THE DYNAMICS OF OVARIAN RESERVE

March 2010

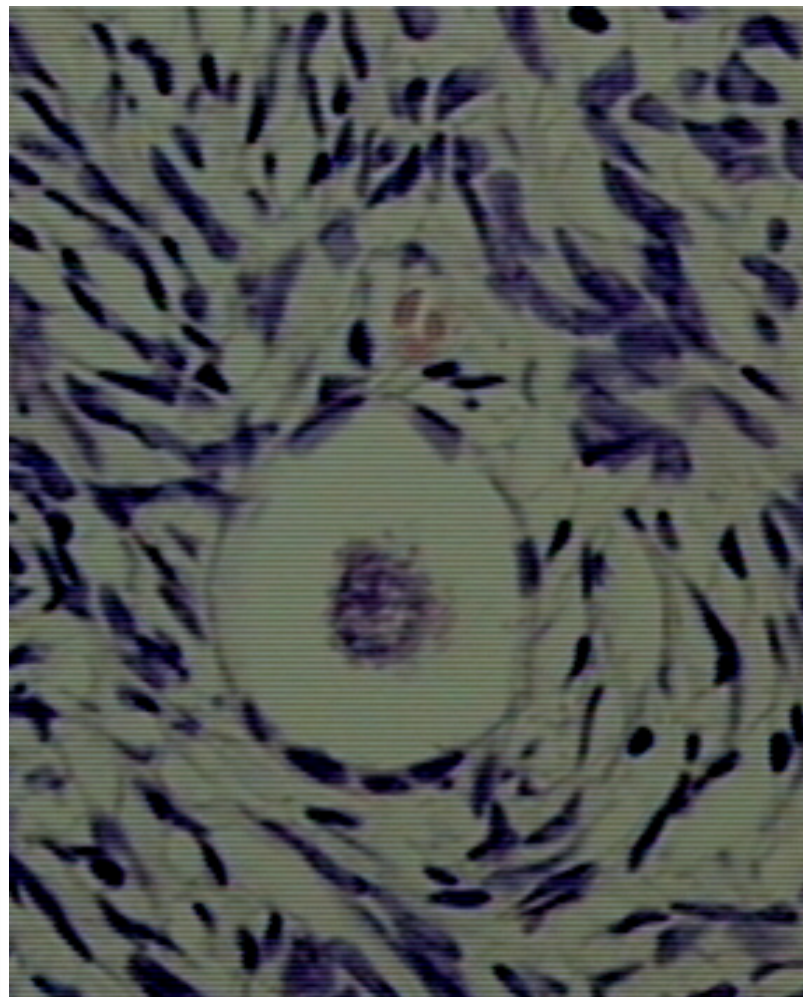**Tom Kelsey**   University of St Andrews, Scotland

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ISCB - Montevideo

Ovarian reserve

- The human ovary contains a fixed number of non-growing follicles (NGFs) established before birth that declines with increasing age
  - culminating in the menopause at 50–51years
  - when about 1,000 NGFs remain

Previous models

- Exponential decline from a population of 1 million at birth

    - Wallace, WHB, Shalet S.M., Hendry, JH. et al. (1989a) Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. Br J Radiol., **62**, 995-8.

- Bi-exponential decline, rate increasing at 37 years

    - after histological evidence of faster decline in the years before menopause

    - no biological justification for this change

    - Faddy, M.J., Gosden, R.G., Gougeon, A., et al. (1992) Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod **7**(10),1342-6.

(More plausible) previous models

- **Faddy & Gosden, 1996**

  - combined data from separate histological studies

  - differential equation (without confidence or prediction intervals) for the average case

  - included data from studies of variations in ages at menopause to ensure that their model conformed with menopausal results

  - Faddy,M.J. and Gosden, R.G. (1996) A model conforming the decline in follicle numbers to the age of menopause in women. Hum Reprod., **11**(7),1484-6.

