FERRITIN MEASUREMENT TRAJECTORIES IN A NEW WHOLE BLOOD DONOR POPULATION_ LONGITUDINAL STUDY (FIND+)

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Background

- Lose of approximately 200 mg of iron, as a result of one whole blood donation
- Difference in optimal donation intervals due to:
  - Decrease in ferritin levels after a whole blood donation
  - The rate of restoring iron stores to pre-donation

WHAT MIGHT BE HELPFUL?

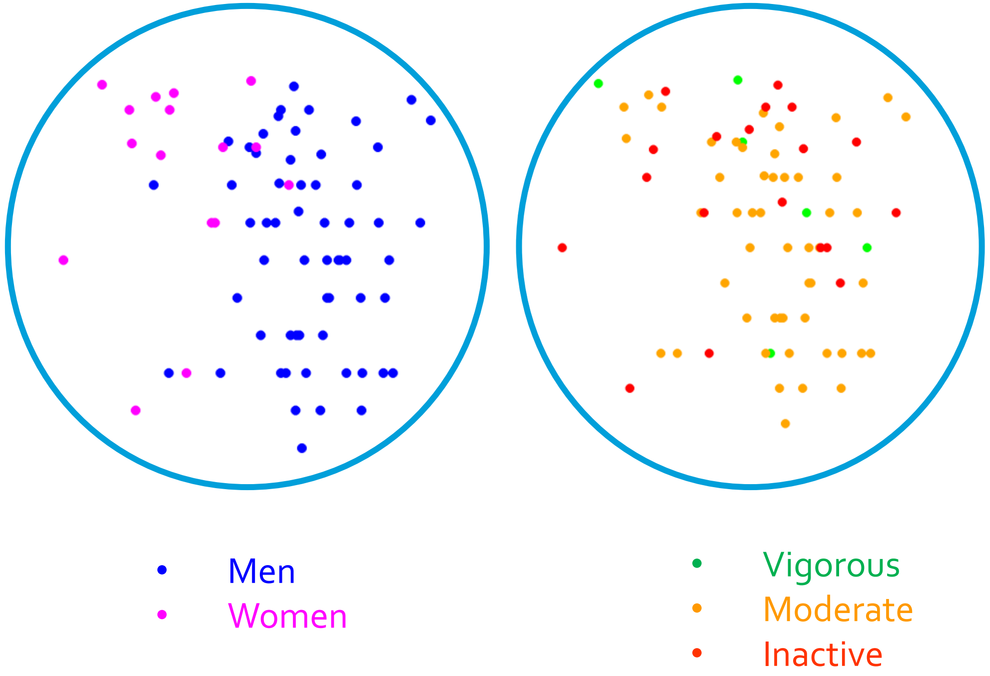
TRAJECTORY ANALYSIS AS A FLEXIBLE STATISTICAL APPROACH

FOR IDENTIFYING AND CLASSIFYING HETEROGENEITY **IN**

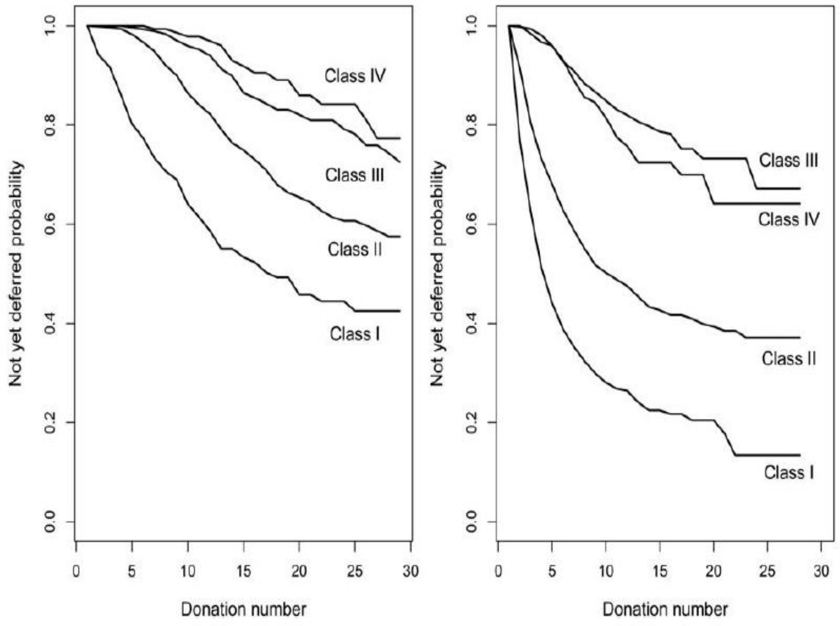
FERRITIN LEVELS DEPLETION BY DONATION TIMES

- What is terajectory analysis and why is it useful?
    - Sub-grouping people
    - In a cross sectional setting
    - For repeated measurements

