Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants

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Paper and Collaborators

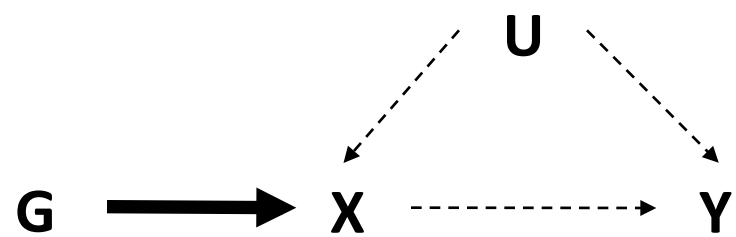
Pierce, B.L., Ahsan, H., and VanderWeele, T.J. (2011). Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *International Journal of Epidemiology, 40:740-752.*

Mendelian Randomization (MR)

Genes as instrumental variables

- **<u>Goal of MR:</u>** estimate causal effect of X on Y, using data on a known genetic determinant (G) of X

- Need data on G, X, and Y
  - But not U (if assumptions hold)



- Key MR assumptions: The IV (G) is
  - (1) associated with X
  - (2) independent of X-Y confounders (U)
  - (3) independent of Y given X and U (X-Y confounders)

What will be the implications for Mendelian Randomization of…

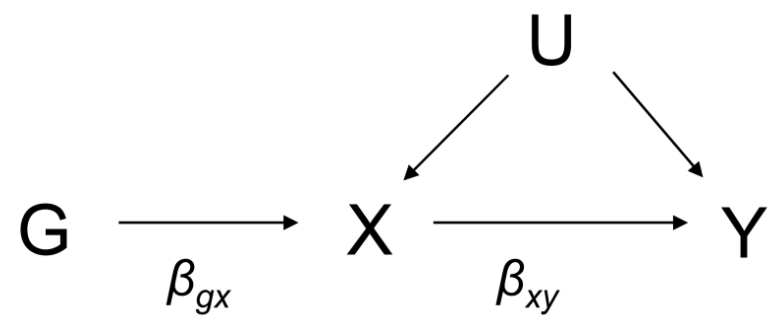
1. More potential IVs
2. Using knowledge of genetic architecture

<u>Goal of this work</u>:

Evaluate power and IV strength requirements for MR studies that utilize multiple variants

Methods for Simulations

- Simulate data on a gene (G), exposure (X), and outcome (Y)
  - G is biallelic, X and Y ~N(0,1)
  - With and without confounding (U)
  - 10,000 datasets



- Vary parameters:
  - f(G), β_{gx}, β_{xy}, n, β_{ux}, β_{uy}

- Two-stage least squares regression (2SLS)
  - Stage 1: regress X on G (the IV)
  - Stage 2: regress Y on fitted X values
  - Equivalent to the "Wald Estimator"

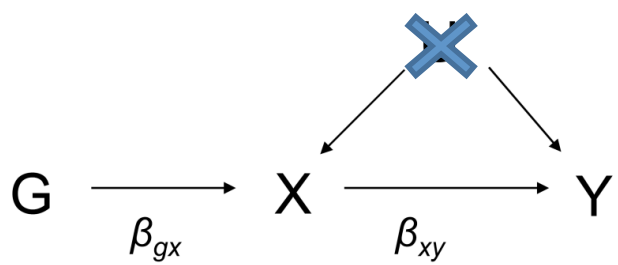
Wald Estimator:

$$\hat{\beta}_{MR} = \frac{\hat{\beta}_{gy}}{\hat{\beta}_{gx}}$$

- Retain F statistic from the first-stage regression
  - Rule of thumb: A "strong IV" has F>10 (Stock et al, 2002)
  - Weak IVs bias towards the confounded OLS estimate
- Retain estimates and p-values from stage 2, determine empirical power

