Recombinant FSH dosing during controlled ovarian stimulation in IVF treatment

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Background

During IVF treatment, **recombinant FSH (rFSH)** is used to induce **multi-follicular growth (controlled ovarian stimulation; COS).**
Insufficient rFSH dose negatively impacts the number of oocytes retrieved, whereas *excessive* dose risks the potentially life-threatening complication **ovarian hyperstimulation syndrome (OHSS).**
Hence, appropriate **rFSH dosing** is regarded as **a key treatment decision** affecting both the **success** and **safety** of IVF treatment.
Current dosing calculators for rFSH are derived to number of oocytes retrieved, however we investigated whether rFSH dosing can more accurately predict follicular growth.

Aims

- Evaluate pharmacokinetics of rFSH by assessing serum FSH level.
- Identify dose-response relationships between rFSH dose and follicular growth.
- Determine the impact that rFSH dose adjustment has on follicle growth and number of mature oocytes retrieved.

Methods

A single centre retrospective cohort study of 1,034 cycles (Jan 2012-Jan 2016) at Hammersmith IVF unit, where rFSH (GonalF) alone was used to induce follicular growth. Size of each individual follicle at each ultrasound scan and rFSH doses during COS were collated. Parametric groups were compared by ANOVA with post hoc Tukey's and non-parametric data by Kruskall Wallis test with post hoc Dunn's tests. $*p<0.05$, $**p<0.01$, $***p<0.001$, $****p<0.0001$.

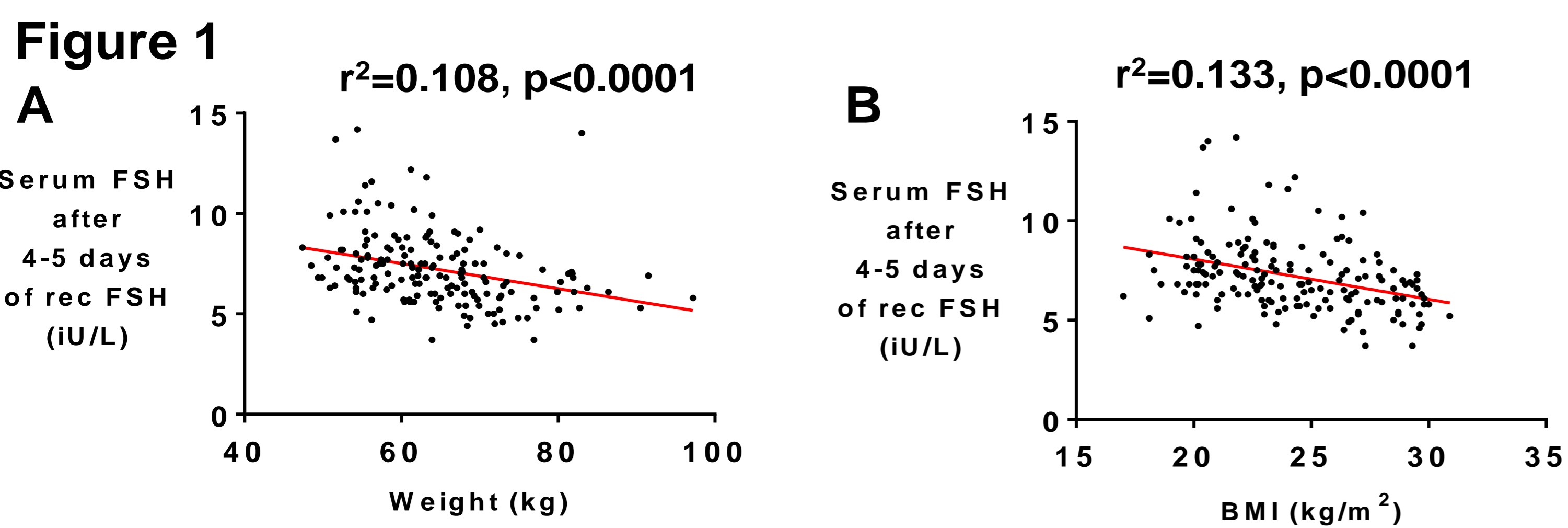## Results – Dose of GonalF adjusted for weight predicts serum FSH level