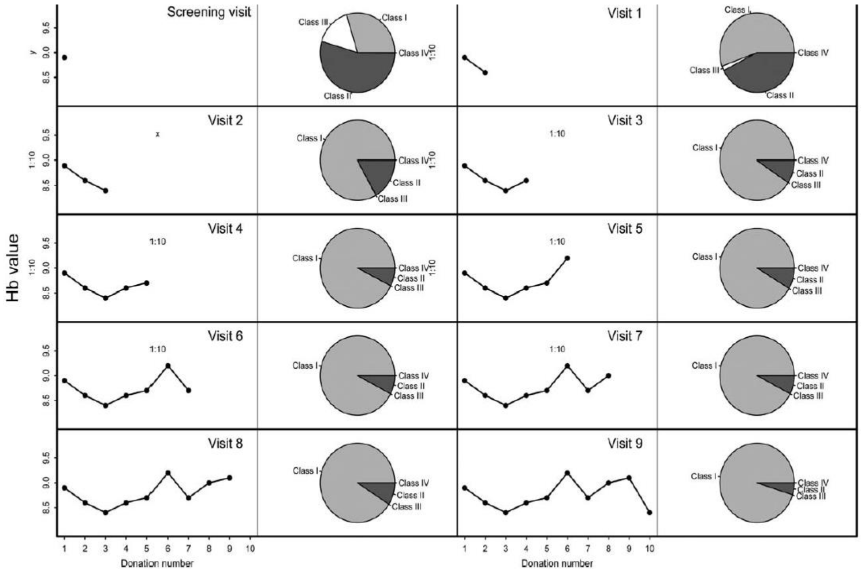
Sub-grouping people



Insight study; Findings from 5388 Dutch blood donors



Proportion of deferral in each of the latent classes for male donors (left) and female donors (right) separately



Class-membership probabilities at the first nine visits of a male donor with a Hb level of 8.9

Since haemoglobin levels do not reflect iron stores of donors, information regarding ferritin trajectories may provide superior information on donors more and less prone to the development of iron deficiency and becoming at risk for low Hb deferrals

FIND+ Study aim

To define subpopulations of donors with different ferritin

trajectories over repeated donations

Methods

- Ferritin levels of 300 new whole blood donors were measured from stored (lookback) samples from each donation over a two year period.
- Donors were selected if stored samples from at least two whole blood donations were available.
- Variation in ferritin level trajectories was investigated using a growth mixture model which assumes that each donor belongs to one of several subgroups with specific longitudinal traits.
- Separate analyses were performed for male and female donors

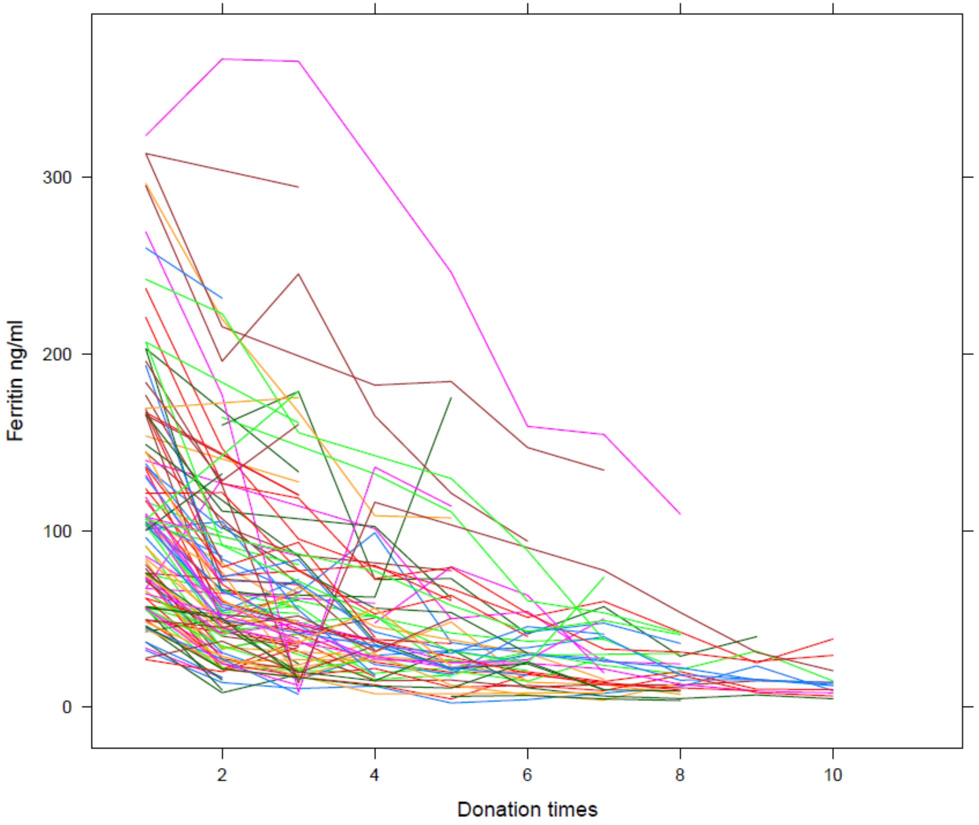
Baseline characteristics of the participants

