



University of St Andrews
School of Computer Science

Mathematical Modelling and Biological Models

ESLCCC 2014

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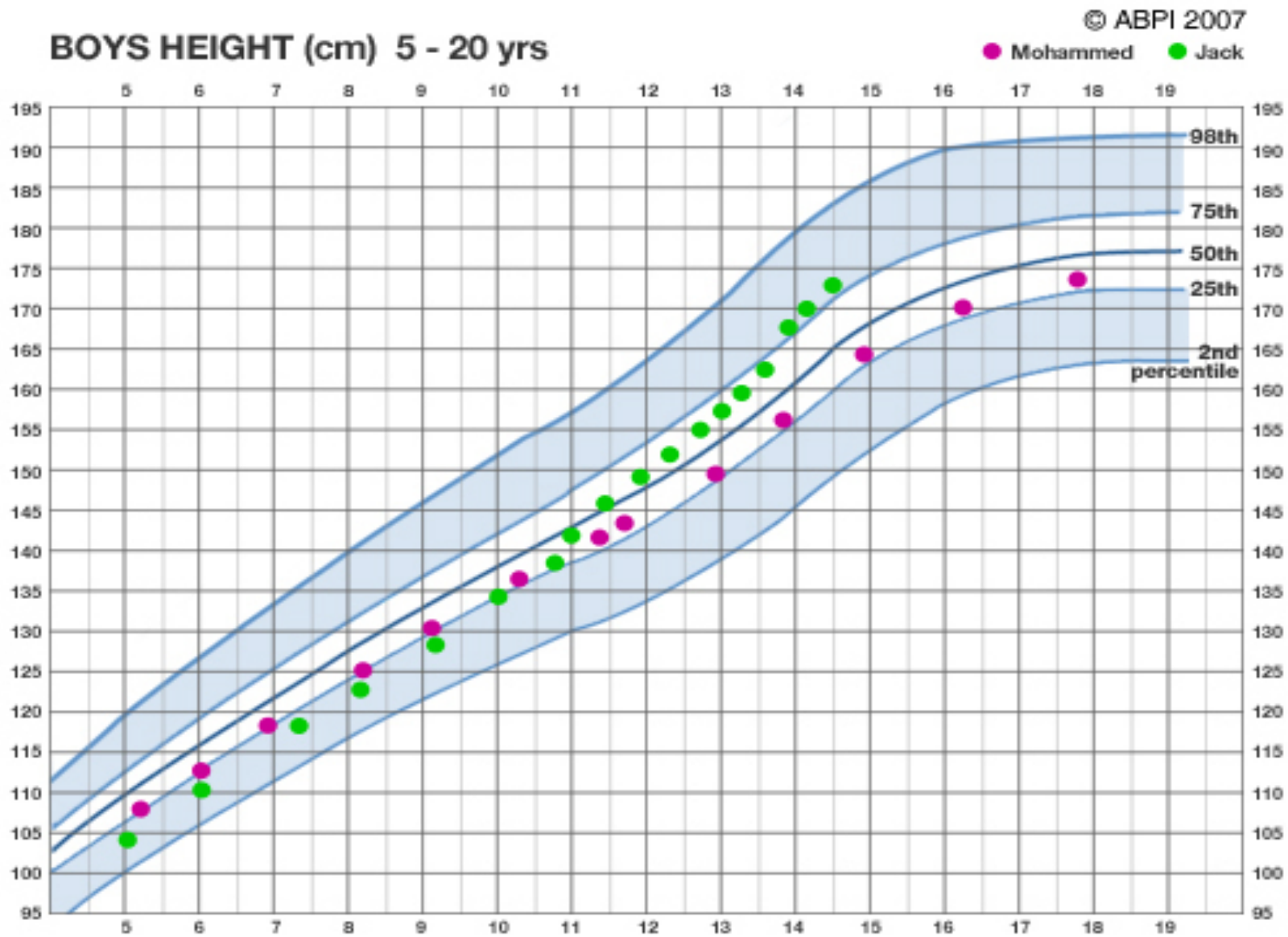
- Well-known examples
- Non-growing follicles
- AMH
- Total Testosterone
- Relevance



- Equations
- Statistics
 - p-values
 - Correlation coefficients
 - Confidence intervals
- Derivation details

