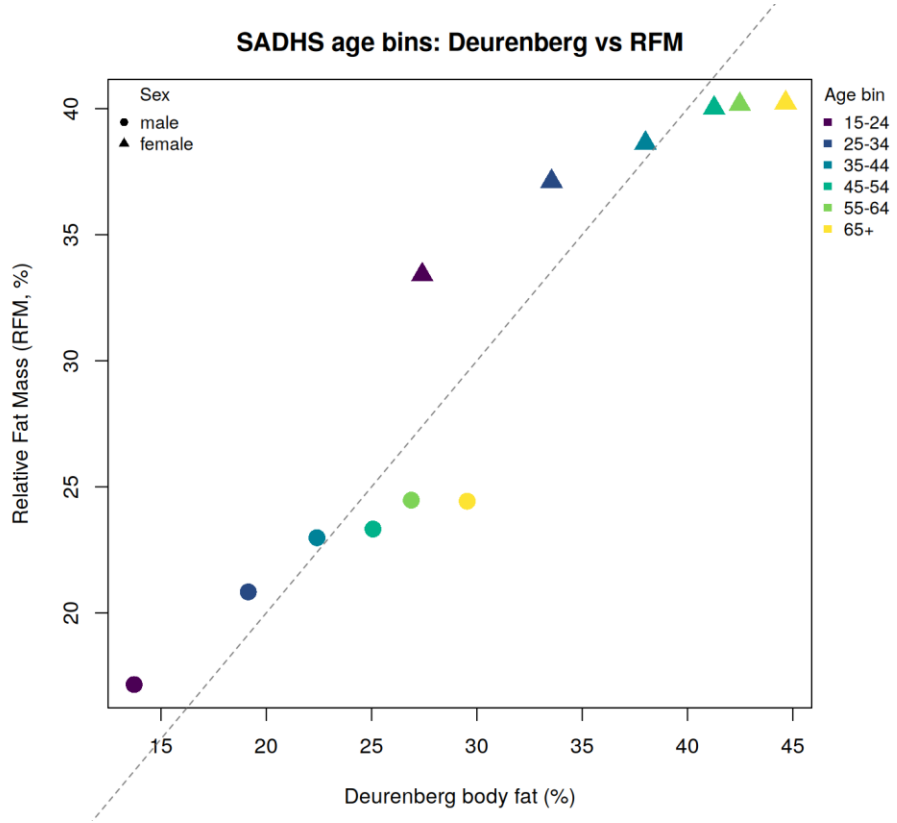

Dashed lines = study mean liver weight (no matched body weight reported)

- The Mubbunu study is the only one with paired organ, height, and weight data
- Other studies only report the average liver weight, without matched body weight/height
- All are dry weight (i.e., without blood content)

➔ The Mubbunu mean liver weight is consistent with other literature values, assuming the same average body weight

# Fat content

## Comparison of Deurenberg and RFM-based predictions




- RFM based on waist circumference was shown to be more predictive of fat volume, but we don't have waist circumference for the Mubbunu population.
- Waist circumference was reported for the SADHS report
- Equation: $RFM = 64 - (20 \times \frac{height}{waist}) + (12 \times sex)$

✓ RFM estimation is always higher
✓ Somehow linear for age range 15-44 for both sexes
✓ Better aligned for
✓ Above 45yo, the methods diverge

# Systematic literature review for additional SSA physiological data

- A population-based Zimbabwean study of 769 healthy adults from Harare:

| Population | Hct reference interval | Median |
|---|---|---|
| Women | 33.9–48.7% | 41.7% |
| Men | 42.0–55.1% | 48.5% |
| Combined | 34.7–54.2% | 45.4% |

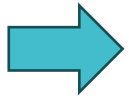
- A multicentre study that included Lusaka, Zambia, together with sites in Kenya, Uganda and Rwanda found:
  - Men: Hct approximately 35.0–50.8%
  - Women: Hct approximately 29.4–45.4%

