

Weight-based prescribing of thiopurines may not accurately optimise metabolite levels in the safe and therapeutic range: A Paediatric IBD study

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Background:

In recent years, a better understanding of thiopurine metabolism has resulted in optimising treatment doses based on the metabolite profiles rather than the conventional weight-based dosing.

For the major metabolite 6-TGN, levels between 235-450 pmol are adopted in IBD treatment guidelines as therapeutic thresholds associated with increased likelihood of efficacy and reduced risk of cytopenias, whereas 6-MMPN > 5700 pmol is associated with hepatotoxicity.

There is a scarcity of paediatric assessing the association of thiopurine metabolite profiles with treatment doses.

Aims:

This study investigates the relationship between weight-based thiopurine dosing and thiopurine metabolite levels in a paediatric IBD cohort.

Methods:

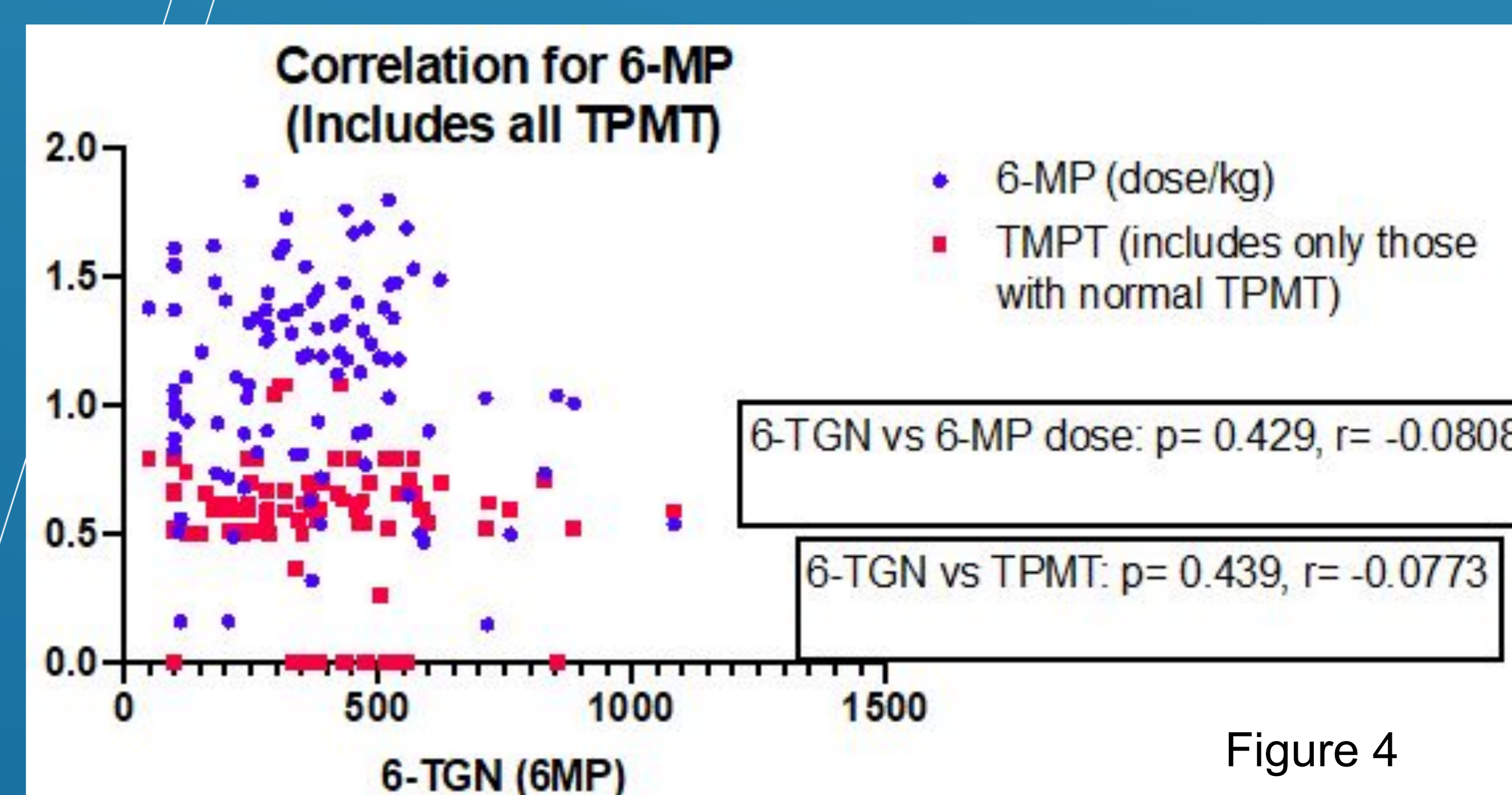
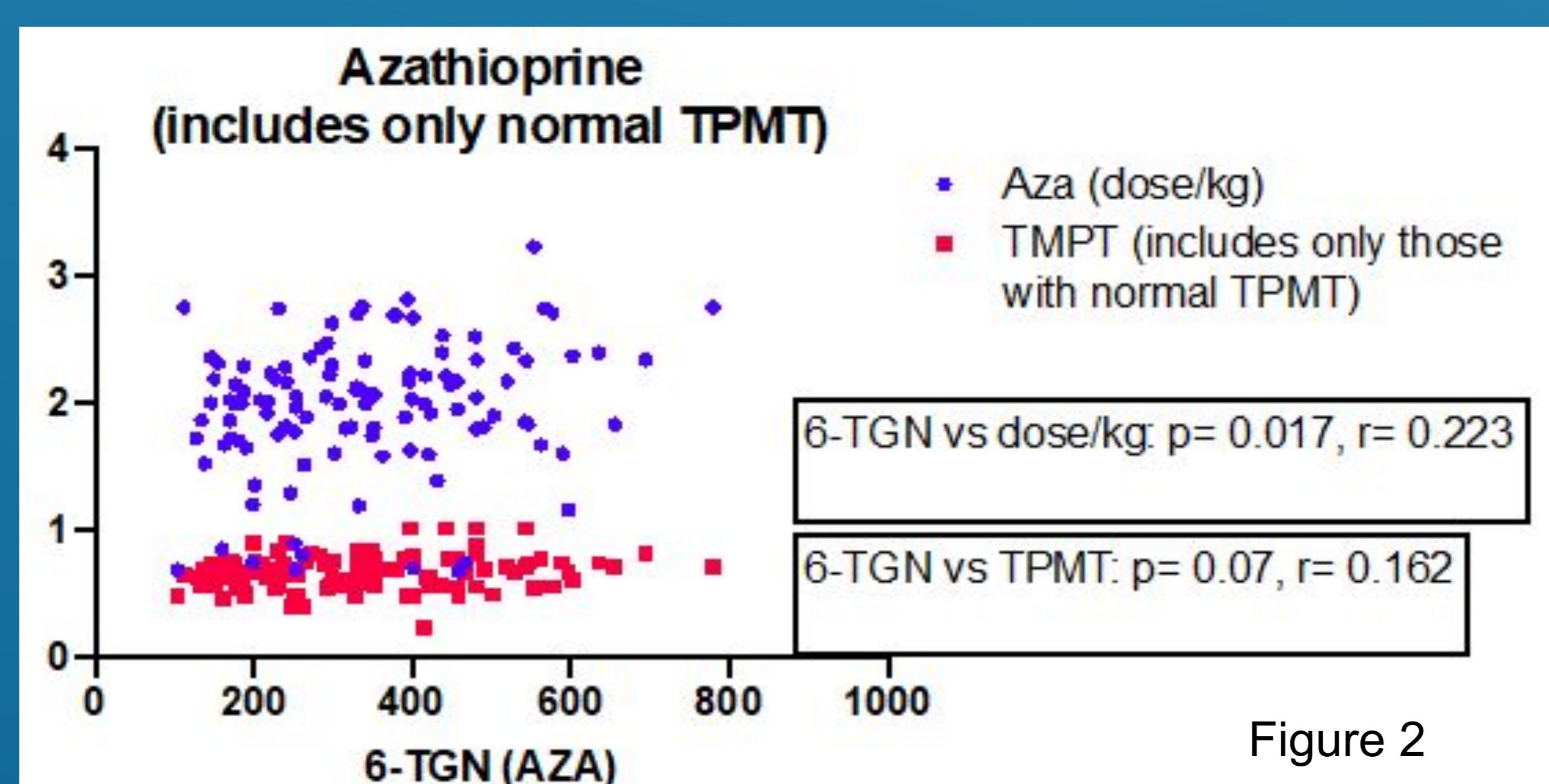
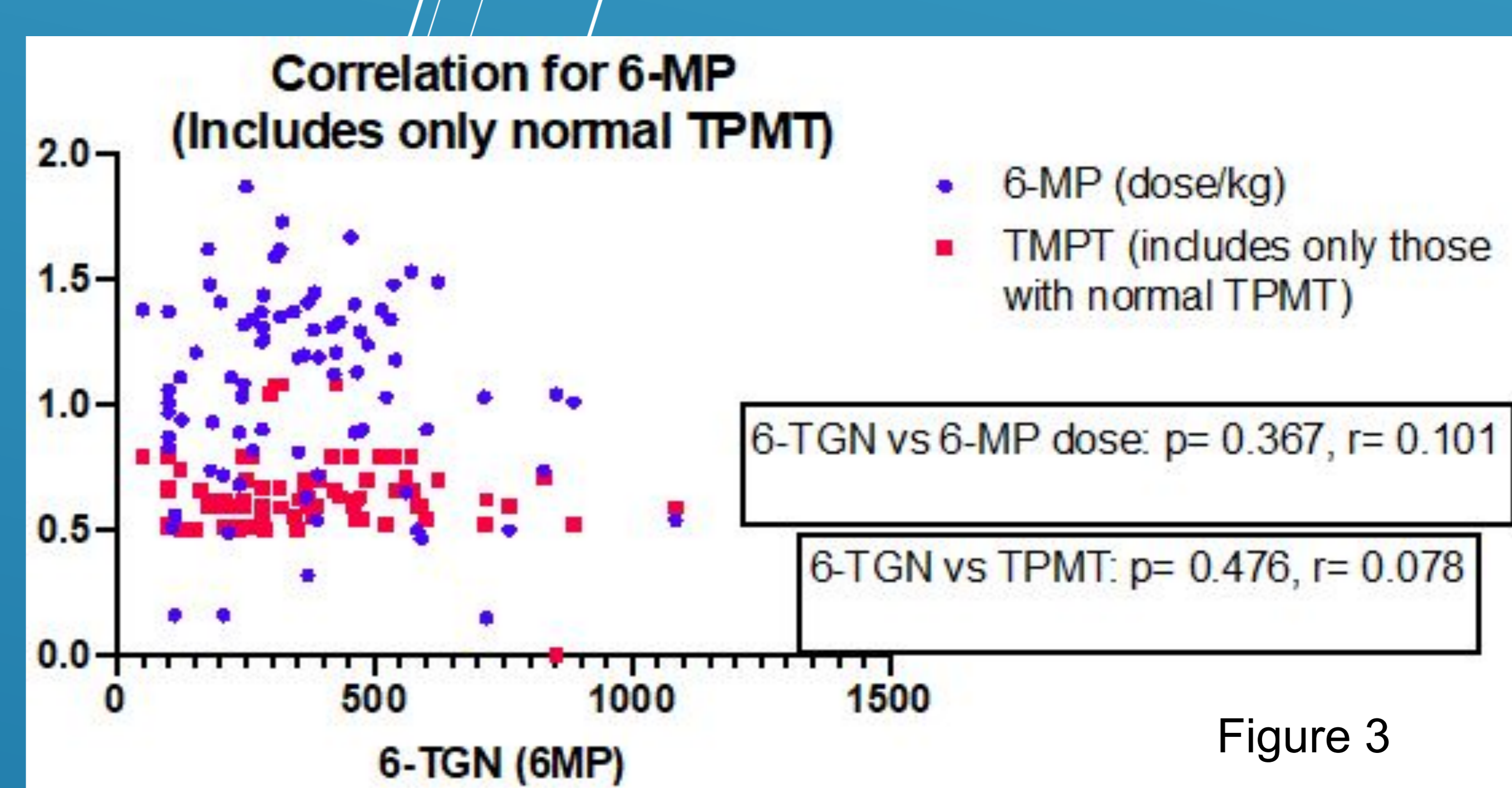
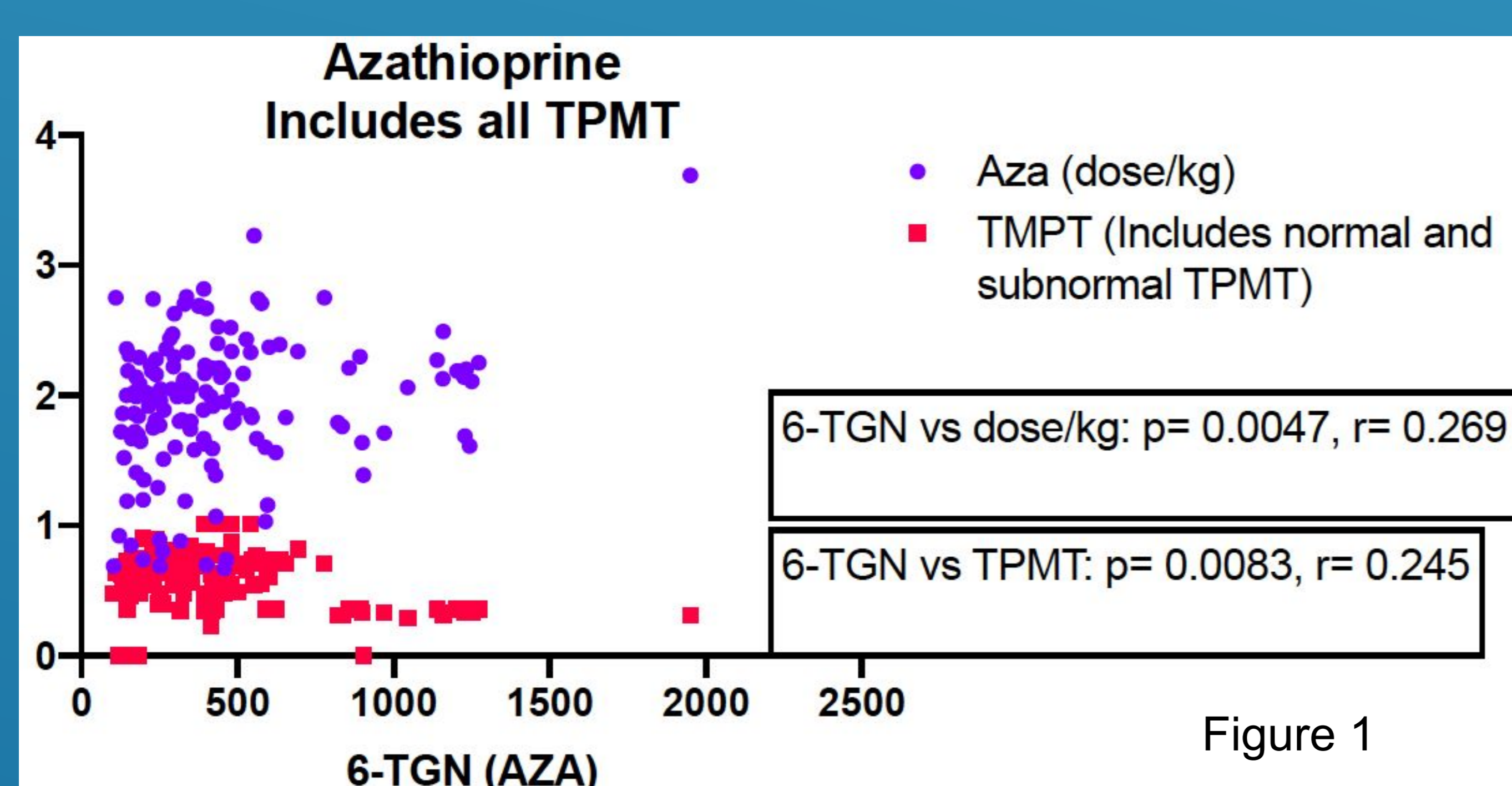
The study included children recruited to the 'Genetics of Paediatric IBD Study- Southampton', diagnosed with IBD before the age of 18 years.