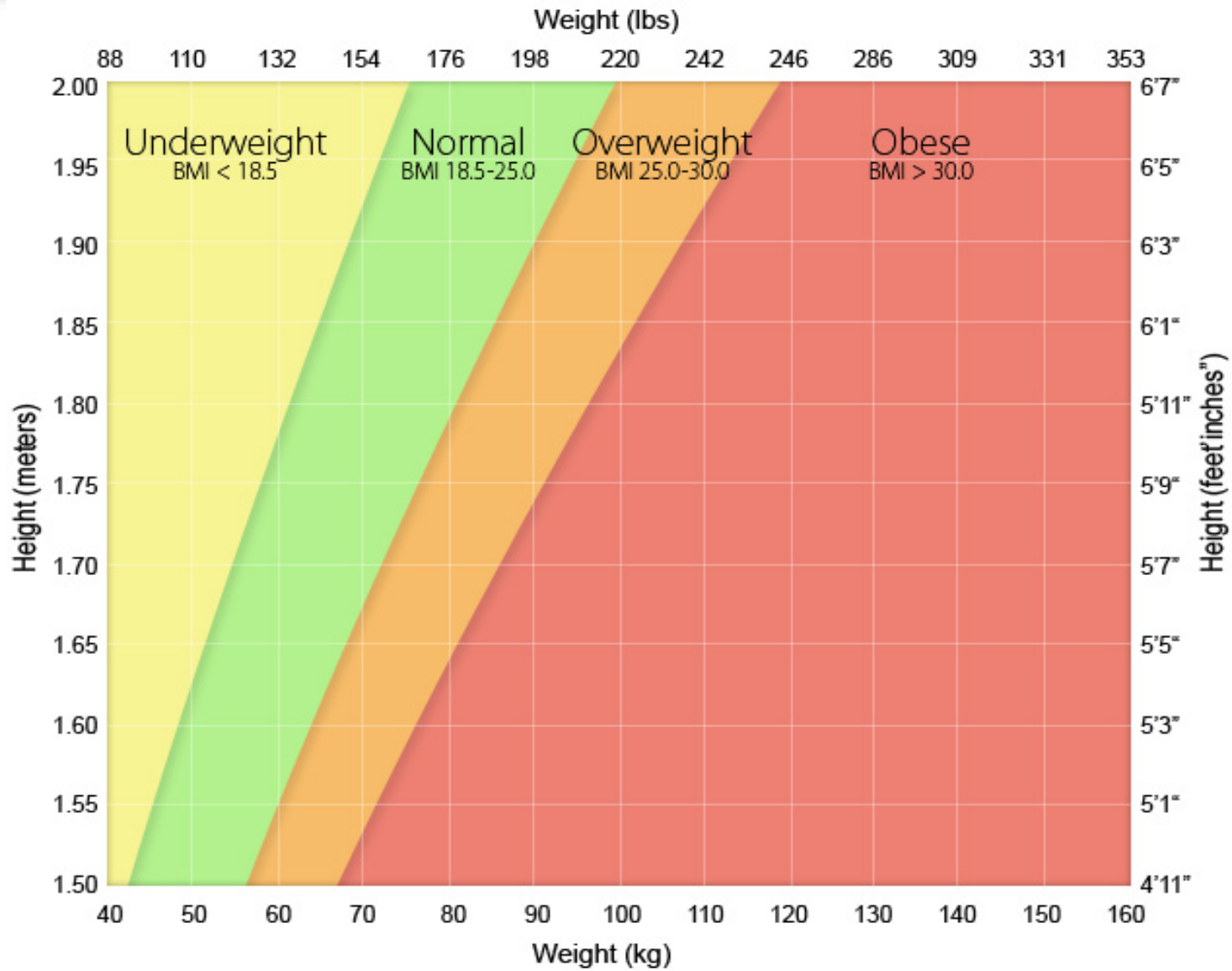


Growth Charts





BMI





George Box wrote:

“Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful.”

This is usually misremembered as:

“All models are wrong, but some are useful.”