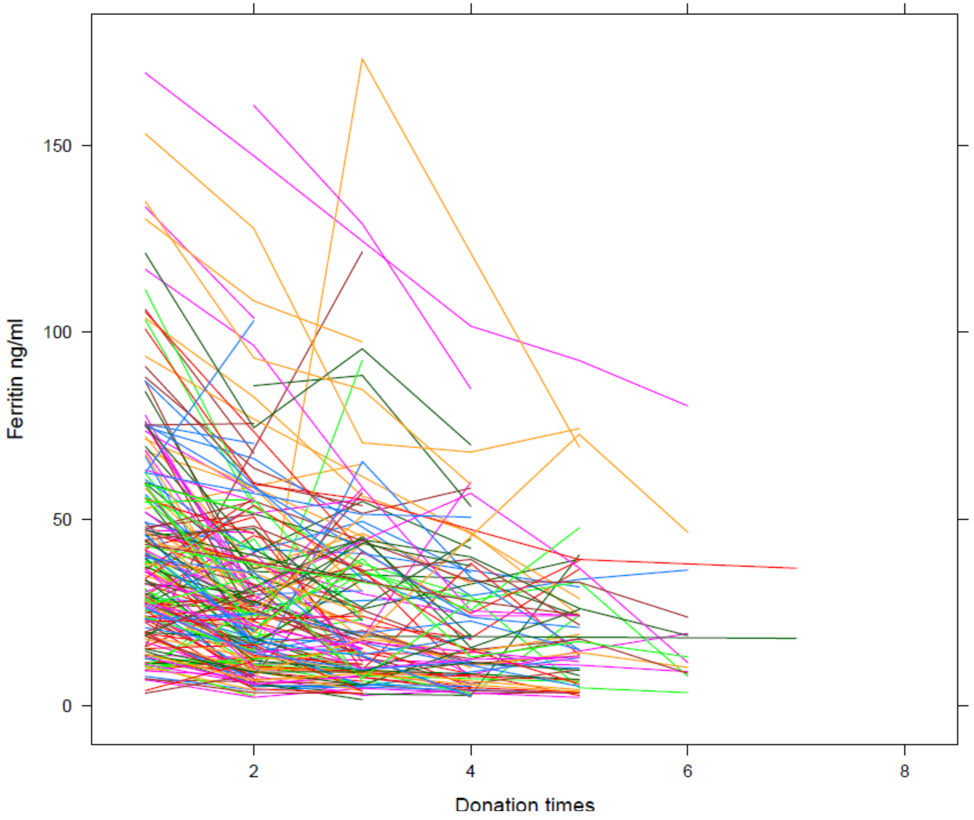
VARIABLES	MALE DONORS (N=101)	FEMALE DONORS (N=199)
Age (years)	29.96 (25.08-38.12)	24.62 (22.58-29.60)
BMI (kg/m²)	24.22 (22.48-26.10)	23.14 (21.55-26.44)
Number of donations	4 (2-6)	3 (2-4)
Hb level at screening visit (ng/ml)	9.30 (8.90-9.60)	8.30 (8.00-8.70)
Ferritin at screening visit (ng/ml)	103.35 (56.77-137.76)	36.66 (23.21-56.59)
Ferritin at last donation [2] (ng/ml)	28.13 (17.80-43.24)	13.04 (10.63-29.30)
Inter-donation interval (weeks)	10.00 (9.00-17.00)	20.00 (17.00-26.00)
Donation in cold seasons (%)	47.1	48.2

[1]The variables are presented as median and interquartile range or as stated otherwise.

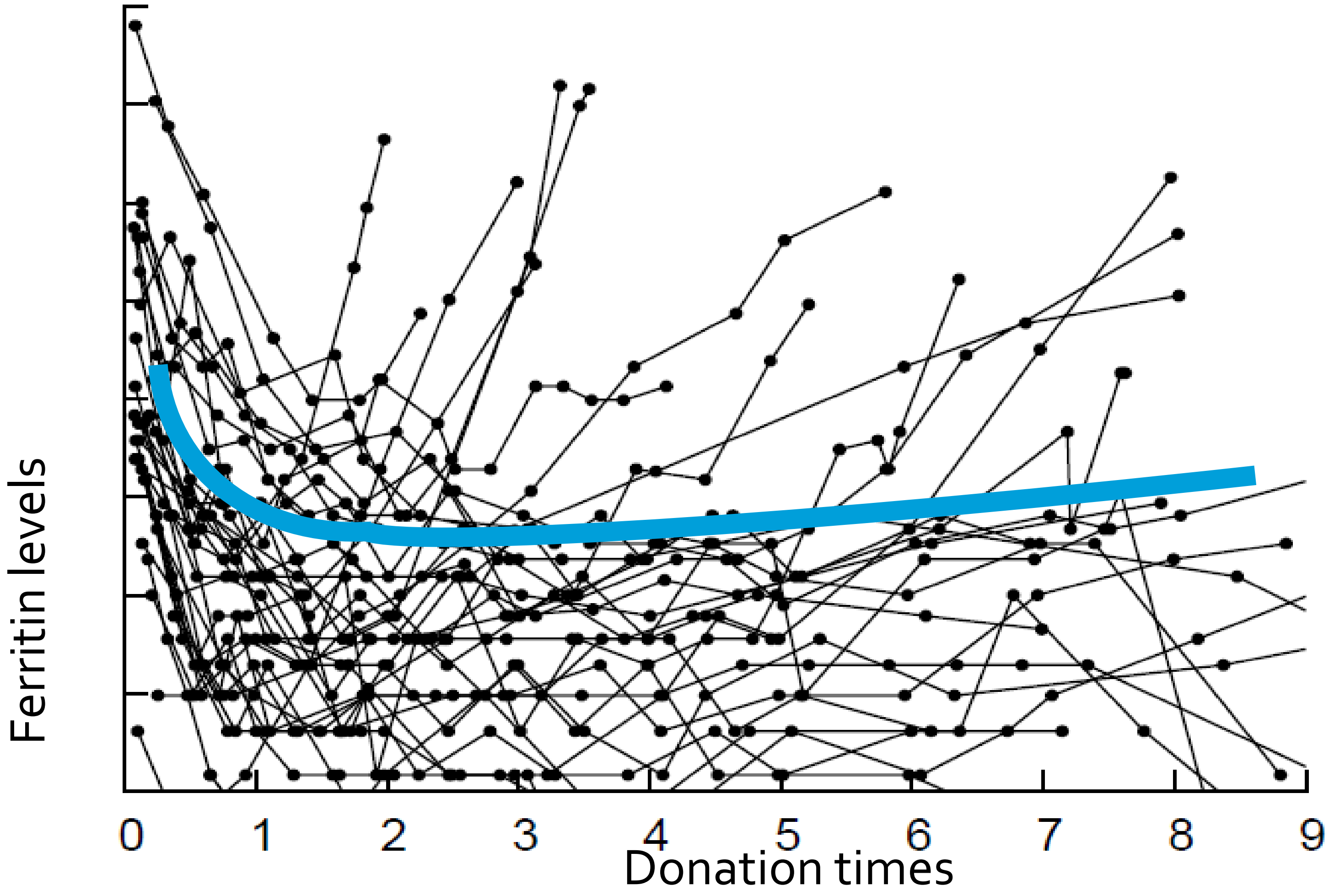
[2].Ferritin levels at 6th donation in men and 4th donation in women during study period (September 2017-September 2019).