- **Decline only**

(More plausible) previous models

- Hansen *et al.*, 2008

  - single, large-scale histological study

  - n = 122

  - improves on Faddy & Gosden by providing prediction limits

  - accurately predicts ranges of ages at menopause, rather than using these ranges to construct the model

    - Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, et al. (2008) A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. Human Reproduction 23: 699–708.

- Decline only

The Wallace-Kelsey Model
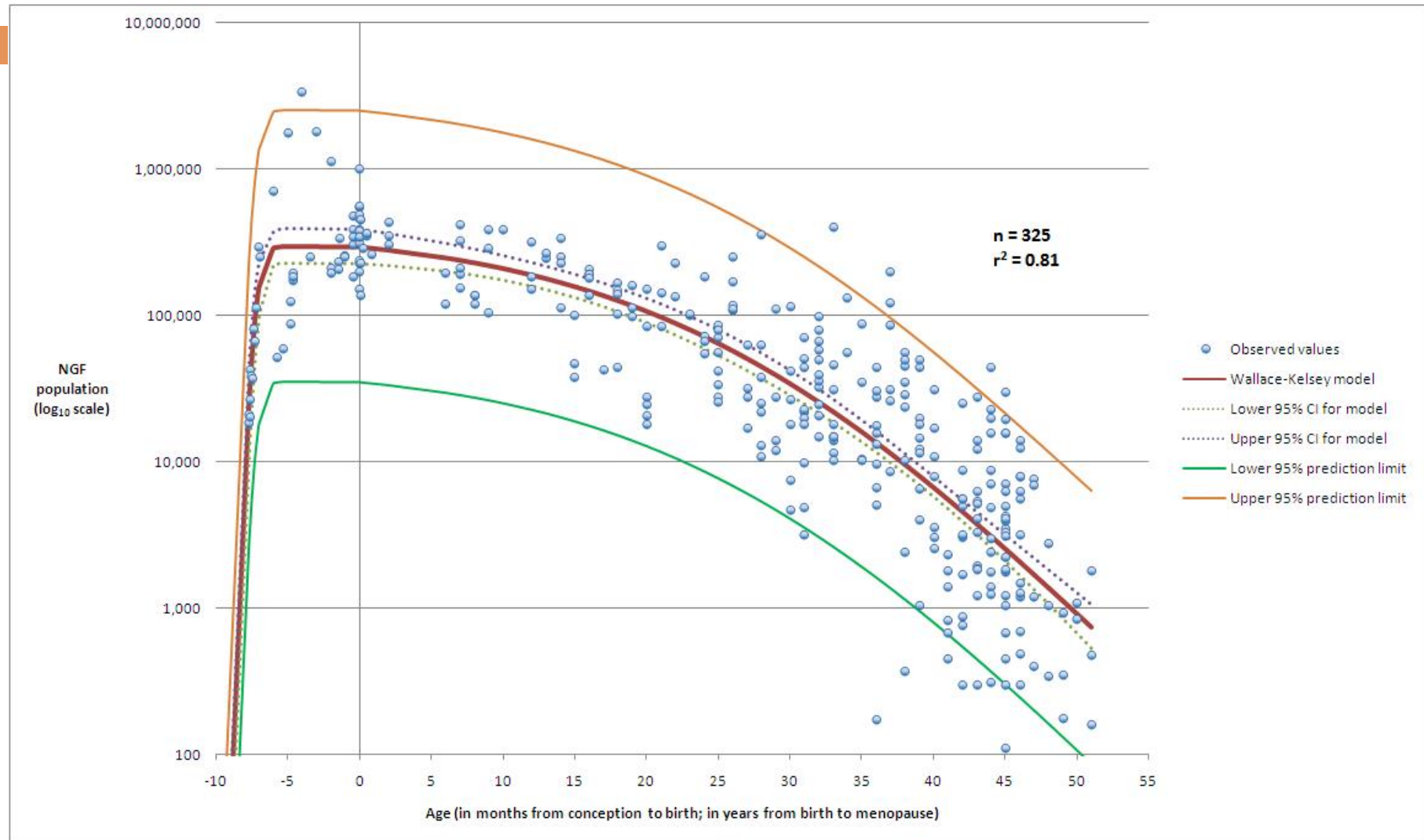
The Wallace-Kelsey Model