NGFs - Faddy & Gosden 1992

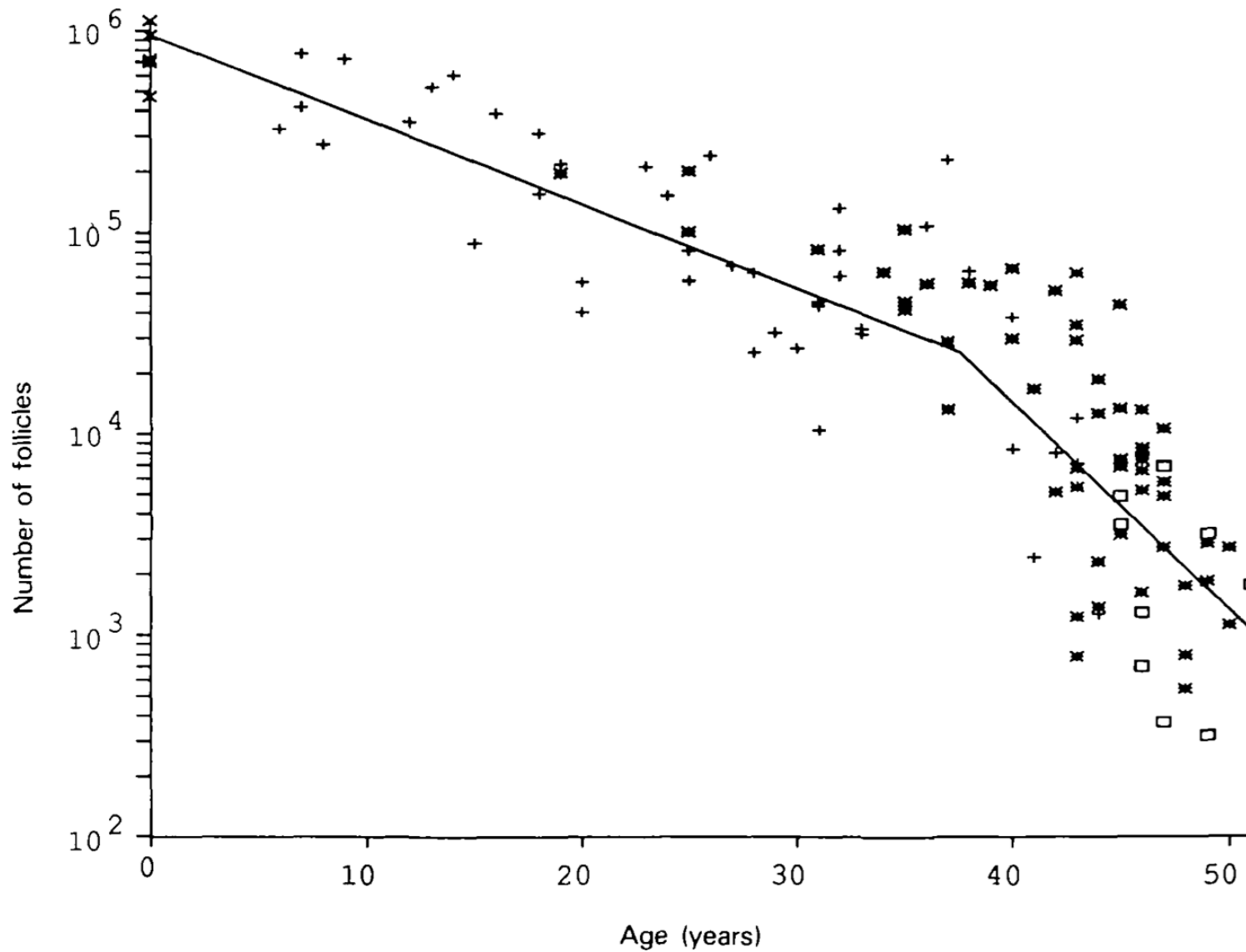