Figure 1

Figure 1 Simple linear regression of serum FSH level (iU/L) after 4-5 days of GonalF by (A) Weight (kg): $r^2=0.108$, $p<0.0001$; and by (B) BMI (kg/m²) $r^2=0.133$, $p<0.0001$ (n=166).
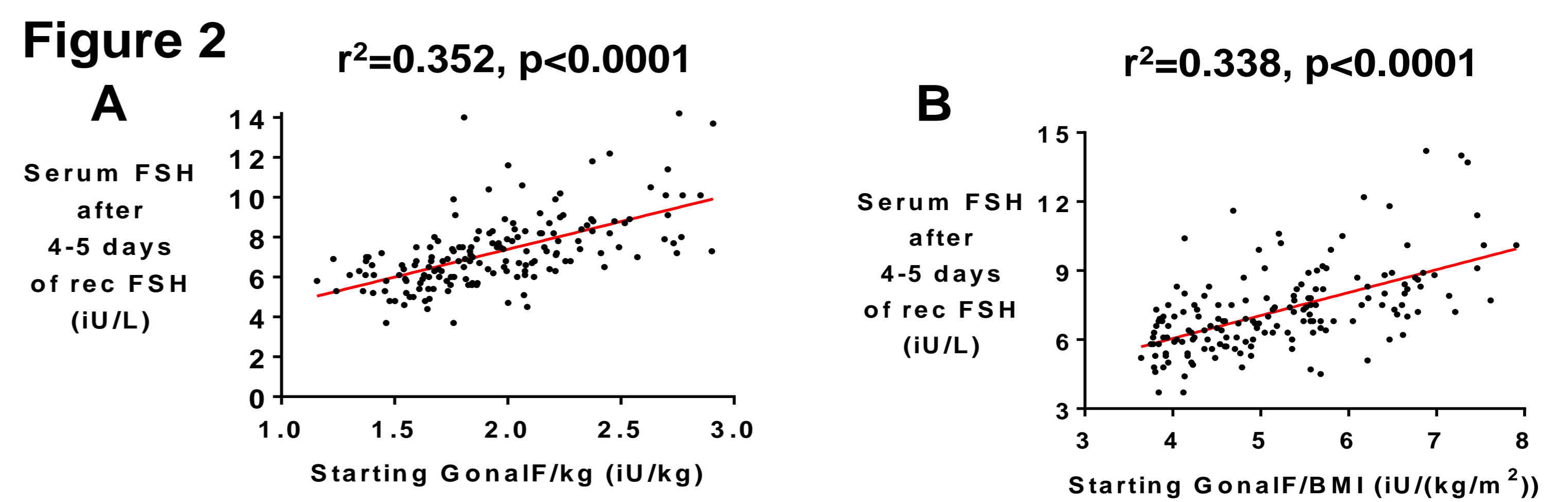
Figure 2

Figure 2: Simple linear regression of serum FSH (iU/L) after 4-5 days of GonalF by (A) starting GonalF dose per kg (iU/kg): $r^2=0.352$, $p<0.0001$; and by (B) starting GonalF dose per unit BMI (iU/(kg/m²): $r^2=0.338$, $p<0.0001$ (n=166).

