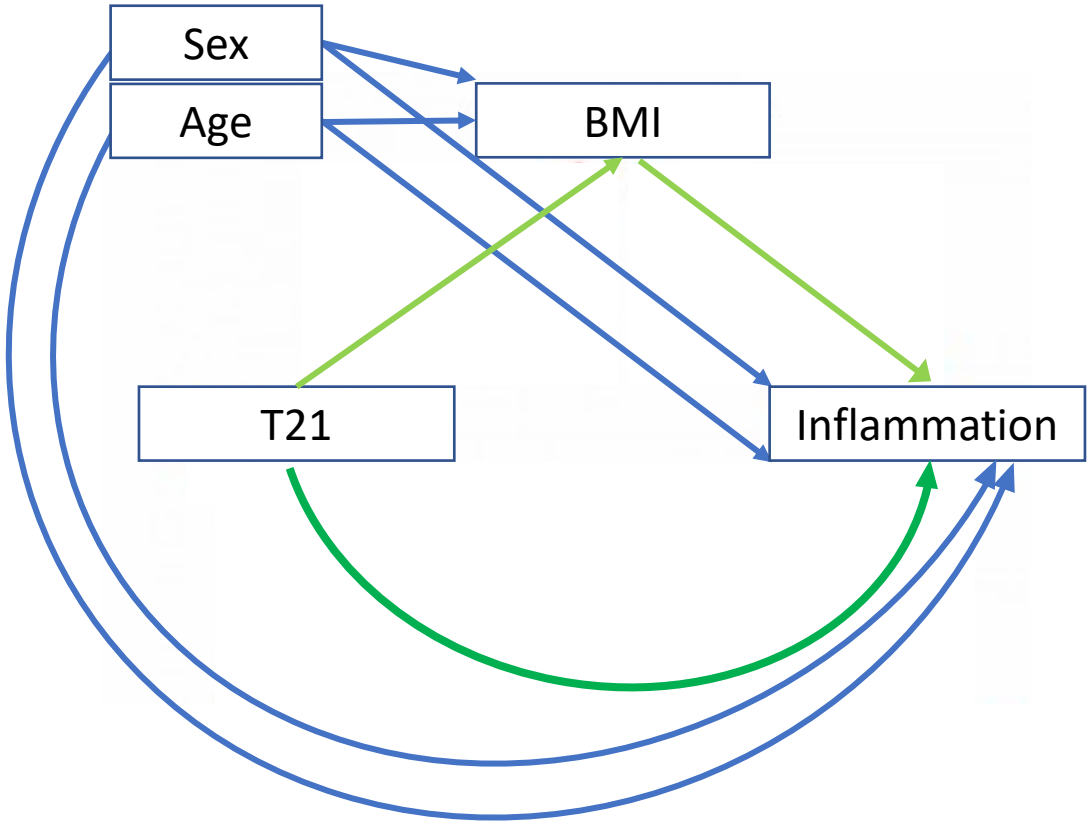
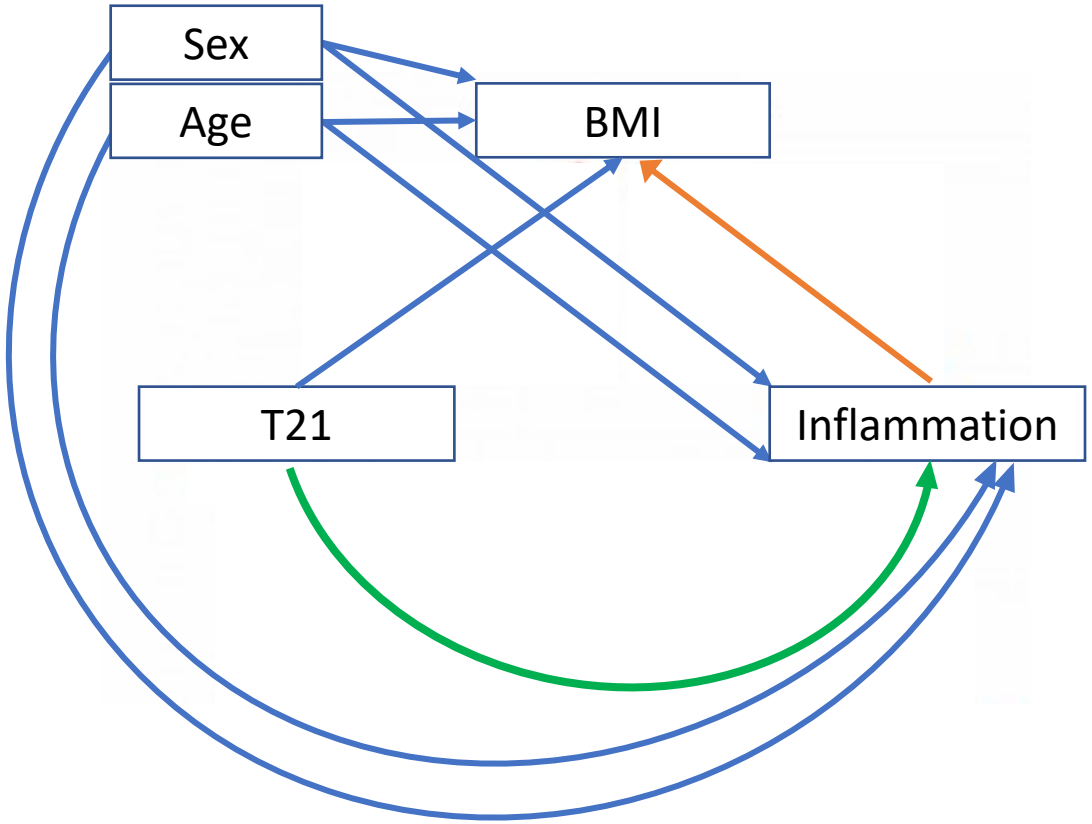
Why we can't treat BMI the same as age and sex