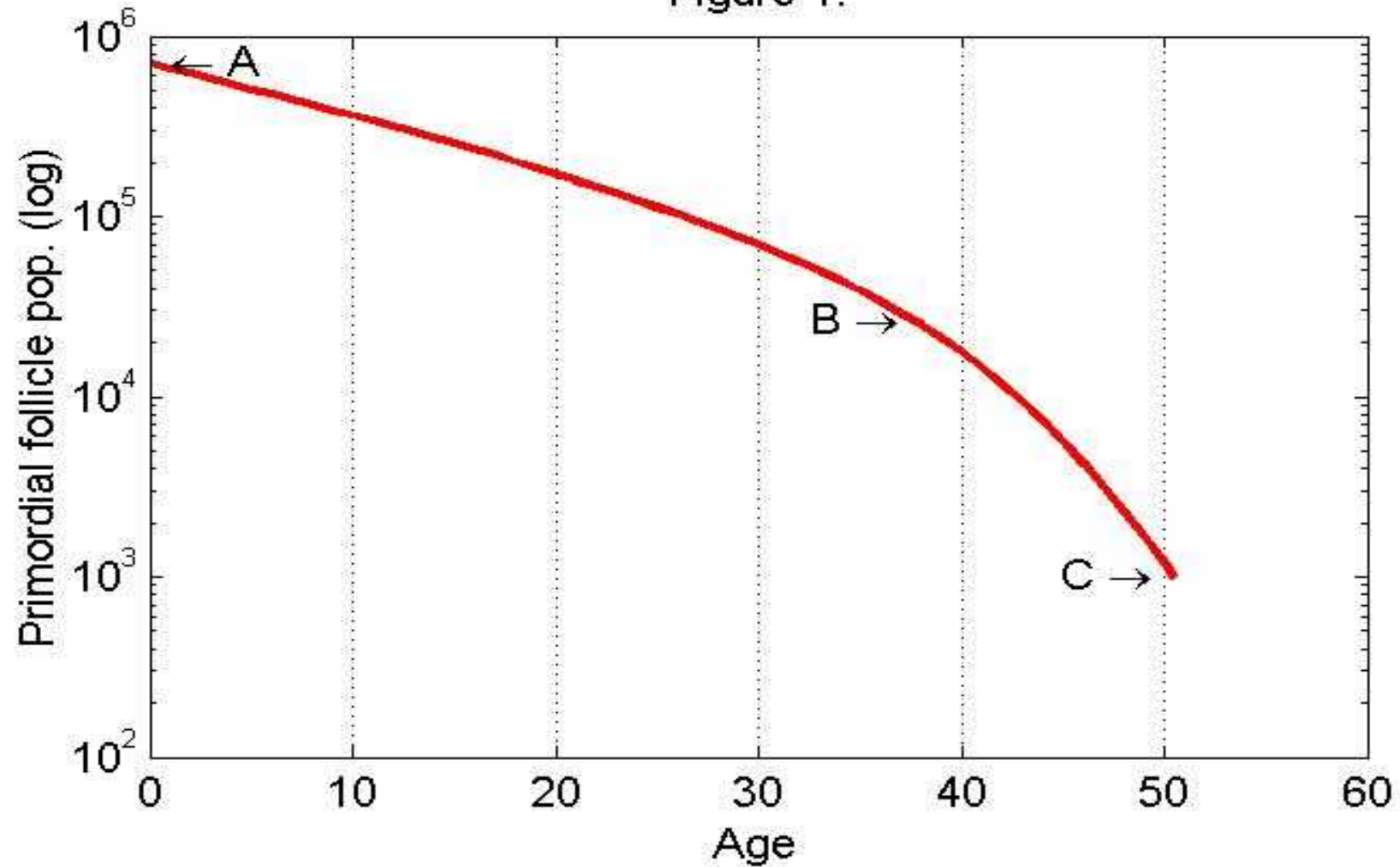
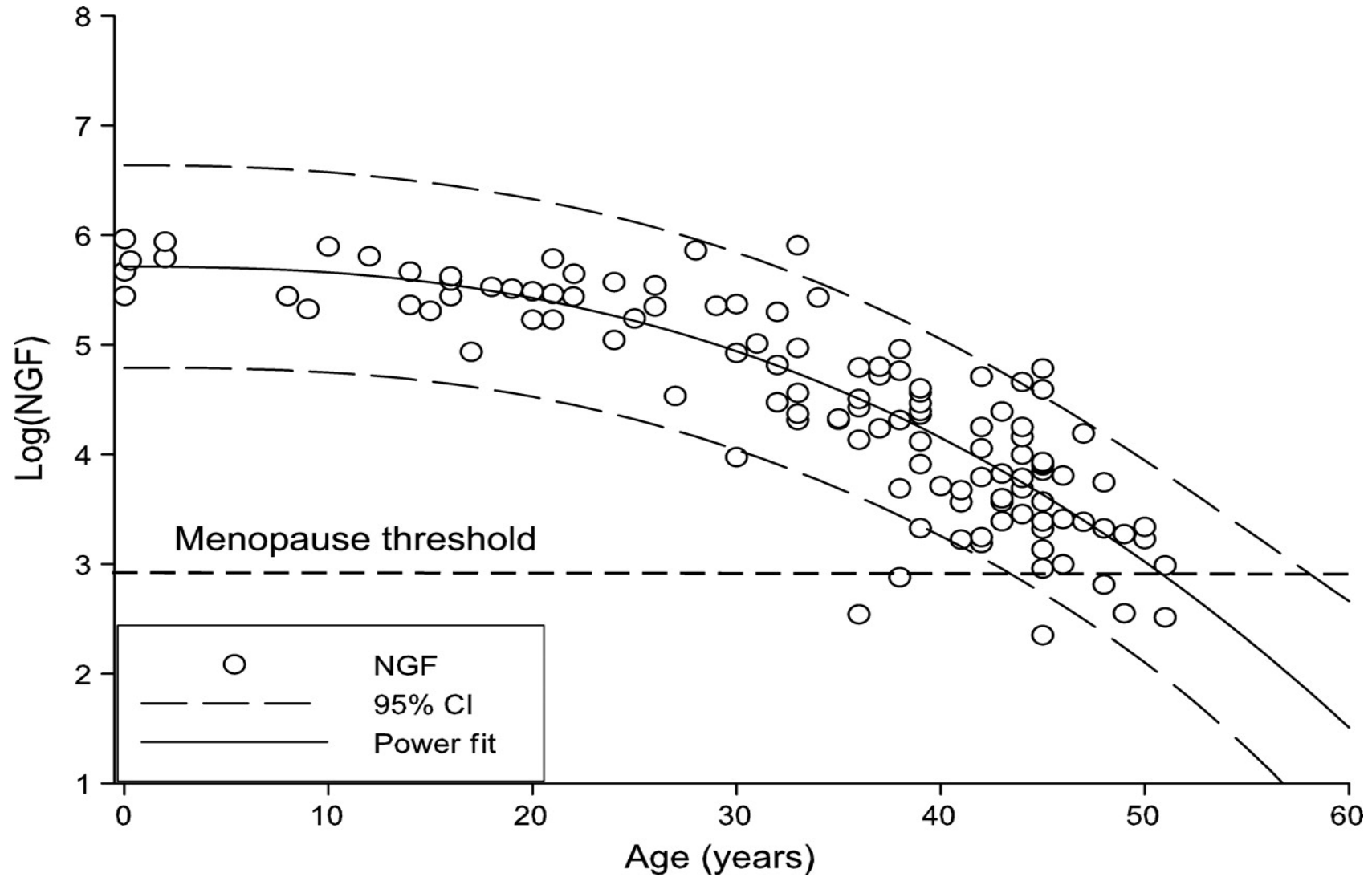