To justify the use of mixture modelling, the presence of heterogeneity of development will be visualized and assessed by plotting variations in ferritin levels through the donation time points in a random selection of subjects (spaghetti plot).





Fitting one line???!!!

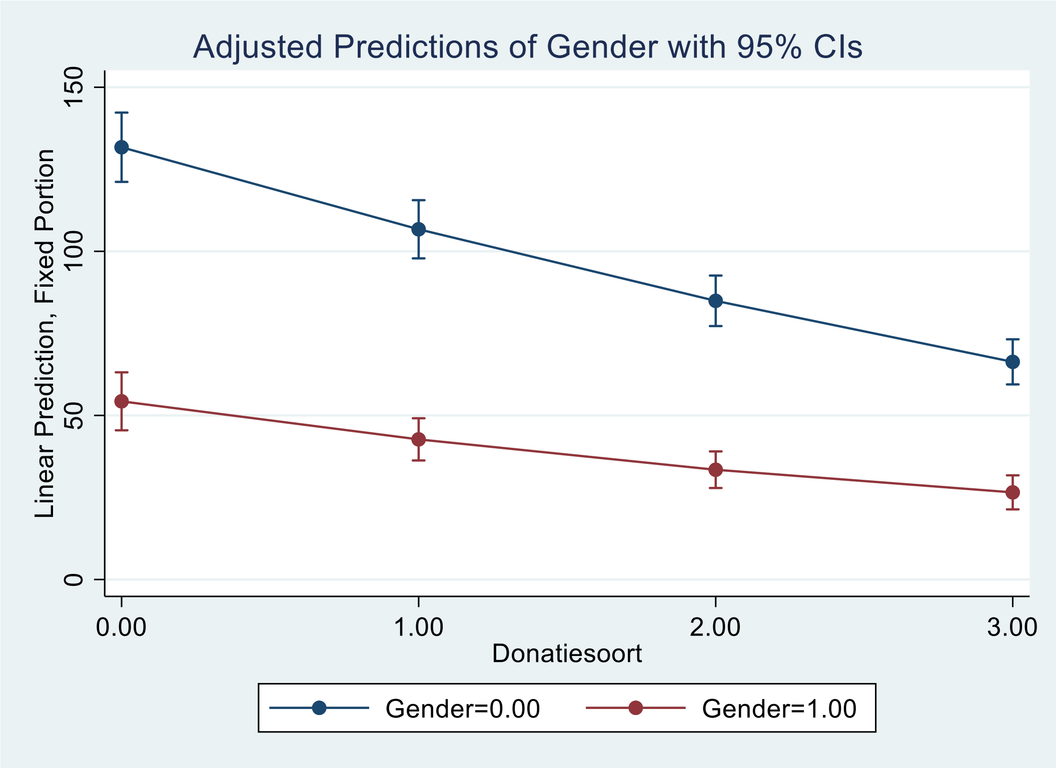


Growth Curve Modeling (GCM) for men (code=0) and female (code=1) donors

Full Model:

Ferritin ij = γ_{00} + γ_{01}(Gender) + u_{0j} + γ_{10}(Donation time) + γ_{11} (Donation time)(Gender) + u_{1j} (Donation time) + γ_{20} (Donation time 2) + γ_{21} (Donation time 2)(Gender) + u_{2j}(Donation time 2) + r_{ij} = γ_{00} + γ_{10}(Donation time) + γ_{20} (Donation time 2) + γ_{01}(Gender) + γ_{11} (Donation time)(Gender) + γ_{21} (Donation time 2)(Gender) + u_{0j} + u_{1j} (Donation time) +u_{2j}(Donation time 2) +r_{ij}

mixed Ferritin iGender##c. Donation time ##c. Donation time || id Donation time, covariance(unstructured) nolog margins i.Gender, at Donation time =(0(1)3)) vsquish marginsplot, name(model_5, replace) x(age)