BMI as mediator

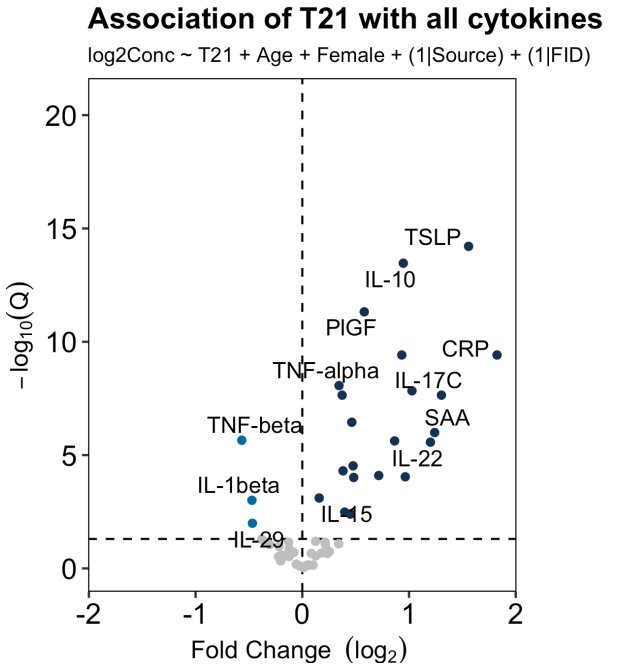


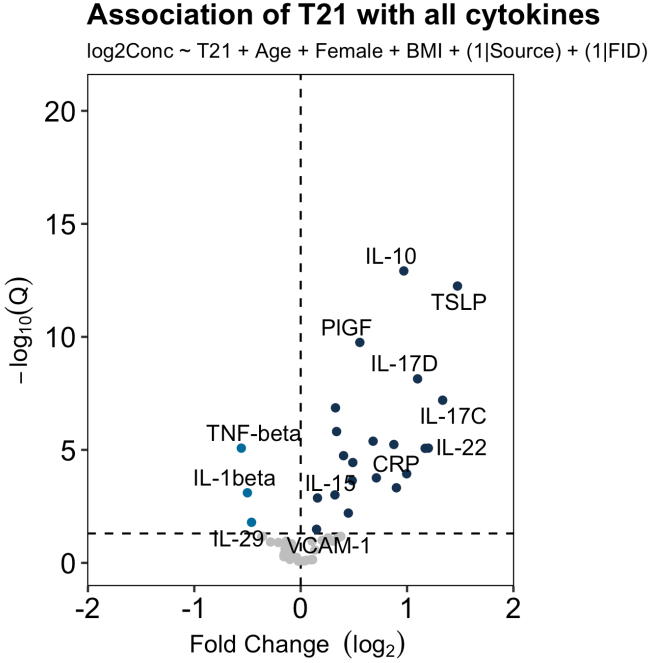
If karyotype influences BMI, and BMI influences log2(Conc.), then BMI is a mediator.

