

# What is Normal? A Meta-Analysis of Phase 1 Placebo Data

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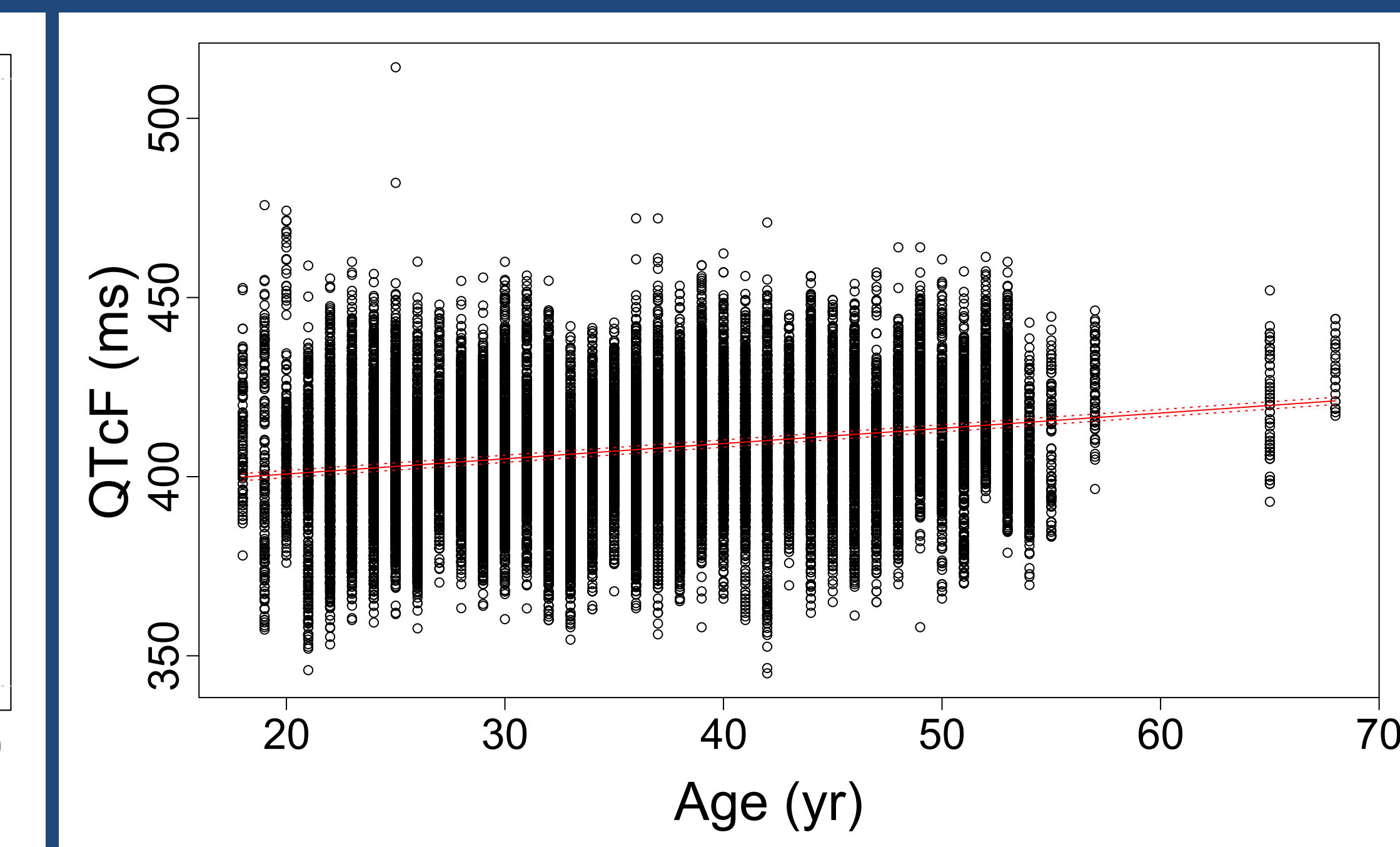
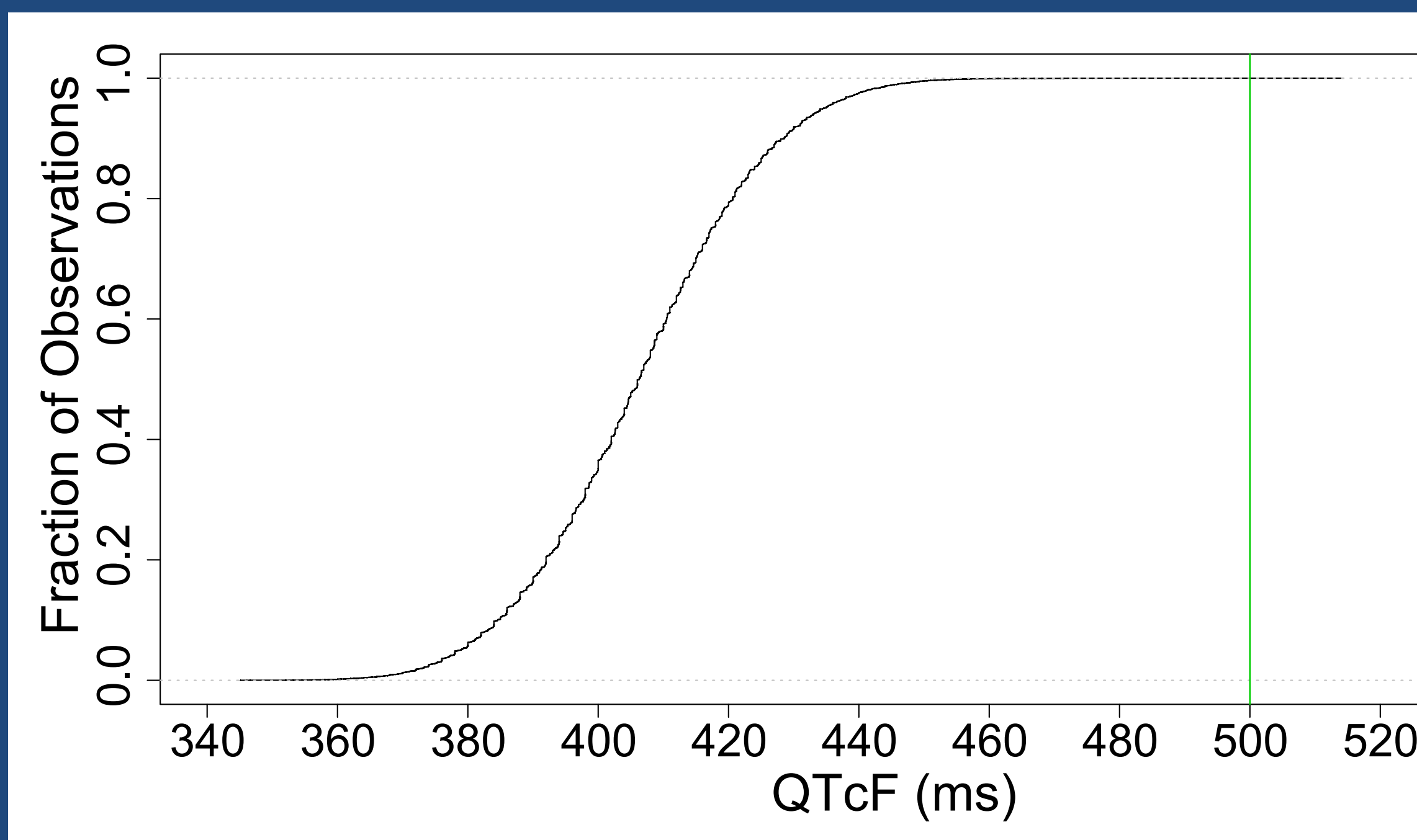
**Objectives:** To summarise all adverse events (AE), vital signs, electrocardiograms (ECG) and lab measurements for healthy subjects receiving placebo in First in Human (FIH) and Multiple Ascending Dose (MAD) studies in Pfizer’s Phase 1 Management System (PIMS) to aid in the interpretation of ‘What is Normal?’ and to provide informative prior distributions for Bayesian analyses.