To select a Maximum K

- Donation numbers (min-max)
  - Women: 1-8 (IQR=2-4)
  - Men:1- 11 (IQR=2-6)
- Sample size (n)
  - Women: 199
  - Men: 101
- Previous theoretical and/or practical insights
  - Previous study shows 4 different terajectoried for Hb levels in doners
- The spaghetti plot, for the initial scoping of potential models
  - We would expect 2 to maximum 3 terajectories

terrelatedness of longitudinal LGM models

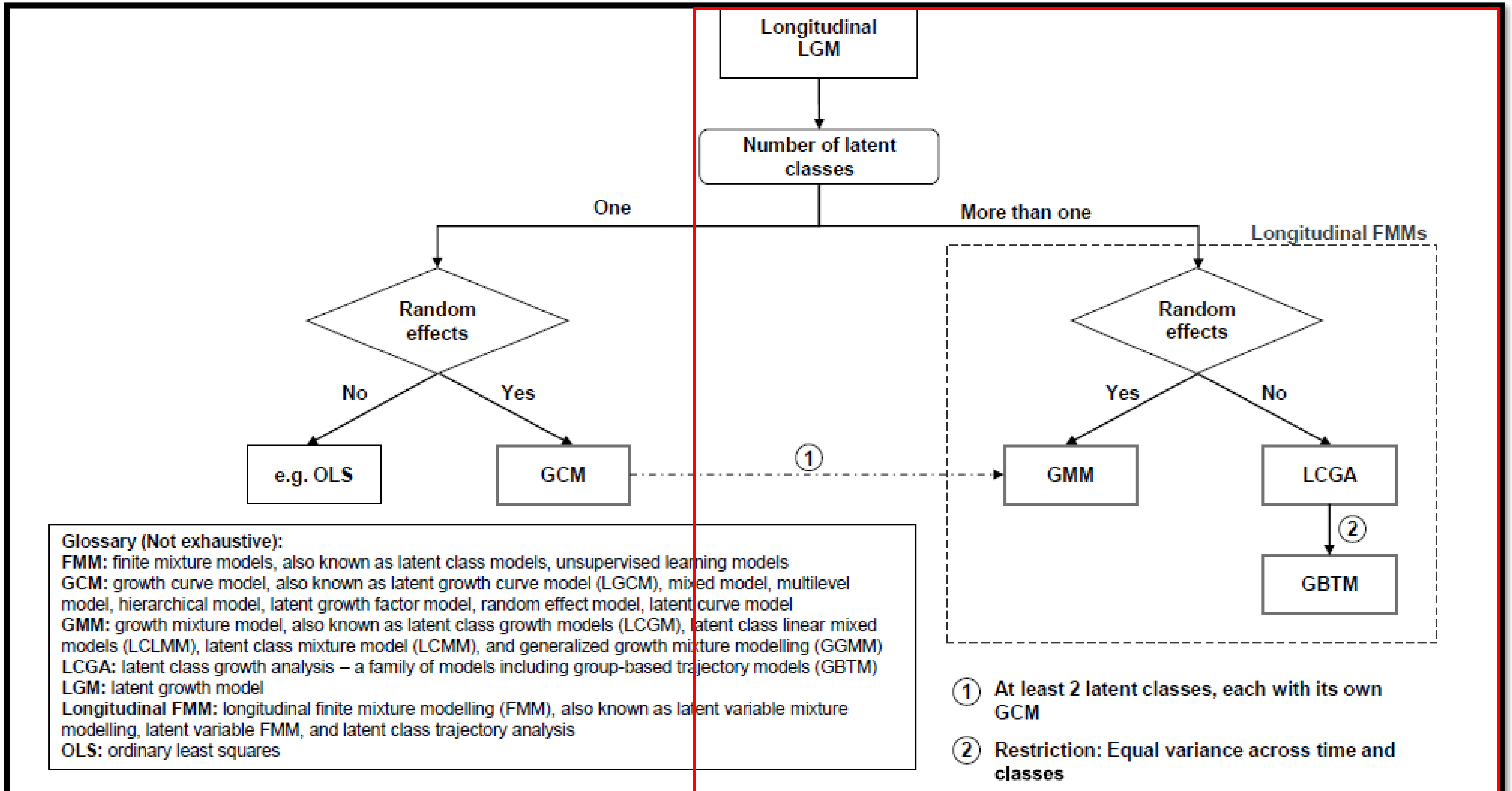
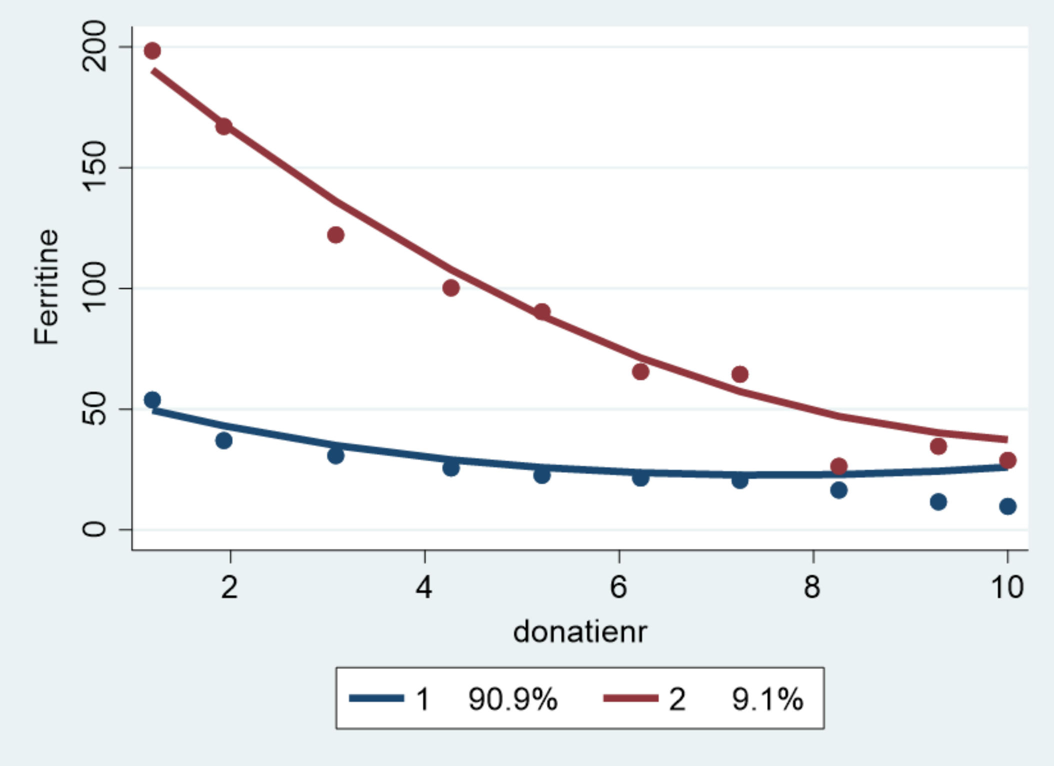