BMI as collider



- If karyotype influences BMI, and log2(Conc.) influences BMI, then BMI is a collider.
- Adjusting for BMI will induce collider bias in the association between T21 and log2Conc.

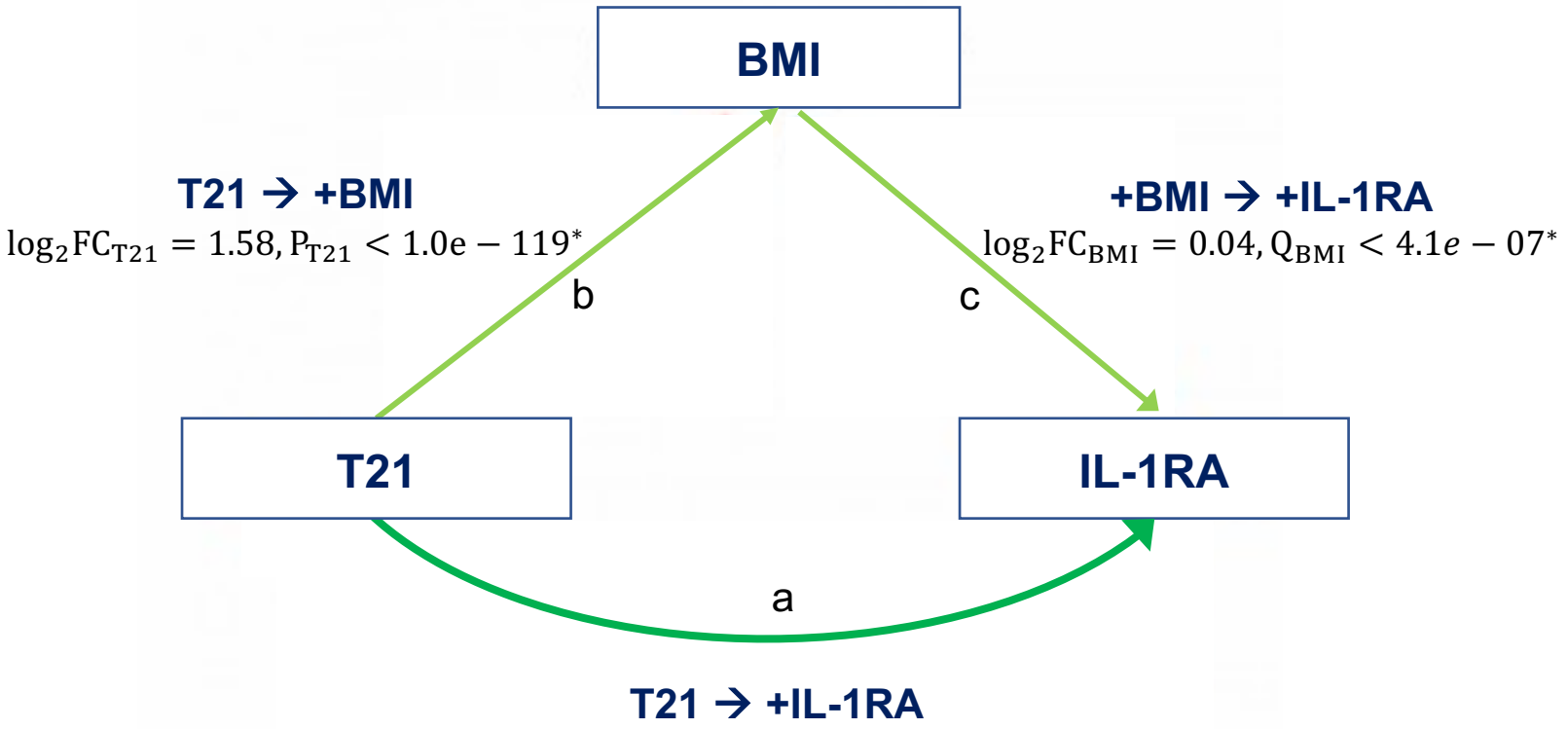




Analyte	log2FC_T21	log2FC_T21_adjBMI	delta_log2FC (%)	Q_T21	Q_T21_adjBMI	Likely role of BMI
IL-1RA	0.40	0.22	-45.1	3.3E-03	1.2E-01	Mediator
CRP	1.82	1.17	-35.9	3.8E-10	8.5E-06	Partial mediator
SAA	1.24	0.90	-27.4	1.0E-06	4.8E-04	Partial mediator
IL-6	0.93	0.68	-27	3.8E-10	4.1E-06	Partial mediator
MIP-1alpha	0.38	0.32	-15.7	5.0E-05	9.8E-04	Partial mediator
VEGF-A	0.46	0.40	-13.1	3.5E-07	1.8E-05	Partial mediator
IL-16	0.37	0.34	-9.5	2.3E-08	1.5E-06	Partial mediator
TSLP	1.56	1.47	-5.4	6.1E-15	5.6E-13	Partial mediator
TNF-alpha	0.34	0.33	-4.9	8.6E-09	1.4E-07	Partial mediator
PIGF	0.58	0.56	-4.2	4.8E-12	1.8E-10	Partial mediator
TNF-beta	-0.57	-0.56	-1.6	2.2E-06	8.4E-06	Partial mediator
IL-29	-0.47	-0.46	-1.2	1.0E-02	1.6E-02	Partial mediator
FGF (basic)	0.72	0.71	-0.7	7.9E-05	1.7E-04	Partial mediator
IL-3	0.45	0.45	-0.4	4.0E-03	6.3E-03	Partial mediator
IL-15	0.16	0.16	-0.3	7.8E-04	1.3E-03	Partial mediator
IL-22	1.20	1.20	-0.1	2.7E-06	8.4E-06	Partial mediator
MIP-3alpha	0.48	0.48	0.6	9.7E-05	2.3E-04	
IP-10	0.86	0.88	1.3	2.4E-06	5.8E-06	
IL-10	0.95	0.97	2.4	3.4E-14	1.2E-13	
IL-17C	1.30	1.33	2.4	2.3E-08	6.4E-08	
IL-8	0.48	0.49	3	3.0E-05	3.6E-05	
IL-9	0.96	1.00	3.3	9.1E-05	1.1E-04	
IL-1beta	-0.47	-0.50	6.1	9.8E-04	7.9E-04	
IL-17D	1.03	1.10	6.9	1.4E-08	7.2E-09	
VCAM-1	0.08	0.15	76.1	2.2E-01	3.3E-02	Effect modifier?