Figure 1.







- Data aggregation
 - Systematic search for data sources from the literature
 - Tables, charts, descriptive statistics
 - Our own data – if available
- Data selection
 - Exclusion & inclusion criteria (e.g. exclude infertile)
- Homogeneous data set that approximates the healthy population for a wide range of ages



- Comparative analysis of biologically plausible models
 - Goodness of fit
- Accurate enough to capture important features
- But not **too** accurate
 - A fantastic fit to the known data
 - Not useful when predicting new data



- Model validation is important
 - the highest-ranked candidate could just be luck
 - small changes in the data could promote other candidates
- Internal validation
 - make small changes to the data and check
- External validation
 - check using data that wasn't used to derive the model

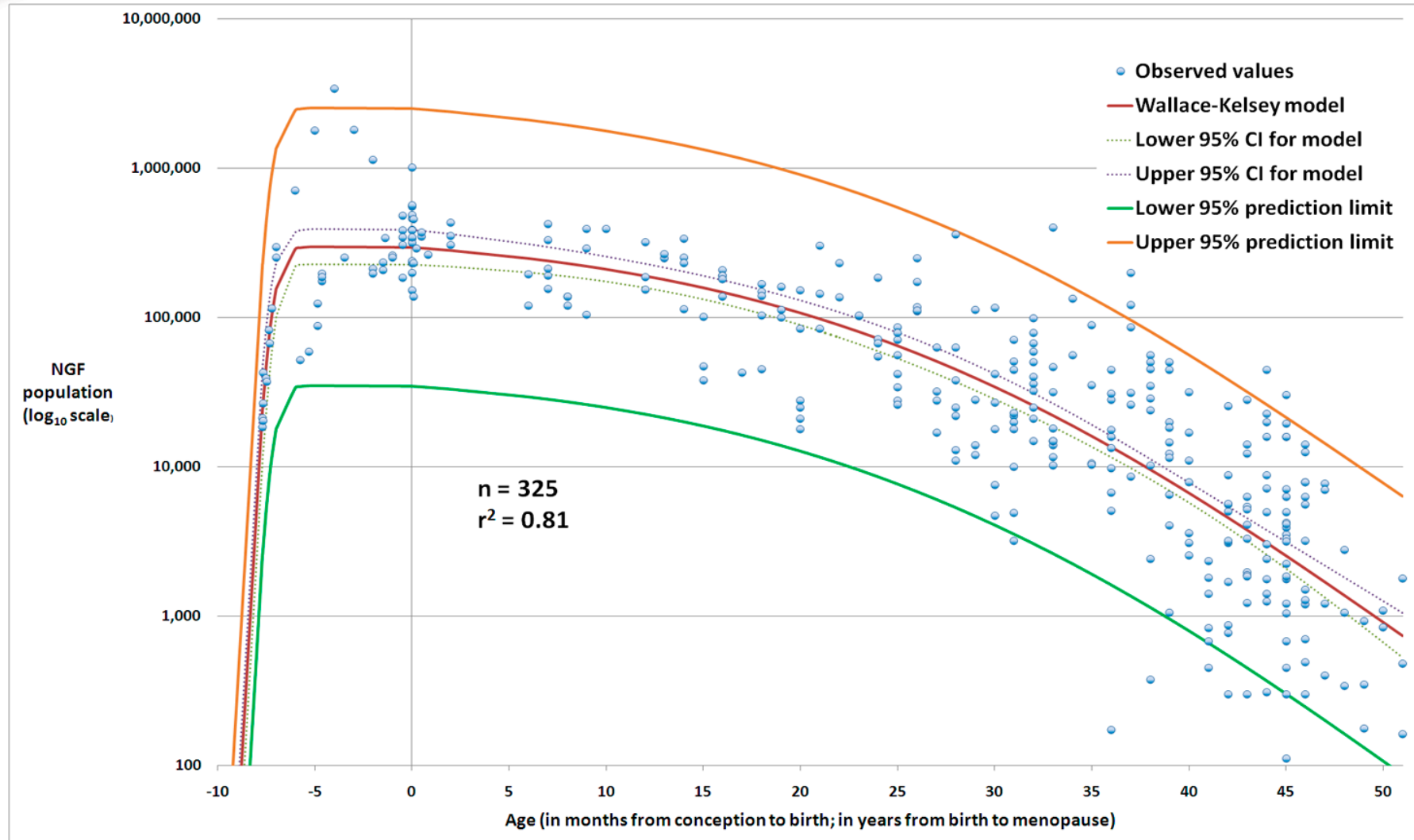


NGF Data: 8 Studies

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Study			Statistics			
Number	First author	Year	No. ovaries	Min. age	Max. age	Median age
1	Bendsen	2006	11	-0.6	-0.6	-0.6
2	Baker	1963	11	-0.6	7.0	-0.2
3	Forabosco	2007	15	-0.5	0.5	-0.3
4	Block	1953	19	-0.2	0.0	0.0
5	Hansen	2008	122	0.1	51.0	38.0
6	Block	1951	86	6.0	44.0	28.0
7	Gougeon	1987	52	25.0	46.0	39.5
8	Richardson	1987	9	45.0	51.0	46.0
Overall			325	-0.6	51.0	32.0



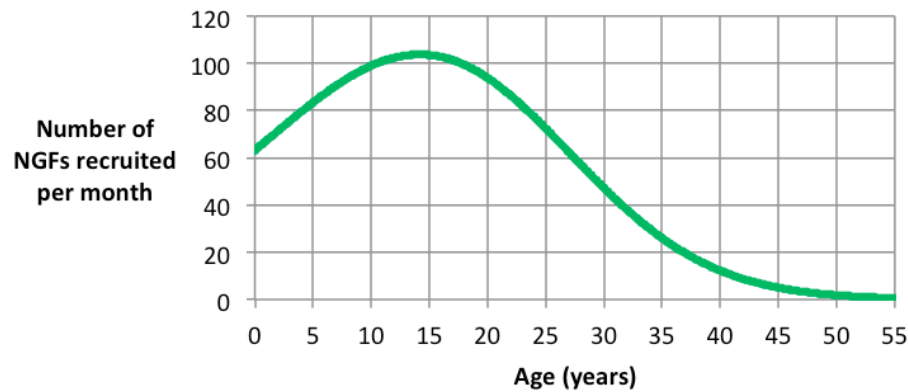




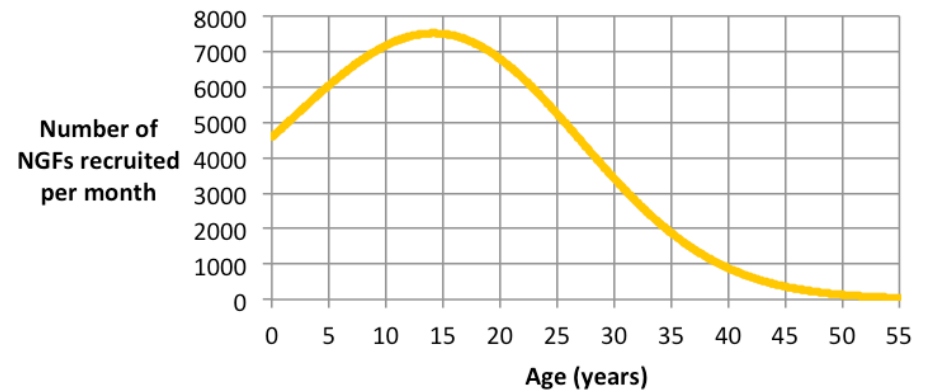
NGF recruitment - average age at menopause