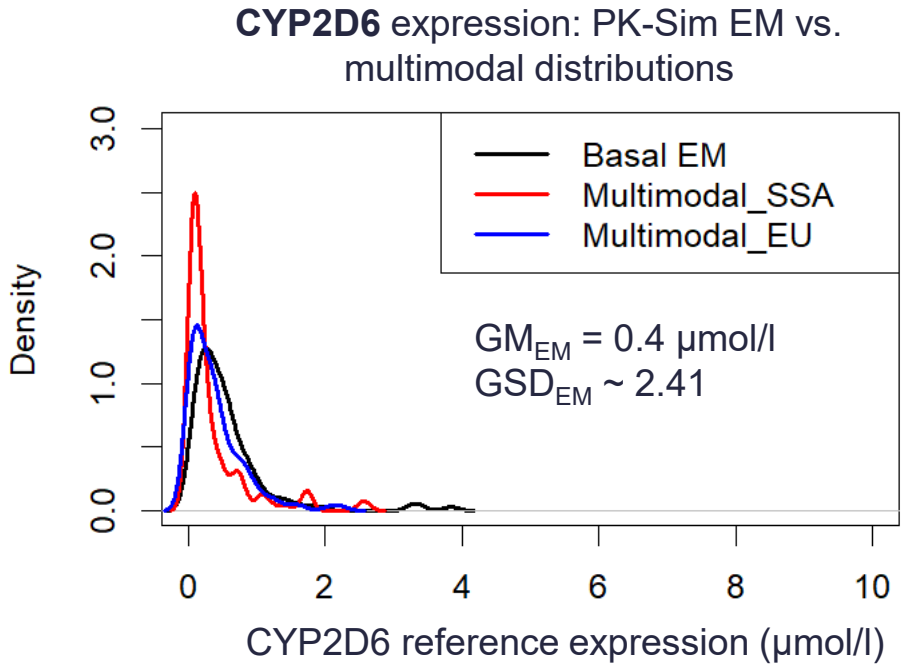
Samaneka WP et al. (2016) . Adult Hematology and Clinical Chemistry Laboratory Reference Ranges in a Zimbabwean Population. PLoS One. 2016 Nov 3;11(11):e0165821. doi: 10.1371/journal.pone.0165821.

Karita E, et al. (2009) CLSI-derived hematology and biochemistry reference intervals for healthy adults in eastern and southern Africa. PLoS One. 2009;4(2):e4401. doi: 10.1371/journal.pone.0004401.

# Implementing a multimodal distribution for CYP2D6

| Phenotype | AS Range | European freq. | Sub-Saharan African freq. |
|---|---|---|---|
| Ultrarapid Metabolizer | >=3 | 0.023 | 0.030 |
| Rapid Metabolizer | >2-3 | 0.025 | 0.040 |
| Poor Metabolizer | 0 | 0.065 | 0.020 |
| Normal Metabolizer | 1.25-2 | 0.477 | 0.227 |
| Intermediate Metabolizer | 0.25-1 | 0.383 | 0.381 |






- The resulting CYP enzyme expression distribution is skewed towards lower levels compared to the basal expression
- Not built-in, requires post-hoc modification the population generated by PK-Sim

# Creation of individuals

As published in

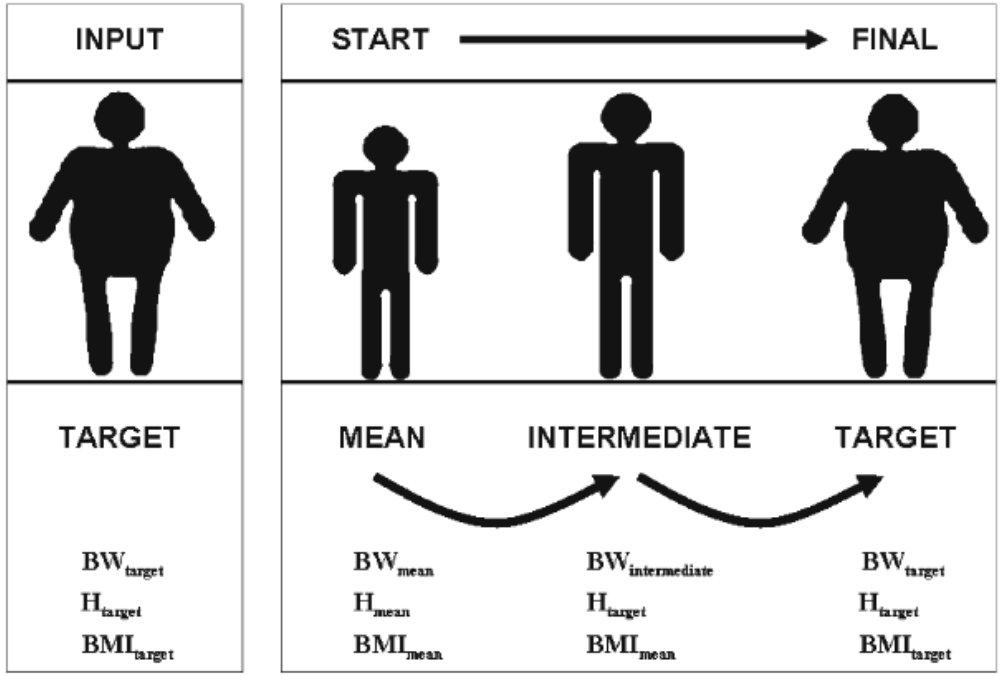



**Fig. 1.** Process for adjusting a single 'mean' virtual individual to a 'target' individual with a user-defined body weight (BW), height (H) and body mass index (BMI).