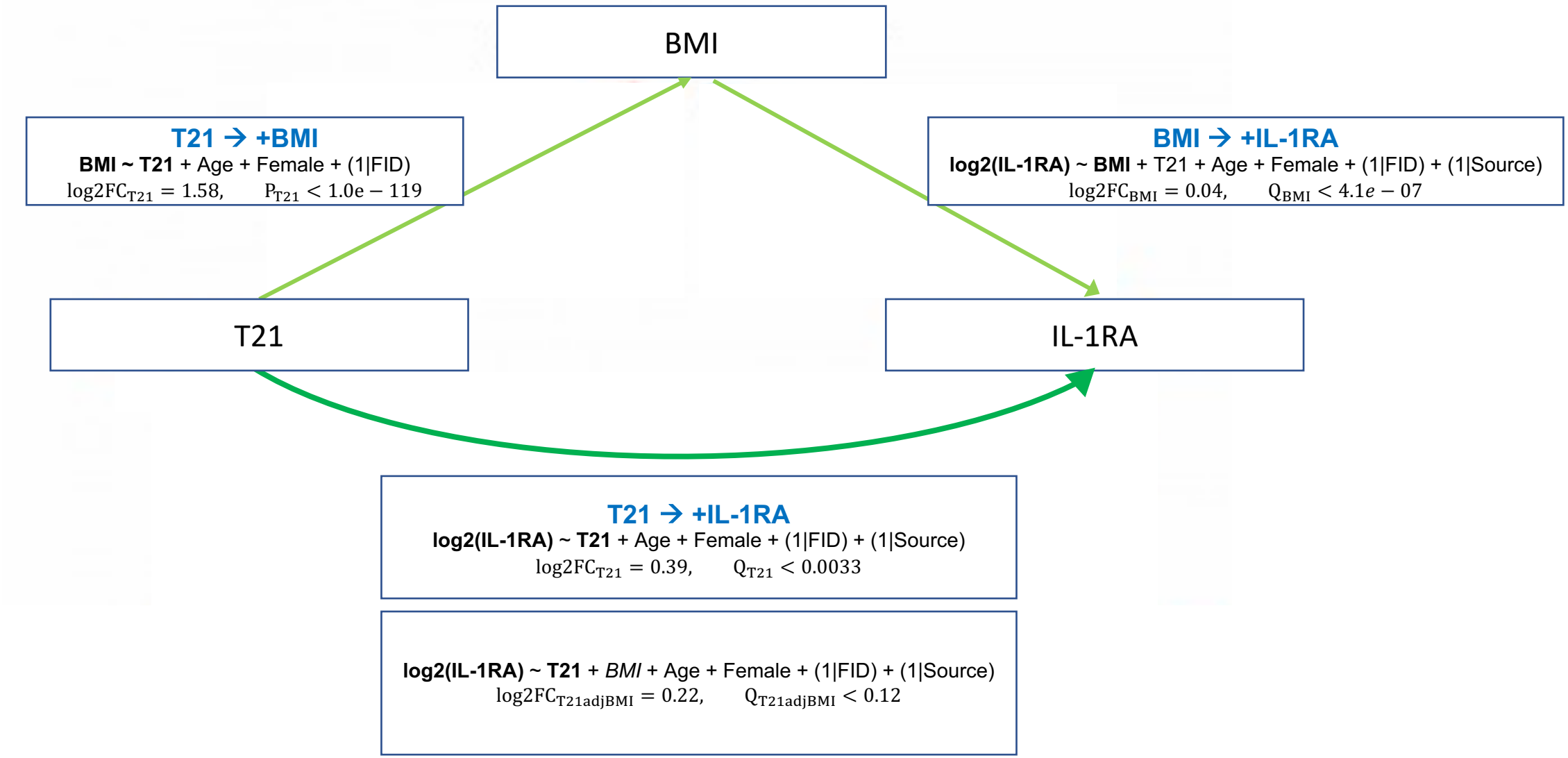
BMI as mediator*

- T21 is associated with a statistically significant increase in IL-1RA (a).
- T21 is associated with statistically significant increase in BMI (b).
- BMI is associated with a statistically significant increase in IL-1RA (c).
- After adjustment for BMI, the estimated effect of T21 on IL-1RA is 45% smaller and this effect is no longer statistically significant (d).
- **45% of the effect of T21 on IL-1RA is mediated by BMI.**



*As defined in Baron and Kenny (1986)