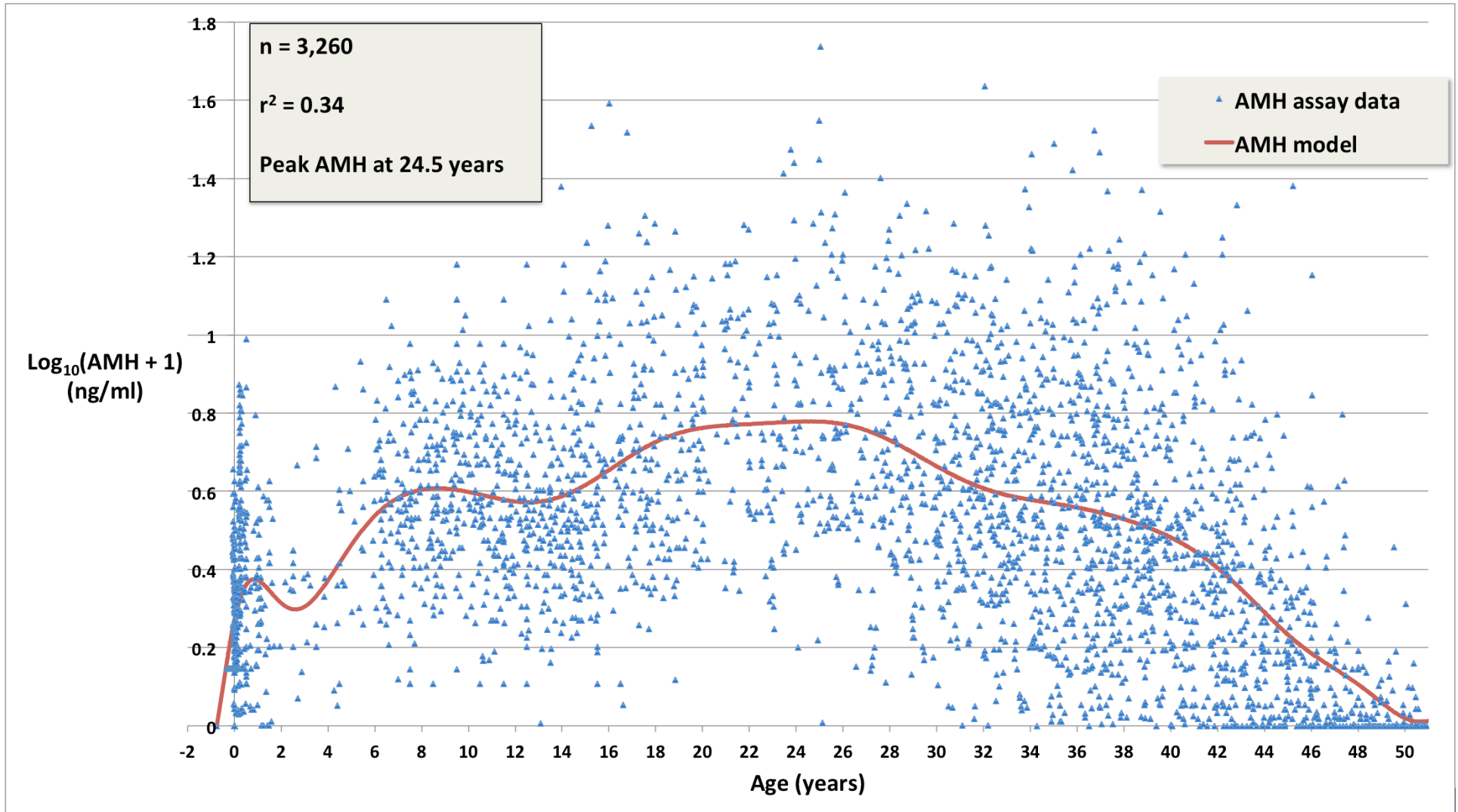


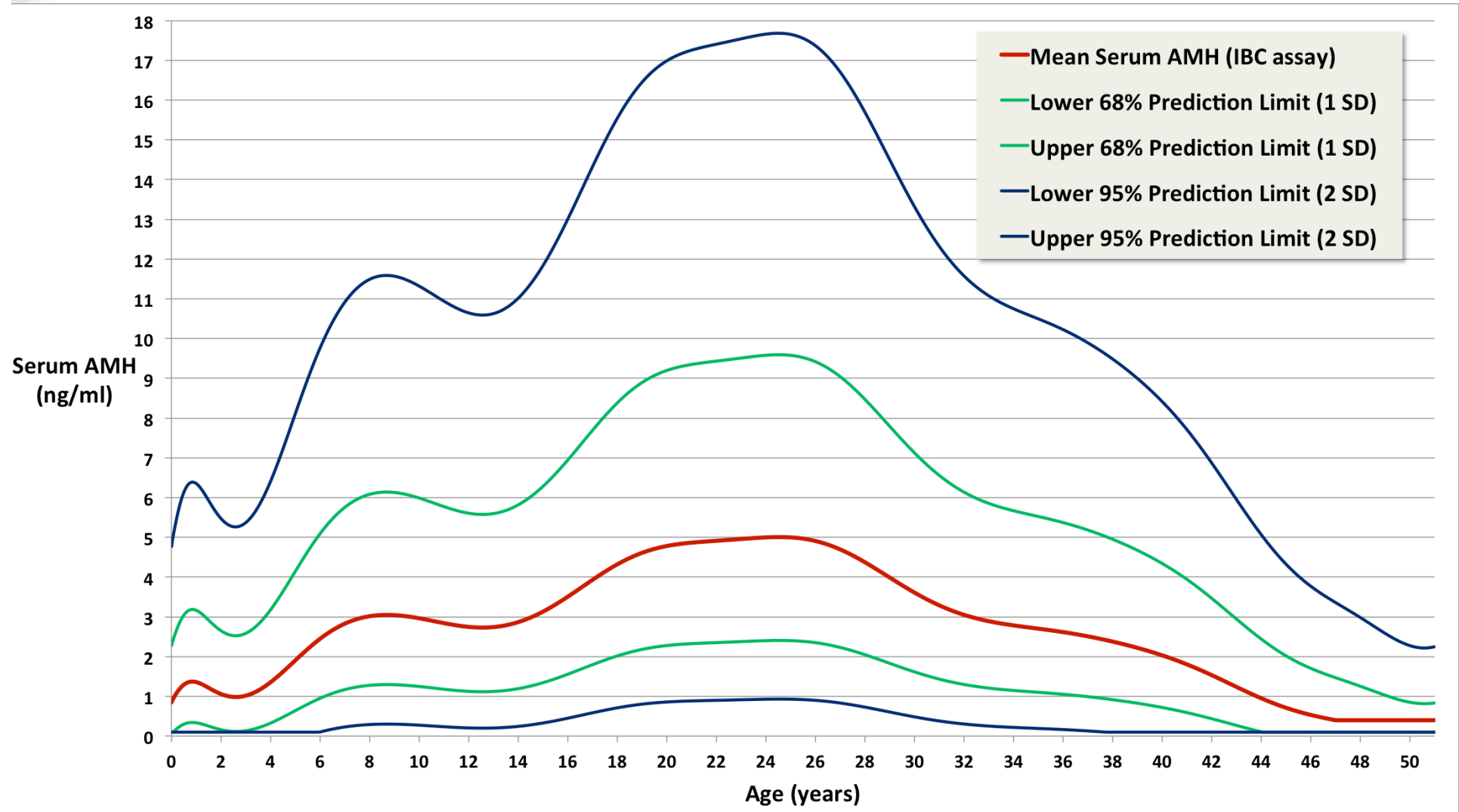
NGF recruitment - early age at menopause