**Methods:** All AE, vital sign, ECG and lab measurement data for healthy subjects receiving placebo in FIH and MAD studies were selected from PIMS. AEs were classified using MedDRA 15.0, lab names and units were standardized and baseline was selected as nominal time equal to zero or any point a multiple of 24 hr prior in the same treatment period. AEs were summarised by numbers and percentages of events, subjects, and studies with events. Additionally the distribution of percentage occurrence by study was summarised for common AEs. For vital signs, ECGs, and lab measurements, baseline, raw values and change from baseline were summarised using distribution quantiles, histograms, and empirical distribution functions. Any numerical measurements with at least 100 subjects were modelled with a linear mixed effect model testing demographic parameters as fixed effects and with random effects on intercept by study and subject within study using the lme4 function in R [1]. Model fits for single and multiple covariates were obtained; the latter were estimated using an automated stepwise modelling procedure.

**Results:** The final data summarised were for 1204 subjects from 82 FIH and MAD studies. Updated ranges for extreme values of labs, vitals, and ECG measurements have been generated, and the importance of demographic parameters on measurements (or lack thereof) has been estimated with many subjects and dense measurements. The results were summarized and posted to an internal website allowing rapid queries without requiring specialized tools.

## What is a very long QTcF interval?

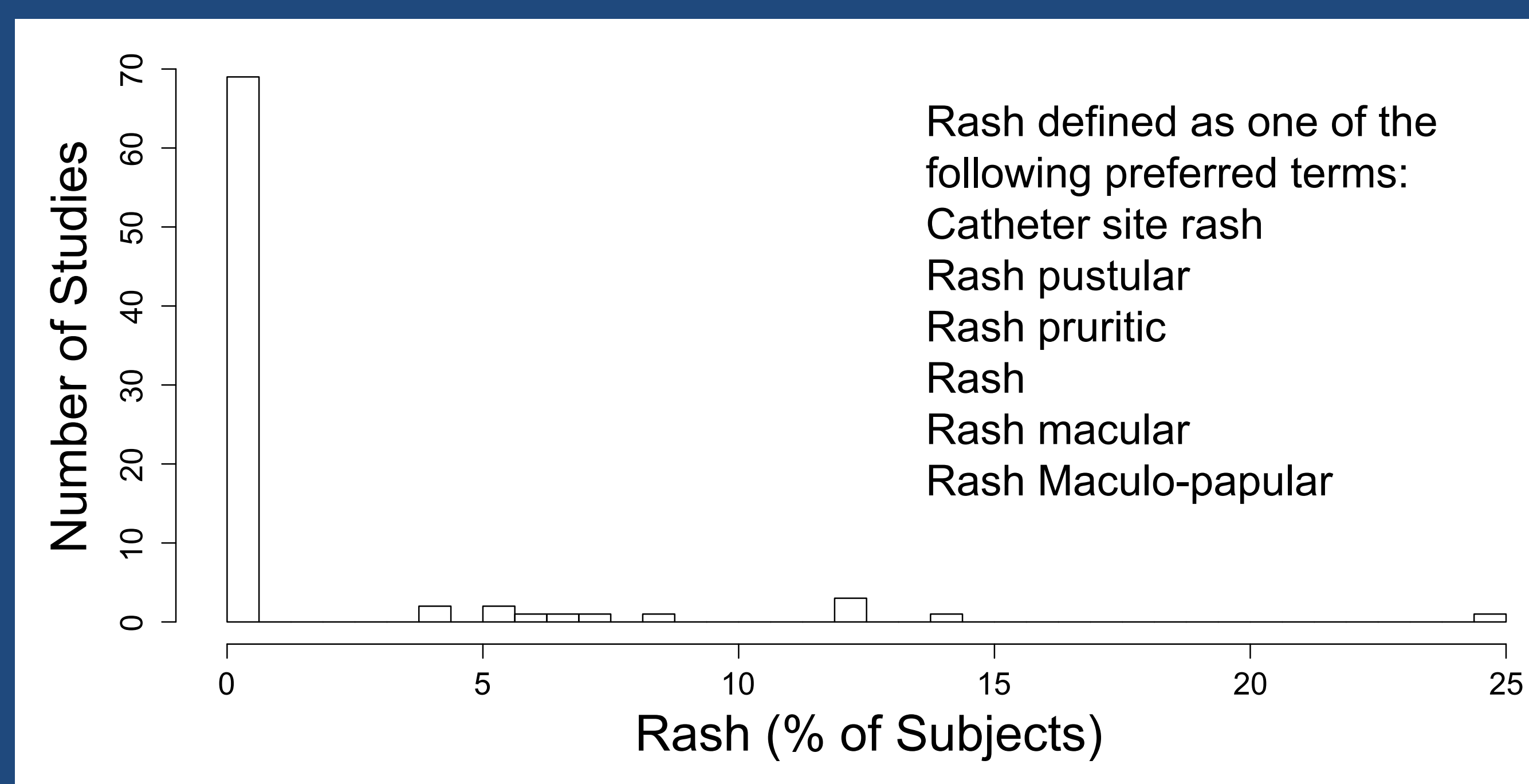
450/460 ms is the standard for an upper limit of normal with QTcF [men/women] and 500 ms is the typical limit of clinical concern. These limits are rarely observed in healthy subjects on placebo (left plot).



## QTcF increases with Age

The large data set enabled a slope, 0.426 [0.345, 0.506] ms/yr (mean [90% CI]), to be estimated with a linear mixed effects model (top right plot).