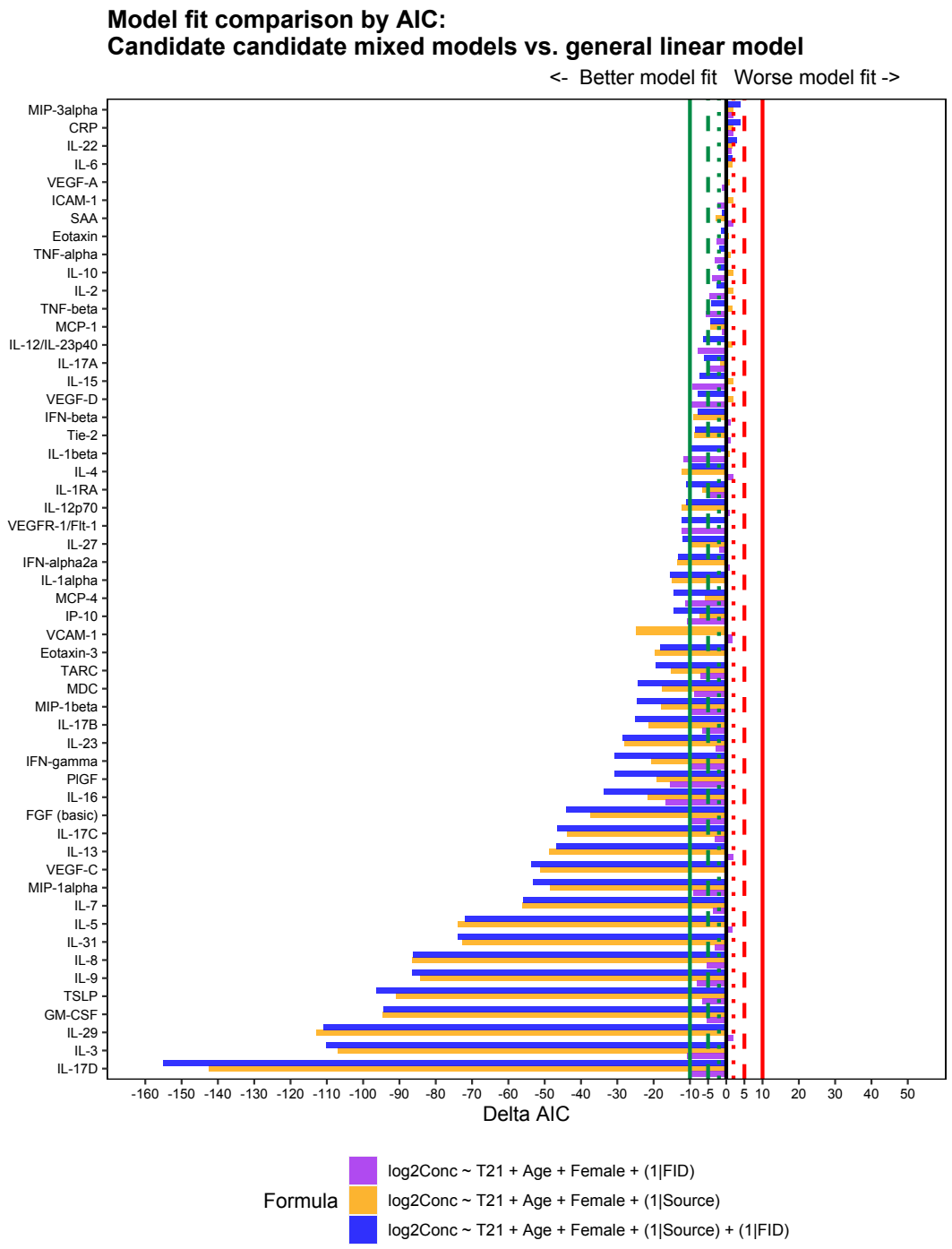
BMI as mediator



Fit of mixed models

vs.