Results – Dose-response relationship between recombinant FSH dose and follicular growth
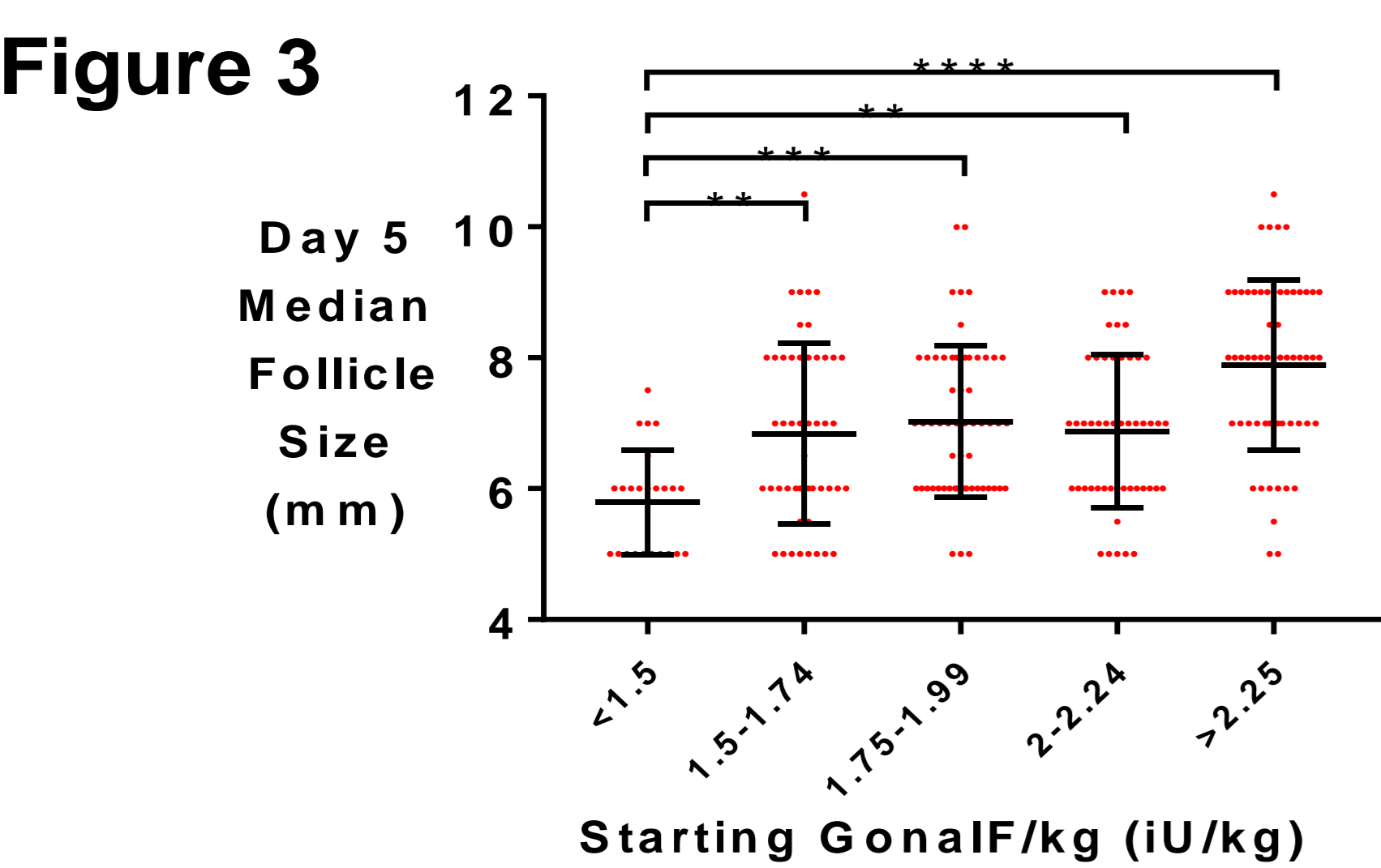
Figure 3

Figure 3: Dose response for rFSH dose: Median follicle size (mm) on day 5 of GonalF (mean ± SD) is determined by starting GonalF dose per kg (iU/kg), in 'good responders' (AFC>15, age<35 years, n=241).
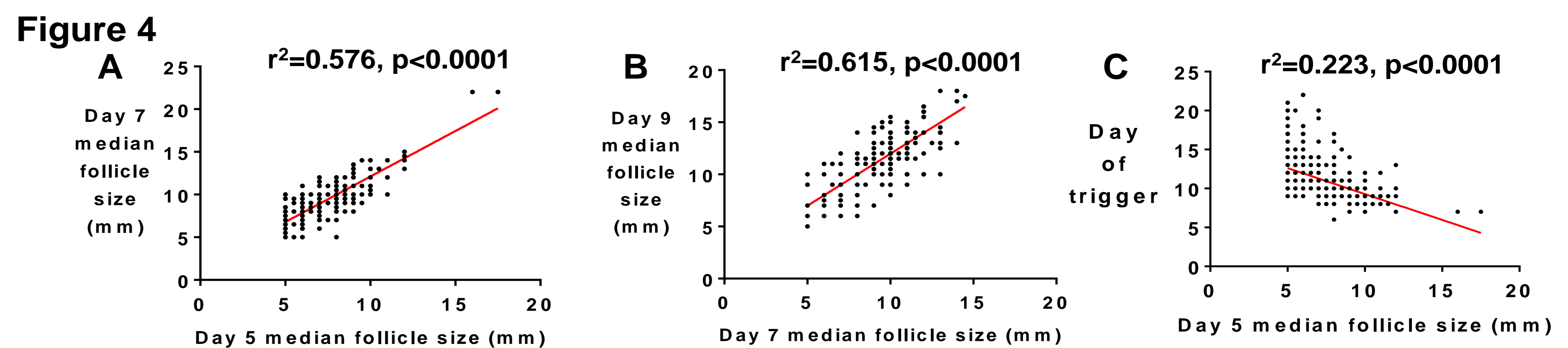
Figure 4