$$log_{10}(NGF) = \frac{5.56}{4} \left[1 + \text{Erf} \left(\frac{age + 25.6 + \frac{52.7}{2}}{0.074\sqrt{2}} \right) \right] \left[1 - \text{Erf} \left(\frac{age + 25.6 - \frac{52.7}{2}}{24.5\sqrt{2}} \right) \right]$$

- Asymmetric Double Gaussian Cumulative (ADC) peak model for log-adjusted NGF populations
  - Rapid establishment followed by years of decline
- PLoS ONE 5(1): e8772. doi:10.1371/journal.pone.0008772

Our model

- Based on 8 histological studies
    - Prediction intervals and confidence intervals
    - 81% of variation due to age alone
- Predicts average age of menopause as 49.6 (95% CI 47.9–51.2) years, SD 5.2 years.
    - in agreement with 2 large-scale prospective studies
    - mean age of 50.4 years, SD 3.9 years
    - mean age of 50.2 years, SD 4.2 years

Derivation

- Embarrassingly straightforward

- Combine the datasets, then input to TableCurve 2-D
  - 266 models tested for goodness of fit
  - Our model is the best one

- Re-calculate for datasets missing 50 random points
  - to check that the ADC model best describes datasets of this general type
  - ADC being best fit could have been serendipity
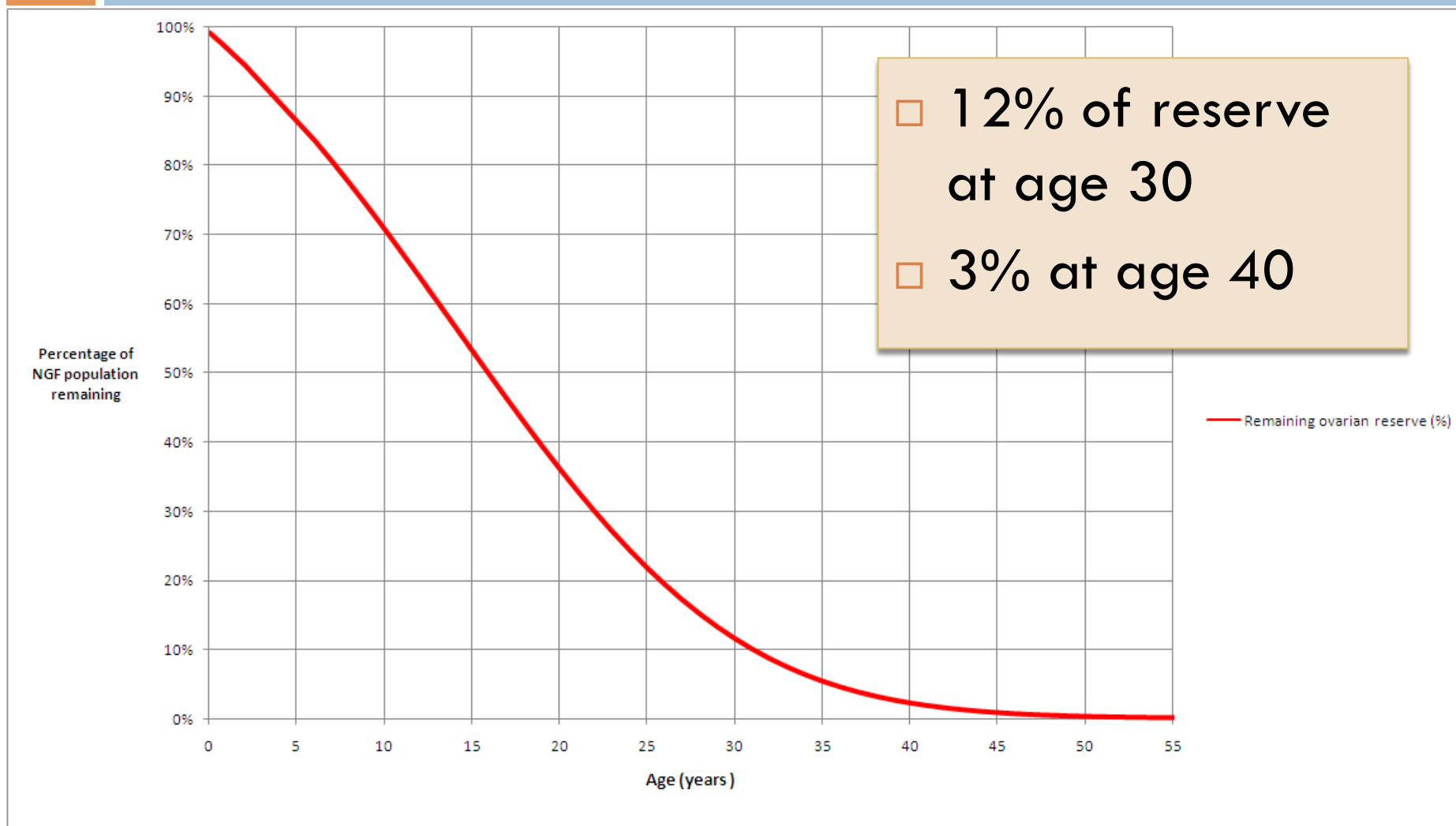 - with another type of model being better in general