**Development of a Physiology-Based Whole-Body Population Model for Assessing the Influence of Individual Variability on the Pharmacokinetics of Drugs**

Stefan Willmann,[1,3] Karsten Höhn,[2] Andrea Edginton,[1] Michael Sevestre,[2] Juri Solodenko,[2] Wolfgang Weiss,[2] Jörg Lippert,[1] and Walter Schmitt[1]

*Journal of Pharmacokinetics and Pharmacodynamics, Vol. 34, No. 3, June 2007 (© 2007)*
DOI: 10.1007/s10928-007-9053-5

**Table I.** Absolute and Relative Organ Volumes (including blood content) and Blood Flows of the "Mean" Caucasian Male (BW = 73 kg, H = 176 cm, BMI = 23.6 kg/m$^2$) and Female (BW = 60 kg, H = 163 cm, BMI = 22.6 kg/m$^2$)

| | Volumes | | | | Blood Flow Rates | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | | Female | | Male | | Female | |
| Organ | V (ml) | % of BW | V (ml) | % of BW | Q (ml/min) | % of CO | Q (ml/min) | % of CO |
| Lung | 1294 | 1.8 | 1009 | 1.7 | 6106 | 100 | 5504 | 100 |
| Brain | 1509 | 2.1 | 1357 | 2.3 | 780 | 12.8 | 708 | 13 |
| Kidneys | 438 | 0.60 | 403 | 0.67 | 1325 | 21.7 | 1121 | 20 |
| Liver | 2358 | 3.2 | 1905 | 3.2 | 423 | 6.9 | 383 | 7 |
| Pancreas | 190 | 0.26 | 169 | 0.28 | 65 | 1.1 | 59 | 1 |
| Spleen | 243 | 0.33 | 219 | 0.37 | 195 | 3.2 | 177 | 3 |
| Stomach | 168 | 0.23 | 163 | 0.27 | 65 | 1.1 | 59 | 1 |
| Small Intestine | 724 | 1.0 | 694 | 1.2 | 650 | 10.6 | 649 | 12 |
| Large Intestine | 412 | 0.56 | 417 | 0.69 | 260 | 4.3 | 295 | 5 |
| Muscle | 32339 | 44.3 | 20276 | 33.8 | 1106 | 18.1 | 665 | 12 |
| Heart | 417 | 0.57 | 328 | 0.55 | 260 | 4.3 | 295 | 5 |
| Adipose | 14868 | 20.4 | 19348 | 32.2 | 325 | 5.3 | 501 | 9 |
| Bone | 11818 | 16.2 | 9122 | 15.2 | 325 | 5.3 | 295 | 5 |
| Skin | 3761 | 5.2 | 2724 | 4.5 | 325 | 5.3 | 296 | 5 |
| Gonads | 40 | 0.06 | 13 | 0.02 | 3 | 0.05 | 1 | 0.02 |

Organ volumes not including their blood content were taken from ICRP (14).

# PK-Sim algorithm to generate a population

User define:
- Age range.
- Height range
- Weight or BMI range

Assign gender & age

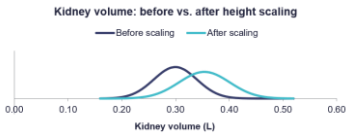
Age

Random sampling of height from the distribution for a given age → **Target Height**

Extract **mean Height** (given the age in the lookup table**)** **(Mean weight?)**

$$H_{rel} = \frac{H_{target}}{H_{mean}}$$

Scale Organ volume distributions* for a given age with $H_{rel}$




Randomly sample organ volumes/weights from scaled distributions
Compute resulting **BW**

Weight is sampled from its distribution
All organ volumes are then **uniformly scaled** (sampled weight/current weight)

Check plausibility of BW (within population range) and BMI (user-defined or from database for the generated combination of age and weight

Scale cardiac output (with $H_{rel}$) and sample from distributions per organ
Recompute final cardiac output (sum of organ)

Sample other distributed param. (hematocrit, CYP ontogeny, etc.)

Repeat

.csv file
Post-hoc modification of population

*Variability within the database for each organ is among individuals of similar height. Assumed to be the same for all ethnicities. Variability due to height is already accounted for in the scaling of the distribution