NGF recruitment - late age at menopause

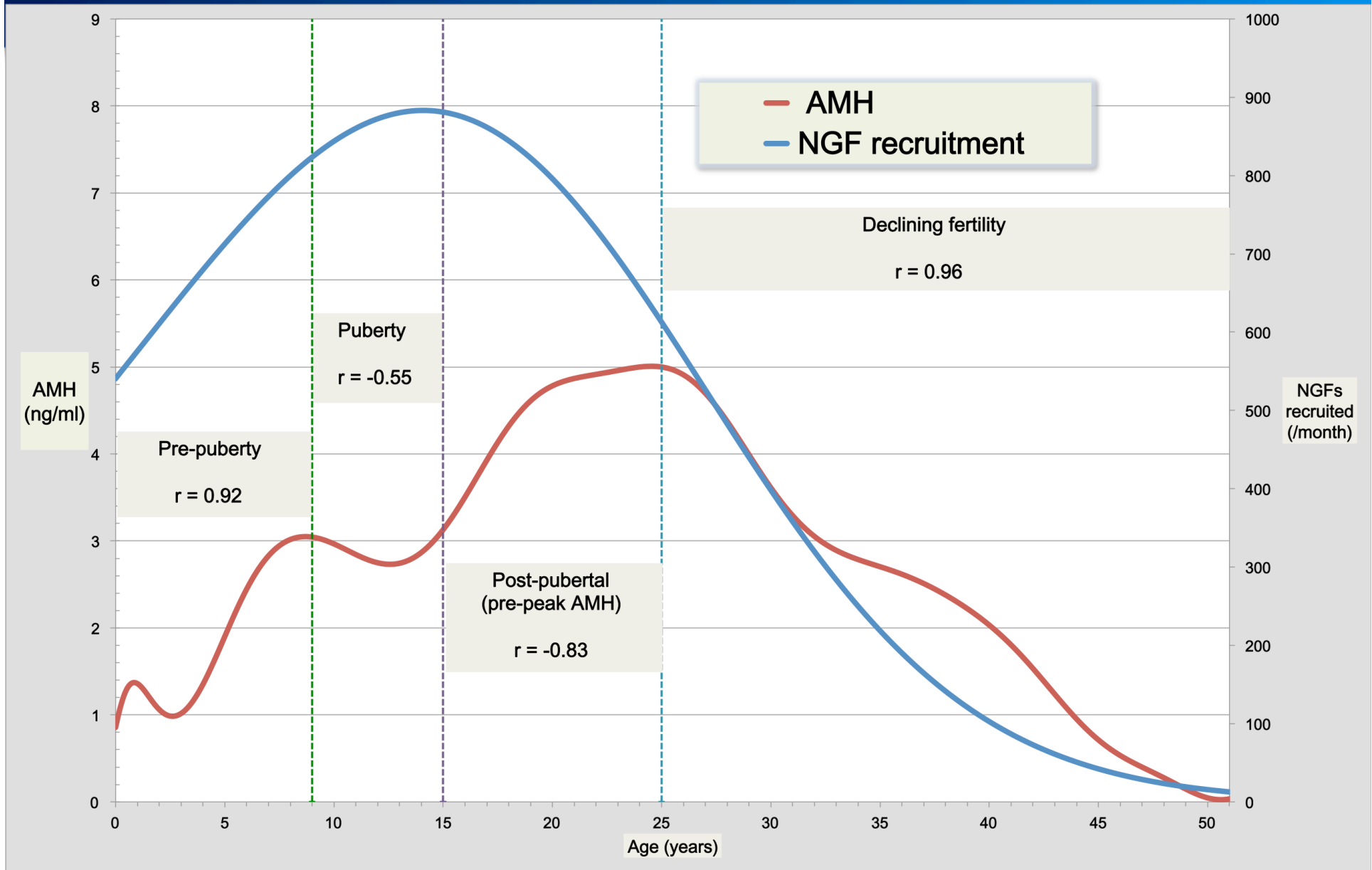








NGFs and AMH – Fleming et al. 2012 17



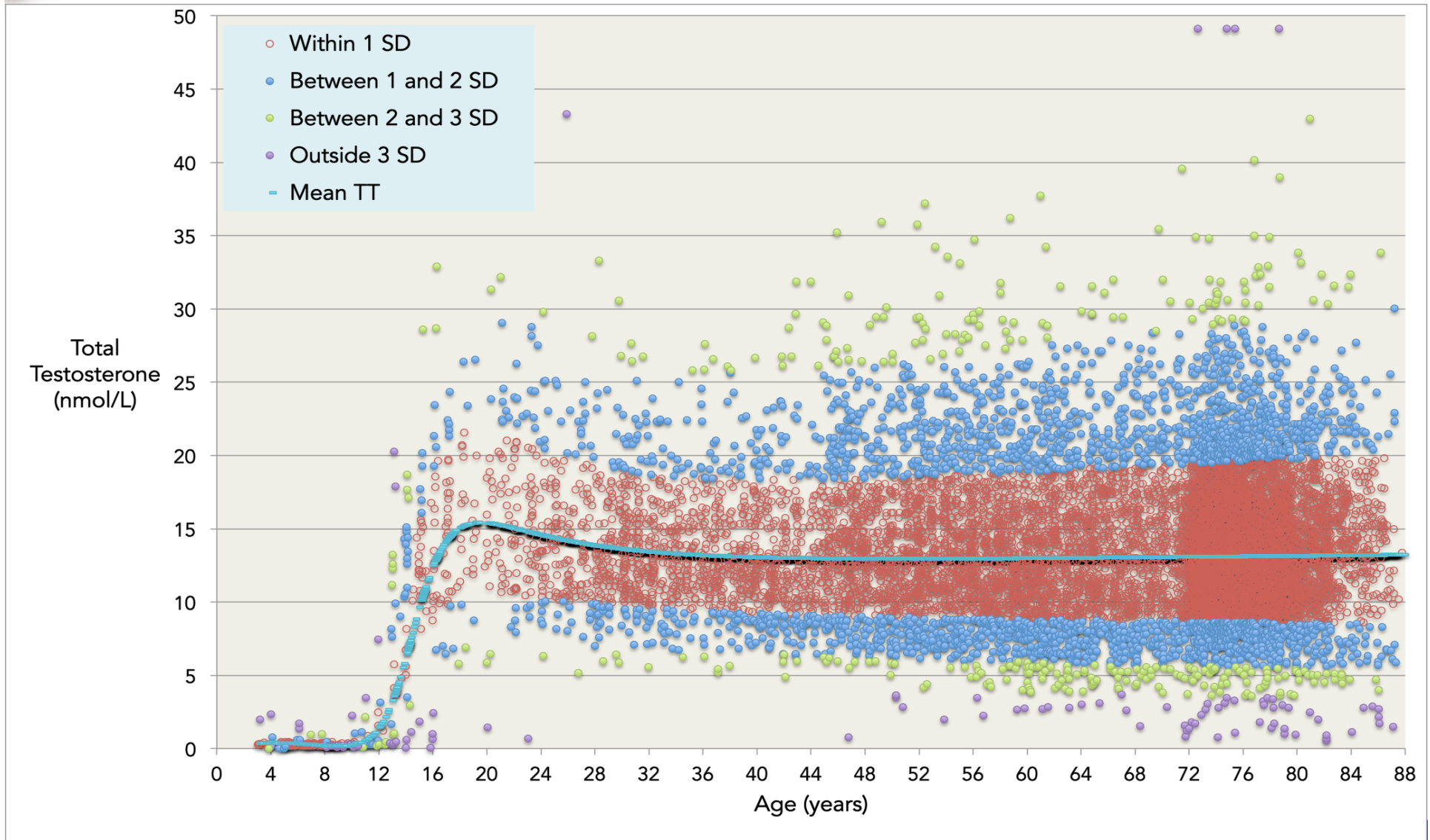


- 10,458 datapoints extracted from 13 studies
- Conversion factors found for assays
- The model quantifies the uncertainty in new TT measurements
 - 68% expected to be within ± 1 SD for that age
 - 95% expected to be within ± 2 SD ...
 - 99% ... within ± 3 SD ...

Kelsey T.W. et al., **A validated age-related normative model for male total testosterone shows increasing variance but no decline after age 40 years**, PLoS One (2014), in press



Testosterone – Kelsey et al. 2014





- Same idea as the models of variability in organ size
 - Florent de Vathaire, ESLCCC14
- Useful for comparisons of treatment effects to population norms
 - Peter Kaatsch, ESLCCC14
- Replacement for population comparison cohorts
 - Anna Sallfors Holmqvist, ESLCCC14
- Androgen deficiency & assessment of Ovarian Reserve
 - Rod Skinner & Wendy van Dorp, ESLCCC14



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- Faddy MJ, Gosden RG. A mathematical model of follicle dynamics in the human ovary. Hum Reprod. 1995;10(4):770-5.
- Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. Hum Reprod. 2008;23(3):699-708.





- Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS ONE. 2010;5(1):e8772.
- Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-müllerian hormone from conception to menopause. PLoS ONE. 2011;6(7):e22024.
- Fleming R, Kelsey TW, Anderson RA, Wallace WH, Nelson SM. Interpreting human follicular recruitment and antimüllerian hormone concentrations throughout life. Fertil Steril. 2012;98(5):1097-102.



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- Wallace WH, Kelsey TW, Anderson RA. Ovarian cryopreservation: experimental or established and a cure for the menopause?. Reprod Biomed Online. 2012;25(2):93-5.
- Kelsey TW, Dodwell SK, Wilkinson AG, et al. Ovarian volume throughout life: a validated normative model. PLoS ONE. 2013;8(9):e71465.



Thank You

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Any questions?