Limitations

- The datasets are homogeneous, but are based on an inaccurate method for population estimates
  - we have a study in Uruguay that aims to solve this
- The "dynamics" are nothing of the sort
  - all data is cross-sectional
  - no longitudinal data exists…
  - … or may ever exist
 - we do the best we can with the data and tools available

Analysis of the model

12% of reserve at age 30

3% at age 40

Analysis of the model

All models comparison
Rank 8 Eqn 6070 High Precision Polynomial Order 20
r^2=0.789 DF Adj r^2=0.775 FitStdErr=0.513 Fstat=58.9

- No evidence of stem cells
- Multiple peaks lead to inferior fit

Analysis of the model

Analysis of the model

NGF recruitment - average age at menopause
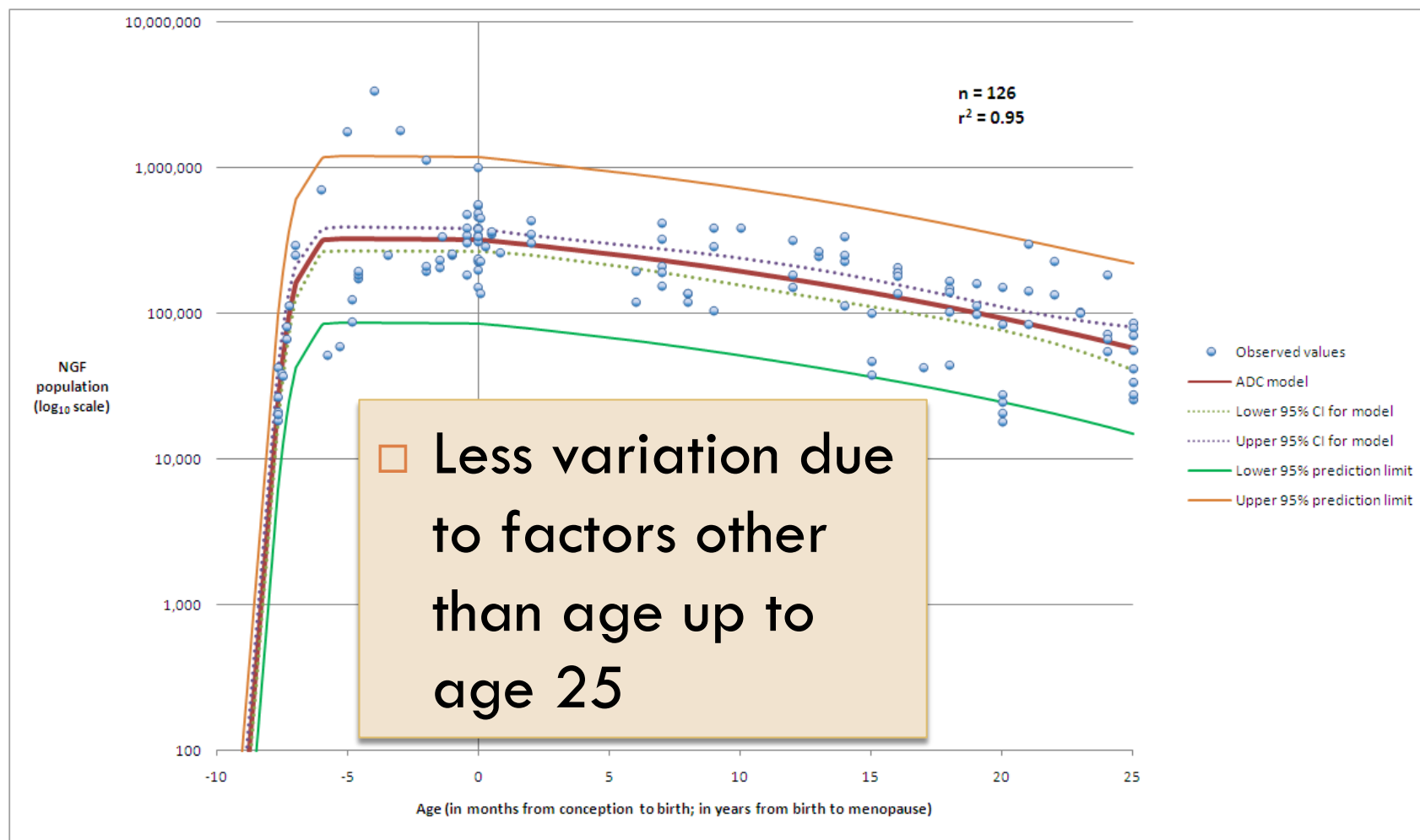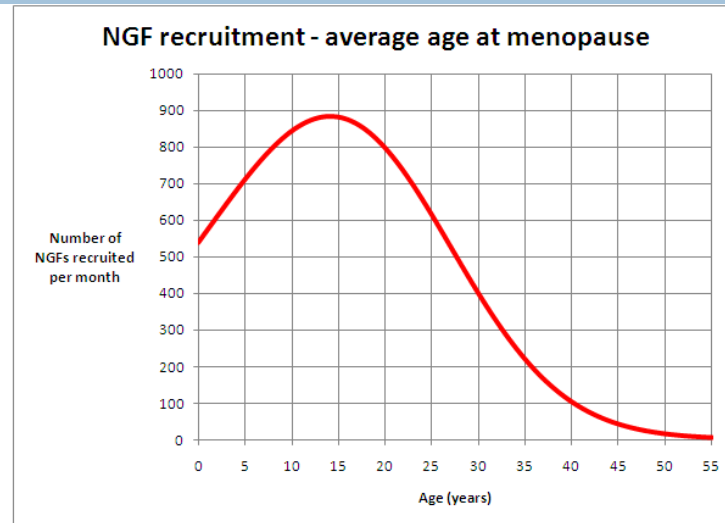
- Recruitment changes at age 14 years
- Probably linked to hormonal changes

NGF recruitment - early age at menopause

NGF recruitment - late age at menopause