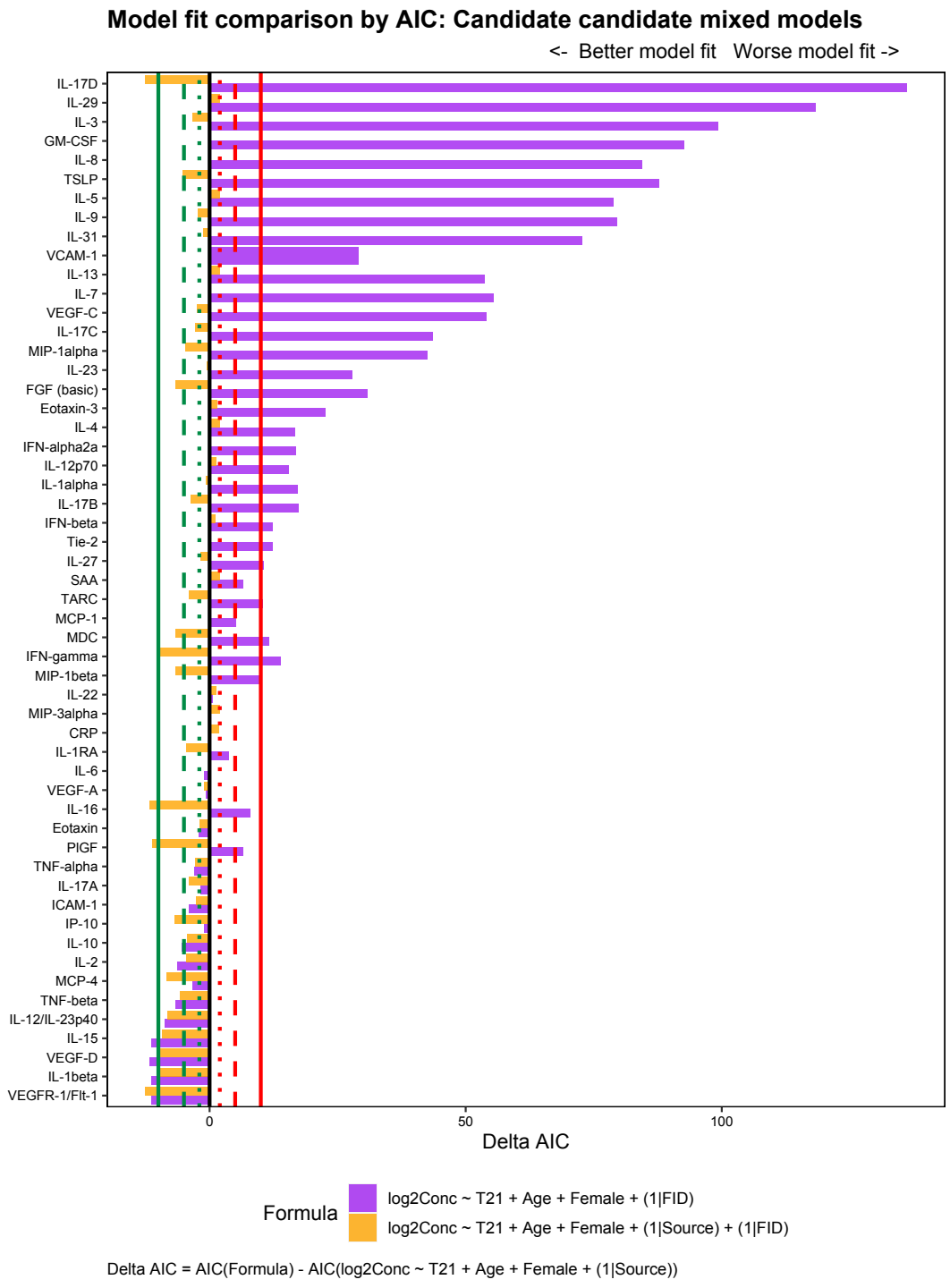
linear model with no random effects (log2Conc ~ T21 + Age + Female)