Fig. 1. Interrelatedness of longitudinal LGM models.

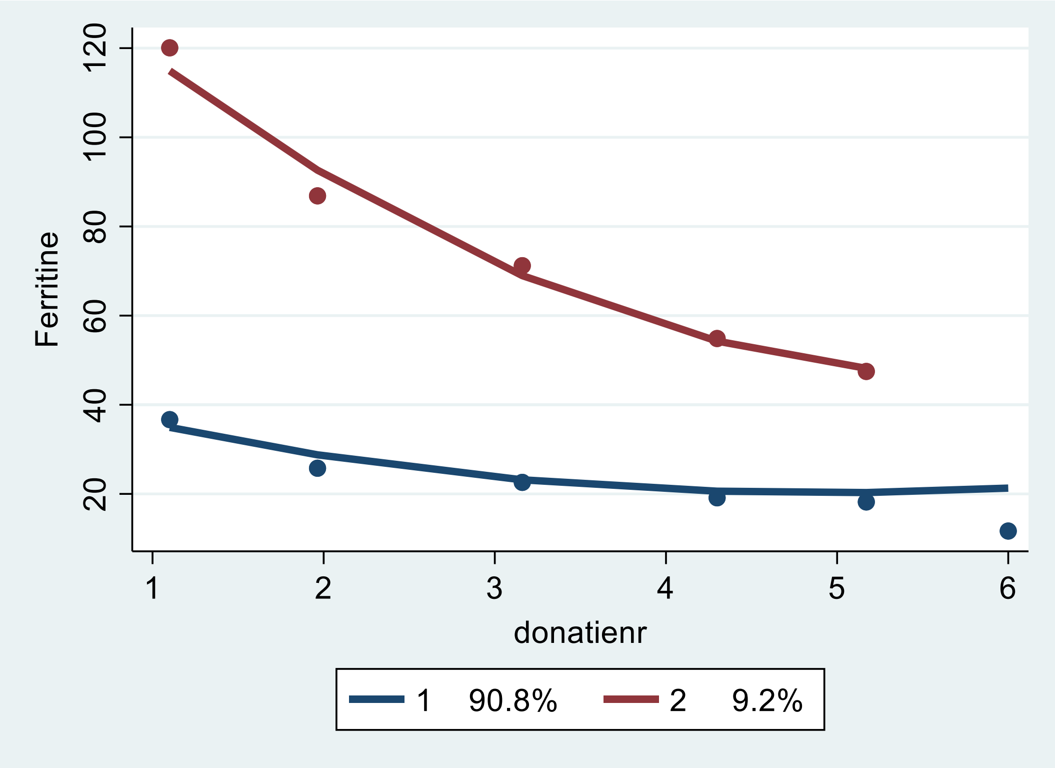
GBTM for doners (both gender)