Figure 4: Once follicles are recruited they grow independently. Simple linear regressions of (A) Median follicle size (mm) on day 5 of rFSH treatment predicts follicles size on day 7 (n=351); (B) Median follicle size (mm) on day 7 predicts day 9 (n=260); (C) Median follicle size on day 5 predicts day of administration of oocyte maturation trigger.
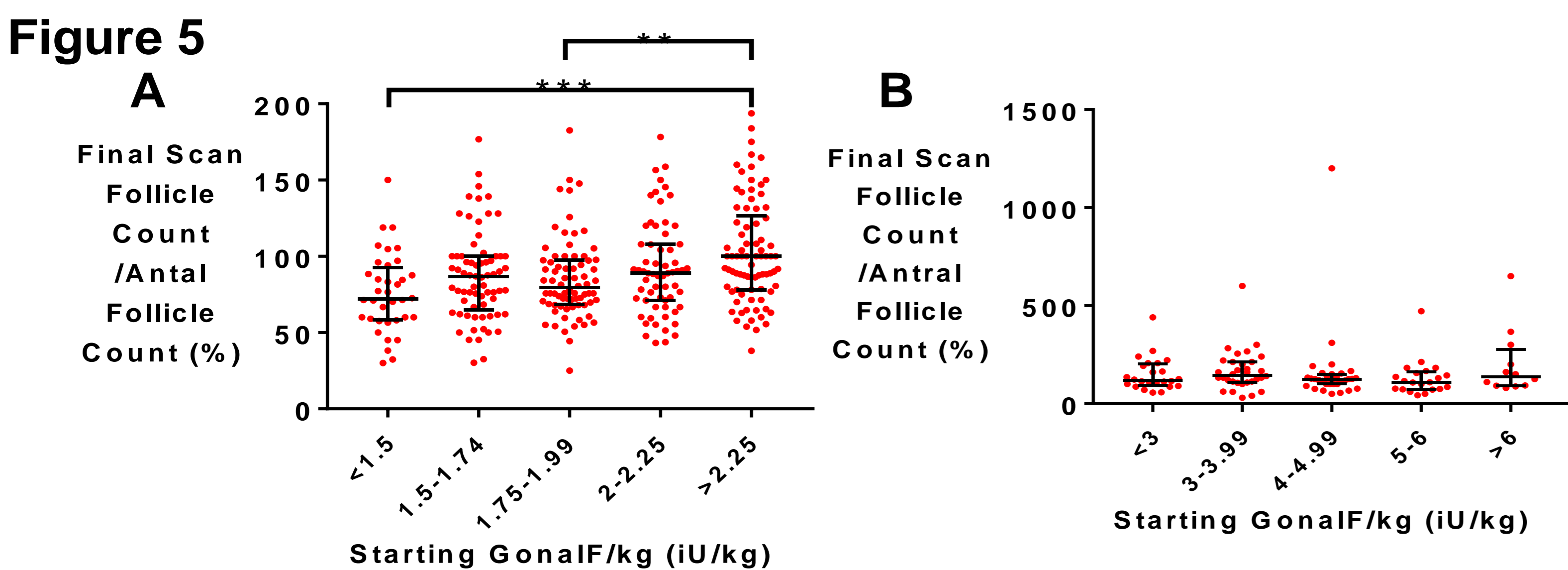
Figure 5

Figure 5: Dose response for rFSH dose: Proportion of the antral follicles (median ±IQR) that grow by starting GonalF dose per kg (iU/kg), in subsets of (A): good responders (AFC>15, age<35 years, n=324) and; (B) poorer responders (AFC≤15, age≥35 years, n=120)