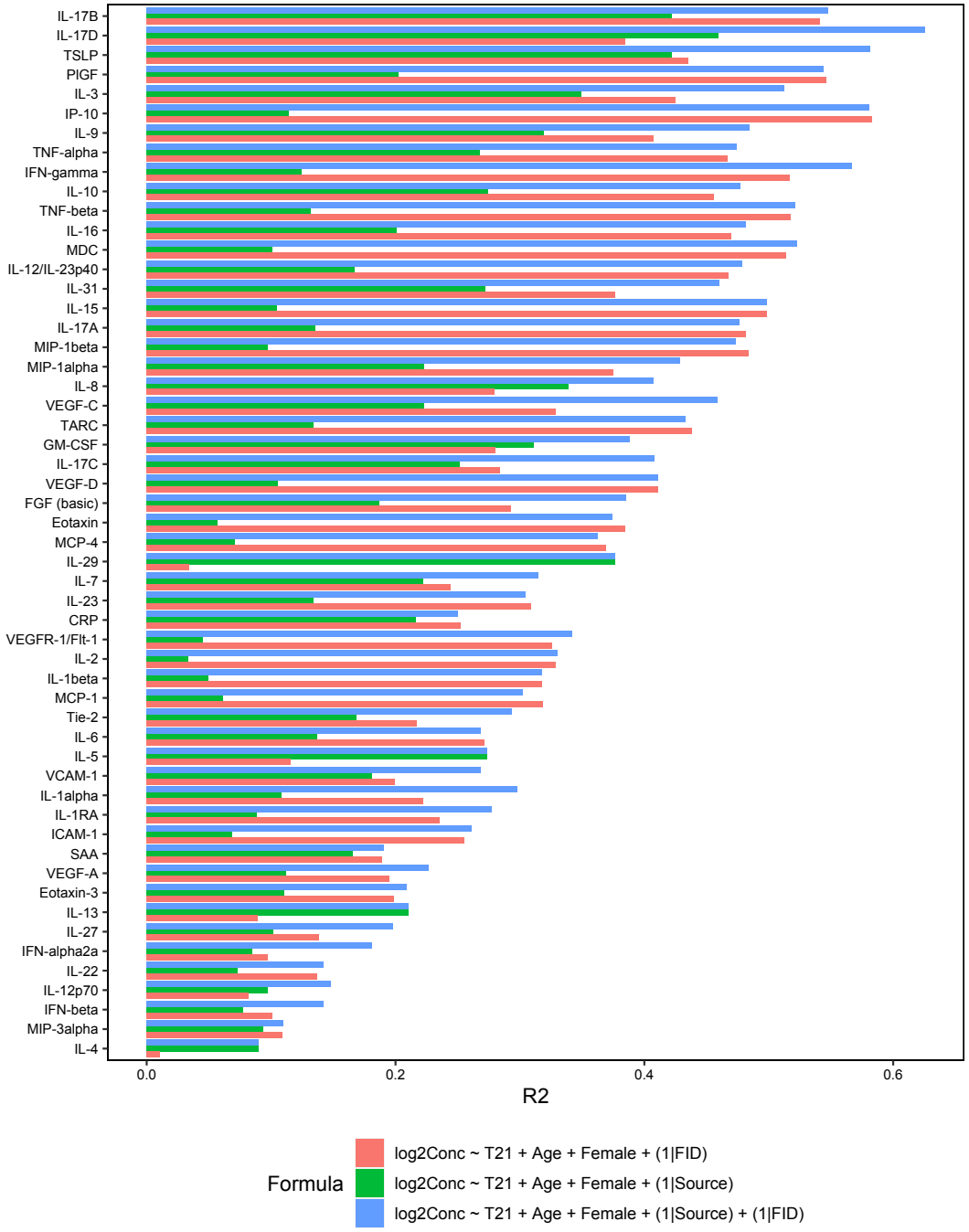
Fit of candidate mixed models

vs.