Group	Parameter	Estimate	Error	Parameter=0	Prob > |T|
1	Intercept	61.95798	3.00969	20.586	0.0000
	Linear	-12.11879	1.68211	-7.205	0.0000
	Quadratic	0.80054	0.19068	4.198	0.0000
2	Intercept	230.85320	9.75750	23.659	0.0000
	Linear	-35.72391	4.37894	-8.158	0.0000
	Quadratic	1.61386	0.44112	3.659	0.0003
	Sigma	31.88543	0.66277	48.109	0.0000
Group membership					
1	(%)	90.91921	1.74341	52.150	0.0000
2	(%)	9.08079	1.74341	5.209	0.0000



GBTM for female doners

Group	Parameter	Estimate	Error	Parameter=0	Prob > |T|
1	Intercept	45.36960	3.27304	13.862	0.0000
	Linear	-11.06815	2.52325	-4.386	0.0000
	Quadratic	1.12249	0.41163	2.727	0.0066
2	Intercept	149.64112	9.67053	15.474	0.0000
	Linear	-34.78355	6.60593	-5.266	0.0000
	Quadratic	2.92942	1.00591	2.912	0.0037
	Sigma	19.94179	0.55917	35.663	0.0000
Group membership					
1	(%)	90.76365	2.15208	42.175	0.0000
2	(%)	9.23635	2.15208	4.292	0.0000



- The model will be extend for the selected K by dropping one constraint at a time (by allowing for the dependence of residual variance on time and/or class), which is a Latent Class Growth Analysis (LCGA). We then select the LCGA or GBTM model with the lowest fit statistic (BIC). If it is an LCGA, we then use the LRT to determine whether that selected model's K can be reduced further. The same strategy will be used when refining the model during the subsequent steps of relaxing the model constraints (by allowing for class-variant or class-invariant random effect variances), that is, select the model with the best BIC and then check how much K can be reduced using the LRT.

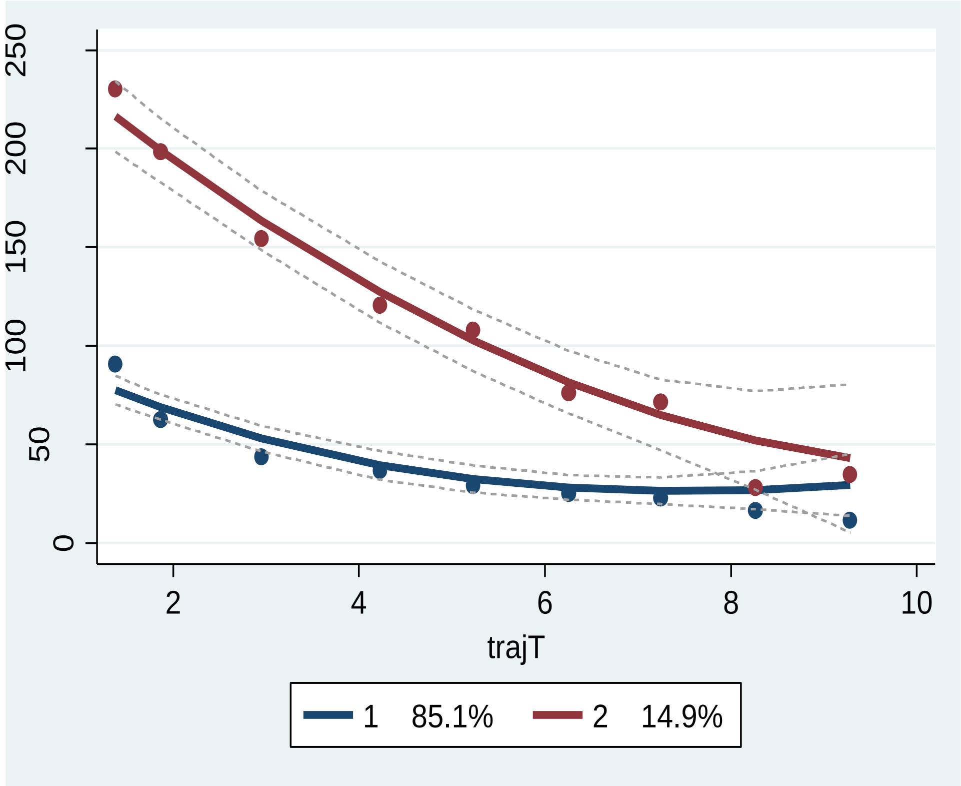
Final GBTM, LCGA and GMM solution for Female doners

Model	GBTM	GBTM	LCGA	LCGA	GMM	GMM
Classes	2	3	2	3	2	3
Specification	Same residual variance over class and over time	Same residual variance over class and over time	Same residual variance over time, different over class	Same residual variance over time, different over class	Class-invariant random intercept variance, same residual variance over time and different over class	Class-invariant random intercept variance, same residual variance over time and different over class
AIC	-3008.51	-2986.46	5846.85	5762.26	5072.43	5687.8
BIC	-3026.68	-3006.21	5866.61	5762.26	5705.36	5687.89
ssBIC	-3026.52	-3013.47	-	-	-	-
Scaled entropy	?	?	?	?	?	?
VLMR P-VALUE	?	?	?	?	?	?
aLMR p-value	?	?	?	?	?	?