Table 1

Variable	Coefficient	95% CI	p-value
Starting GonalF/kg (iU/kg)	0.058	0.02 to 0.095	0.003
Antral Follicle Count	-0.011	-0.013 to -0.008	0.0001
Pre-treatment screening FSH (iU/L)	-0.007	-0.023 to 0.008	0.36
Age	-0.009	-0.017 to -0.0005	0.038
Constant	1.495	1.205 to 1.784	0.0001

Table 1: Multivariate linear regression analysis of proportion of antral follicles recruited by final ultrasound scan and starting GonalF dose per kg, adjusted for antral follicle count, age, and pre-treatment serum FSH level. (n=431); $r^2=0.22$; $p<0.0001$

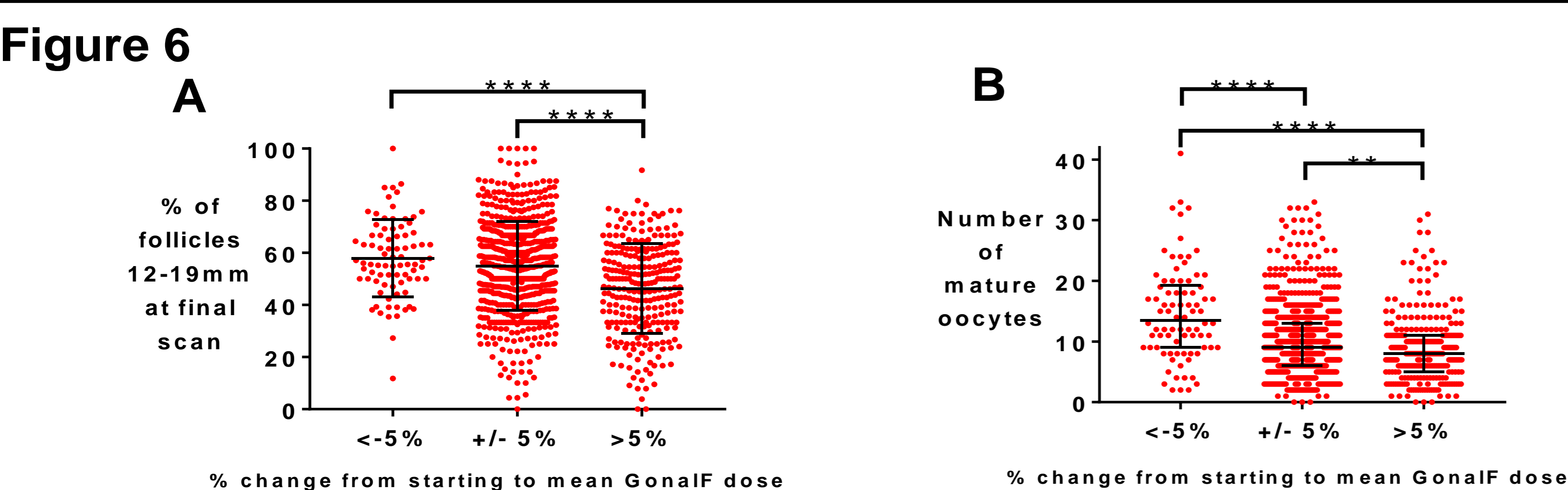## Results – Adjusting rFSH dose and follicle growth

Figure 6

Figure 6: (A) Proportion of follicles of 12-19mm diameter at final scan (mean ±SD) and (B) the number of mature oocytes (median ±IQR); in patients who had at least a 5% reduction in GonalF dose, at least a 5% increase in GonalF dose, or dose adjustment within 5% during the cycle (n=1034)

Conclusion

- *Recombinant FSH should be weight-adjusted.*

- *There is a dose-response relationship for starting GonalF dose at doses between 1.5 and 2.25 IU/kg to median follicle size after 5 days of treatment and to the proportion of antral follicles recruited.*

- *No further increased response beyond an rFSH dose of 2.25iU/kg*

- *Commencing COS with a sufficient starting dose of rFSH is advantageous reducing variability in follicle size and improving the number of mature oocytes retrieved.*

Reproduction

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