log2Conc ~ T21 + Age + Female + *(1|Source)*

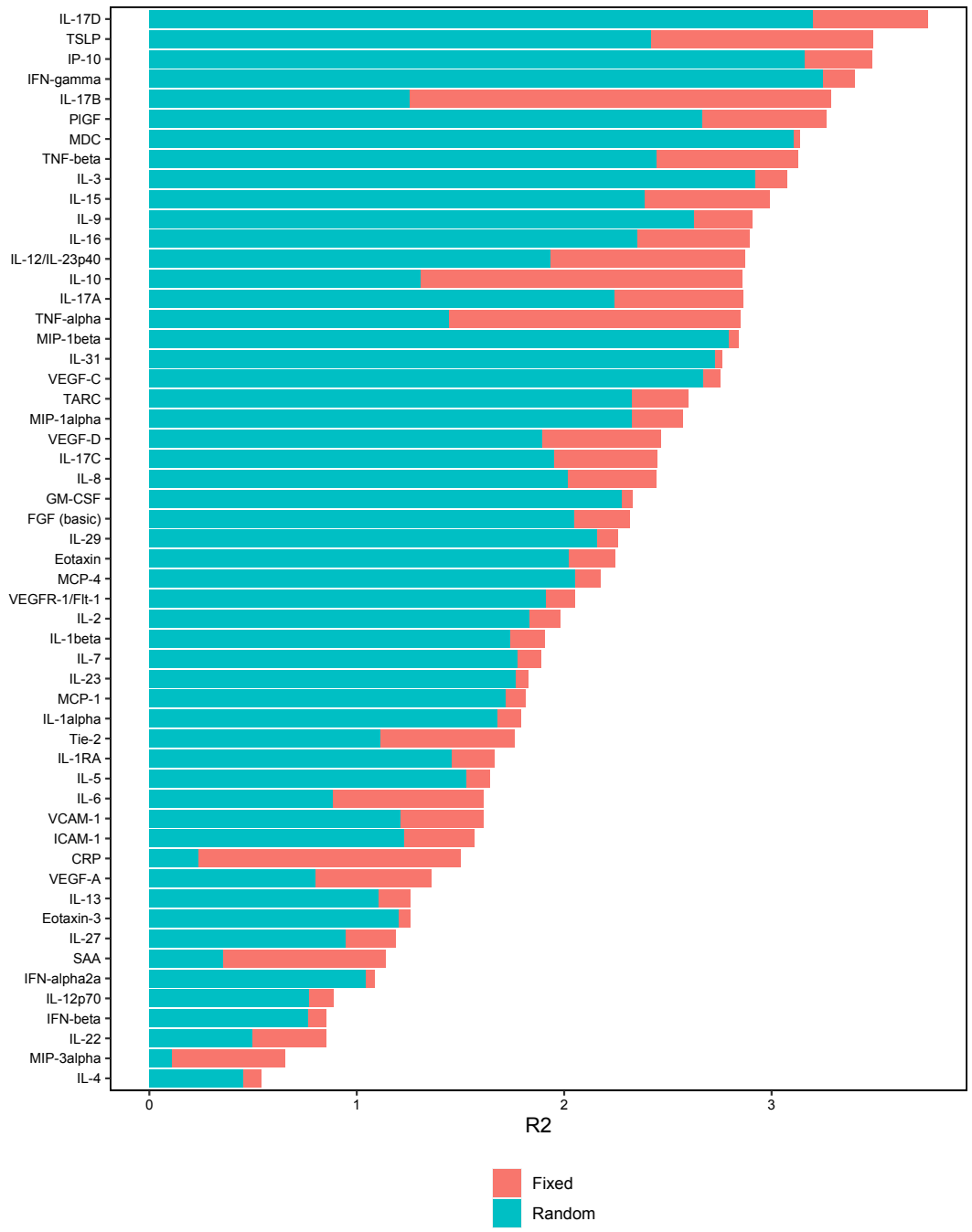


Total proportion of variance explained (R2) by fixed and random effects combined



Proportion of variance explained (R2) by fixed vs. random effects

Model formula: log2Conc ~ T21 + Age + Female + (1|Source) + (1|FID)



Proportion of variance explained by each candidate random effect