QTcF	N Studies	N Subjects	N Obs.	Min	2.5%	50%	97.5%	Max
<b>Raw Values</b>	68	962	32975	345	374	406	440	514
<b>Baseline</b>	67	954	3133	366	378	410	441	463
<b>CFB</b>	67	954	29735	-65.7	-23.7	-3.67	15.7	107

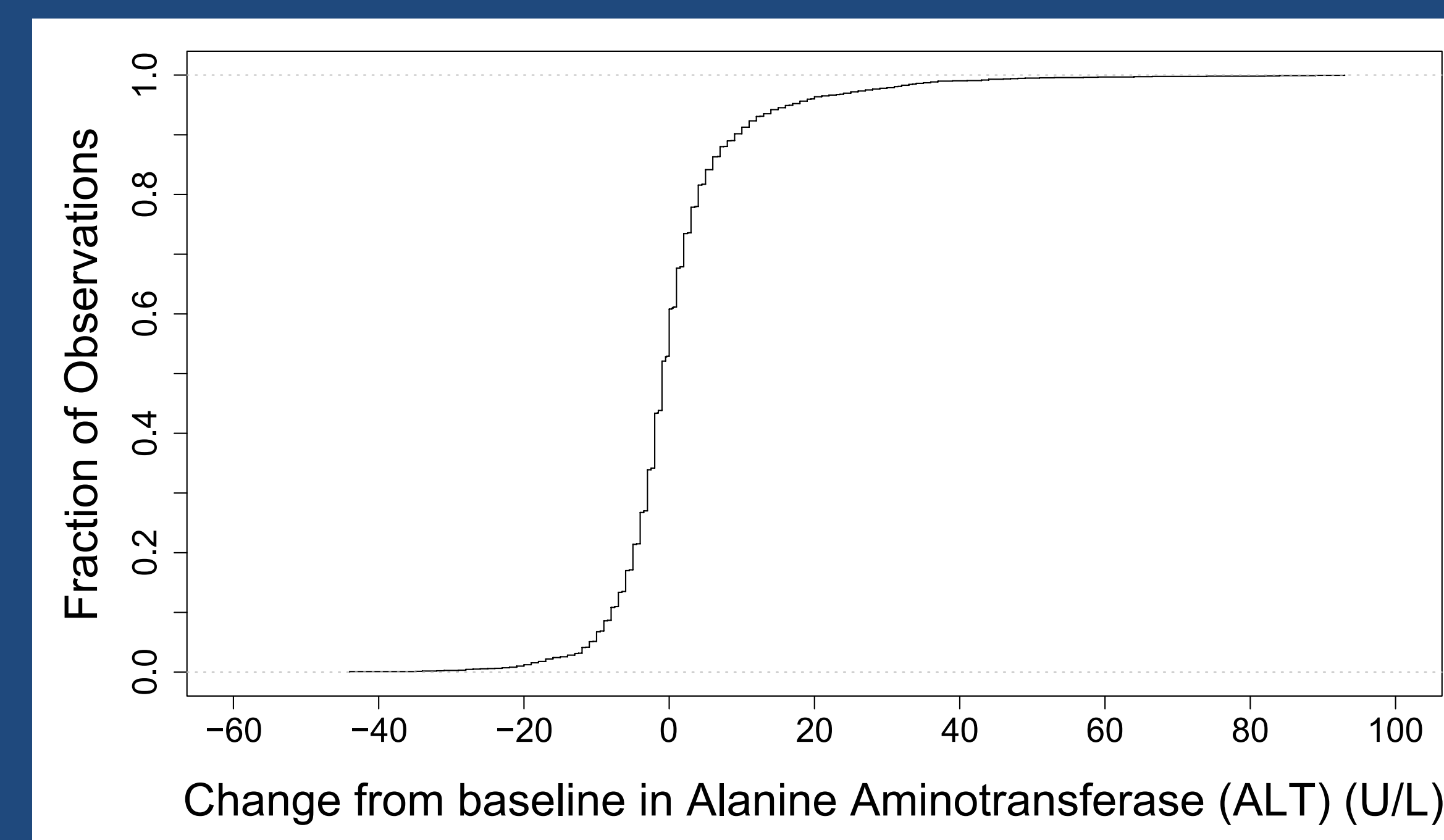
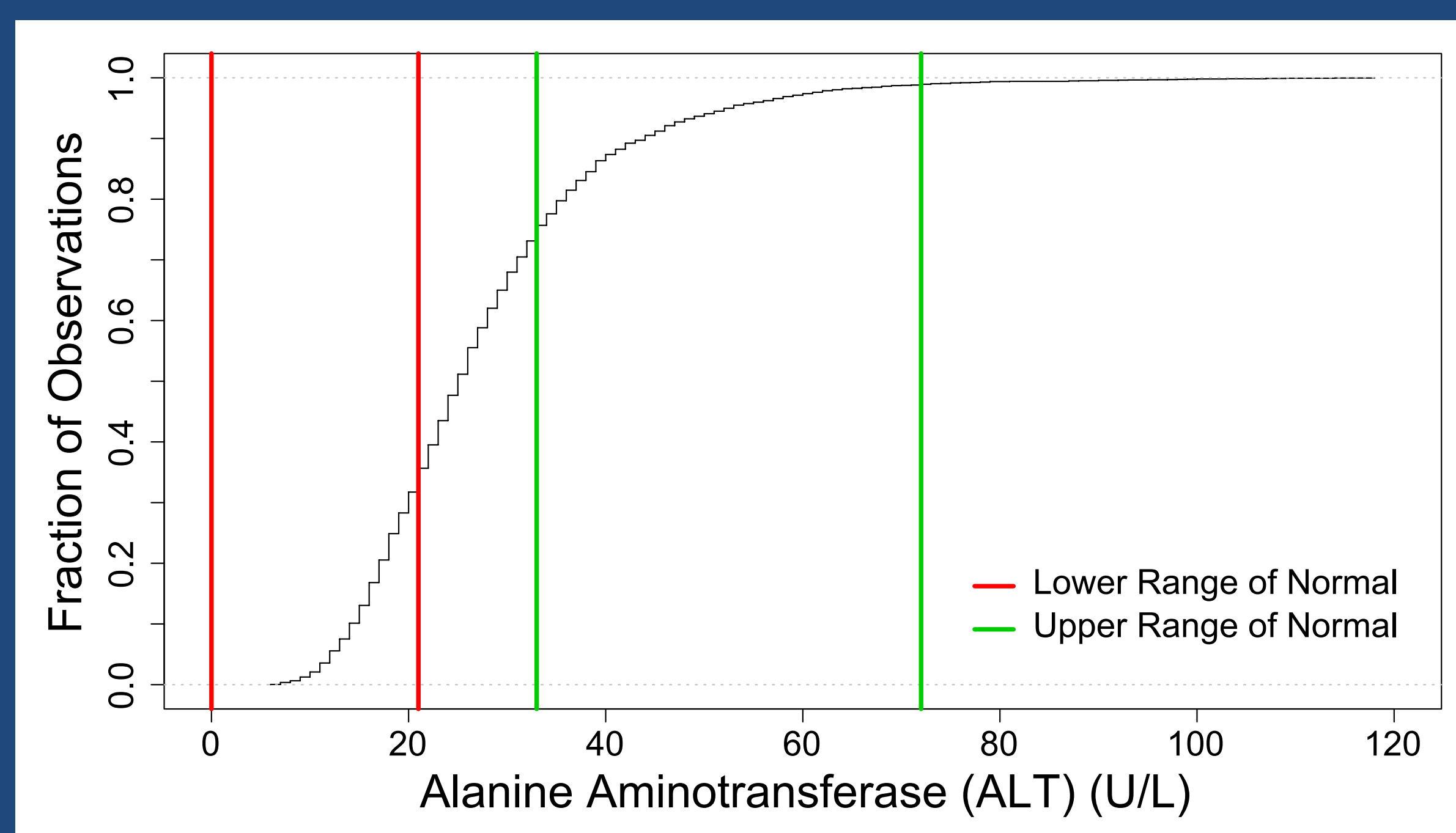


## How many rashes would we expect to observe?

Combining data from multiple studies enables comparison of AE rates within the population as a prior for assessing AE signals in small studies. (left)

## What is a normal liver and how much does it change?

Limits of normality are variable between labs and over time (bottom left), and changes in many tests are evaluated relative to passing the limits of normality (bottom right). The large dataset created for this analysis allowed evaluation of historical ranges of normality and how much of a change can be considered normal.



**Conclusion:** The analysis has allowed classification of potentially abnormal measurements incorporating the large data set of placebo subjects in similar populations—the placebo population within the current study can be augmented and anchored by historical data. It has also provided data that can be used for the formation of informative prior distributions for future Bayesian analyses. The analysis of healthy subjects has enabled a more thorough estimate of what is normal and quantification of potentially abnormal signals in early clinical development.

## References:

[1] Bates, D., Maechler, M., Bolker, B., Walker, S. (2013) lme4: Linear mixed-effects models using Eigen and S4. R package version 1.0-4.