Thiopurine metabolite levels were retrospectively recorded in patients on a stable dose of thiopurines for at least 2 months alongside drug doses adjusted for weight at the time of metabolite testing, TPMT activity and other key descriptive features.

Patients were excluded from the final analysis if concurrent dose and weight measurements were not available at the time of thiopurine metabolite testing. Patients with documented non-compliance were also excluded.

Results:

- A total of 376 IBD paediatric patients were followed for a median of 51 months (IQR 29-81). Males= 218 (58%) and females= 158 (42%).
- A total of 251 readings measuring 6-TGN levels with concurrent dosage (mg/kg) were available in 99 patients. Of those, 69 patients were on Azathioprine (153 measurements) and 30 patients on 6MP (98 measurements).
- The median dose of Azathioprine was 1.99 mg/kg (IQR 1.62- 2.25). Median dose of 6-mercaptopurine 1.19 mg/kg (IQR 0.86- 1.4).
- The median dose of azathioprine and 6-mercaptopurine to achieve 6-TGN levels in the therapeutic range (235-450) was 2.01 mg/kg (IQR 1.64- 2.27, n= 60 measurements) and 1.26 (IQR 0.92- 1.39, n=41) correspondingly.
- In those with normal TPMT activity the median dose observed to exceed the therapeutic upper limit of 450 pmol was very close at 2.11 (IQR 1.7- 2.34, n= 47 measurements) and 1.15 (IQR 0.8-1.45, n= 32 measurements) for azathioprine and 6-mercaptopurine respectively.
- In the azathioprine group: 6-TGN levels correlated positively with the drug dose/kg ($p=0.0047$); 6-TGN levels correlated negatively with TPMT activity ($p= 0.0083$, figure 1), but the association did not reach statistical significance when patients with TPMT activity below the normal reference range were excluded ($p= 0.07$, figure 2).
- In the 6-mercaptopurine group: no significant association was observed for 6-TGN levels with dose/kg ($p= 0.452$) as well as with TPMT activity ($p= 0.439$ including all patients, figure 3, $p=0.476$ for patients with normal TPMT, figure 4).
- No significant gender differences were observed for 6-TGN and 6-MMPN.



Conclusions:

- Our study shows that toxic levels of metabolites can be seen even when thiopurines are prescribed within the 'safe' prescribing dose range and despite normal TPMT levels.
- Thiopurine metabolites should therefore be routinely monitored in all patients treated with thiopurines for better and safer outcomes.