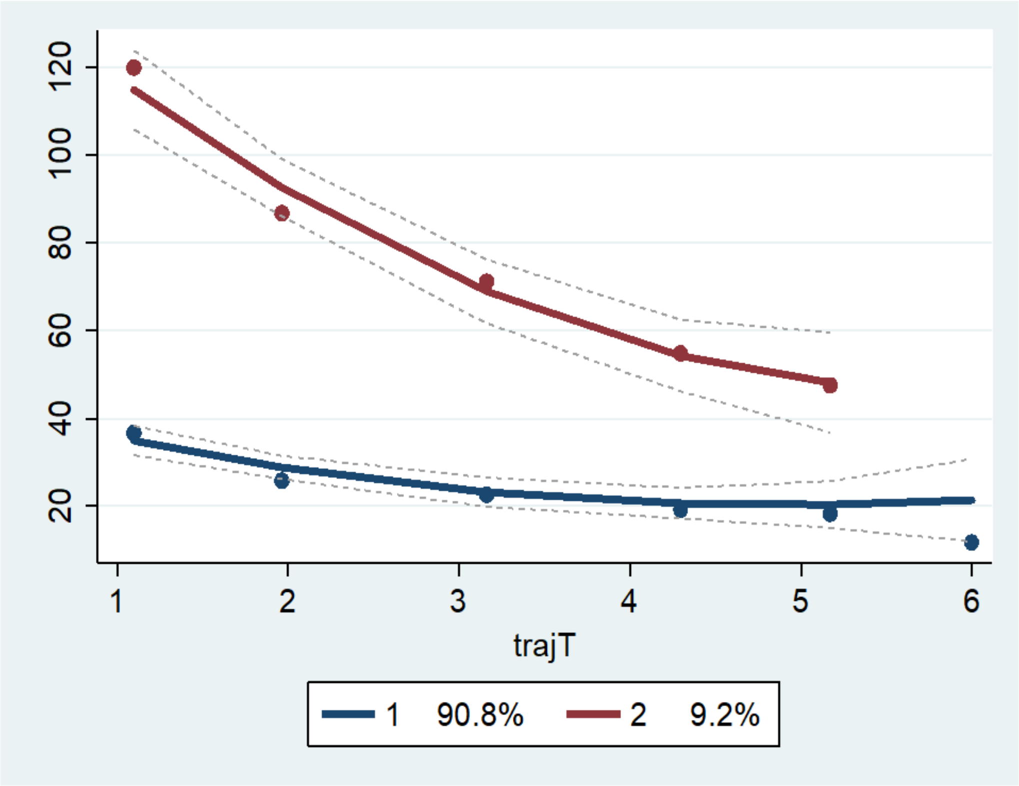
Final GBTM, LCGA and GMM solution for male doners

Model	GBTM	GBTM	LCGA	LCGA	GMM	GMM
Classes	2	3	2	3	2	3
Specification	Same residual variance over class and over time	Same residual variance over class and over time	Same residual variance over time, different over class	Same residual variance over time, different over class	Class-invariant random intercept variance, same residual variance over time and different over class	Class-invariant random intercept variance, same residual variance over time and different over class
AIC	-2631.27	-2640.50	5237.5	5091.43	5010.63	5017.74
BIC	-2631.27	-2640.50	5253.19	5114.96	5047.25	5043.89
ssBIC	-2627.76	-2650.24	-	-	-	-
Scaled entropy	?	?	?	?	?	?
VLMR P-VALUE	?	?	?	?	?	?
aLMR p-value	?	?	?	?	?	?

GBTA for Male doners



GBTA for female donors



Descriptive statistics of the FIND+ data set by gender and group based terajectory of the growth mixture model in study period

	Male doners		**Female doners**	
Variables	Class 1 (n=87)	Class 2 (n=14)	Class 1 (n=181)	Class 2 (n=18)
Age (years)	**28.11 (24.82-34.27)**	**39.43 (31.74-47.64)**	**24.42 (22.36-27.98)**	**35.00 (27.28-47.59)**
BMI (kg/m^2)	23.86 (22.15-25.69)	27.46 (24.81-28.34)	**22.85 (21.48-26.23)**	**25.18 (23.23-29.04)**
Number of donations	4 (2-6)	4 (2-6)	3 (2-4)	3 (2-5)
Hb at screening visit (ng/ml)	9.40 (8.90-9.80)	9.05 (8.82-9.65)	8.30 (8.00-8.80)	8.35 (8.17-8.55)
Ferritin at screening visit (ng/ml)	**85.40 (56.10-120.24)**	**239.62 (181.63-294.61)**	**32.69 (20.34-48.90)**	**114.13 (102.55-135.31)**
Ferritin at last donation [2] (ng/ml)	**24.89 (14.16-31.10)**	**53.26 (43.78-133.74)**	**13.52 (6.30-28.46)**	**53.45 (39.01-68.89)**

Conclusion

- Based on the Bayesian Information Criterion, two classes are detected for both genders.
- Among female donors, models with four and three classes showed slightly improved BIC values, however, the additional classes were discarded because of the small size (<1%). Therefore, we selected a model with two classes for female donors.
- Using ferritin levels measured at 10 donations for male donors and 6 donations for female donors, it can be concluded that a male donor has a probability of 85.1% to belong to Class 1 (the class with rather linear reduction in ferritin levels) in 10 donations and a female donor has the chance of 90.1 to belong to Class 1 after 6 donations.

Thanks for your attention