Power estimates for MR with a single IV

	n=1,000				n=5,000				n=10,000			
β_{gx}	F	β_{xy}			F	β_{xy}			F	β_{xy}		
		0.1	**0.3**	**0.5**		**0.1**	**0.3**	**0.5**		**0.1**	**0.3**	**0.5**
***f(g)* = 0.1**												
0.1	1.8	0.00	0.02	0.06	9.2	0.02	0.13	0.31	17.8	0.05	0.24	0.55
0.3	16.1	0.04	0.24	0.52	81.8	0.15	0.78	**0.98**	>100	0.25	**0.96**	**1.00**
0.5	46.2	0.10	0.51	0.88	>100	0.30	**0.99**	**1.00**	>100	0.58	**1.00**	**1.00**
***f(g)* = 0.3**												
0.1	4.1	0.01	0.04	0.13	20.8	0.07	0.27	0.61	41.5	0.09	0.49	**0.88**
0.3	37.9	0.08	0.46	**0.84**	>100	0.27	**0.99**	**1.00**	>100	0.51	**1.00**	**1.00**
0.5	>100	0.18	**0.85**	**1.00**	>100	0.65	**1.00**	**1.00**	>100	**0.90**	**1.00**	**1.00**
***f(g)* = 0.5**												
0.1	5.1	0.02	0.07	0.16	25.0	0.07	0.33	0.69	49.5	0.09	0.57	**0.92**
0.3	45.1	0.10	0.53	**0.89**	>100	0.31	**0.99**	**1.00**	>100	0.56	**1.00**	**1.00**
0.5	>100	0.19	**0.91**	**1.00**	>100	0.73	**1.00**	**1.00**	>100	**0.94**	**1.00**	**1.00**



Power estimates for MR with a single IV

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β_{gx}	F	β_{xy}			F	β_{xy}			F	β_{xy}		
		0.1	0.3	0.5		0.1	0.3	0.5		0.1	0.3	0.5
f(g) = 0.1												
0.1	1.8	[illegible]	[illegible]	[illegible]	23.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.24	0.55
0.3	16.1	0.04	0.24	0.52	81.8	0.15	0.78	**0.98**	>100	0.25	**0.96**	**1.00**
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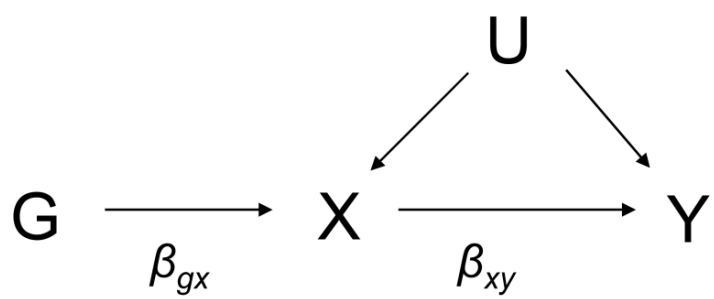
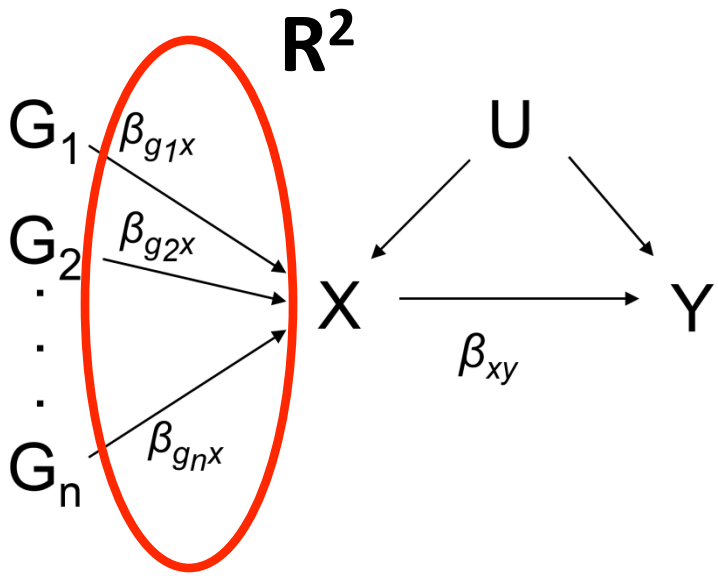
Well-powered scenarios (>80%) and weak IV scenarios (F<10) are mutually exclusive (for this single IV scenario)

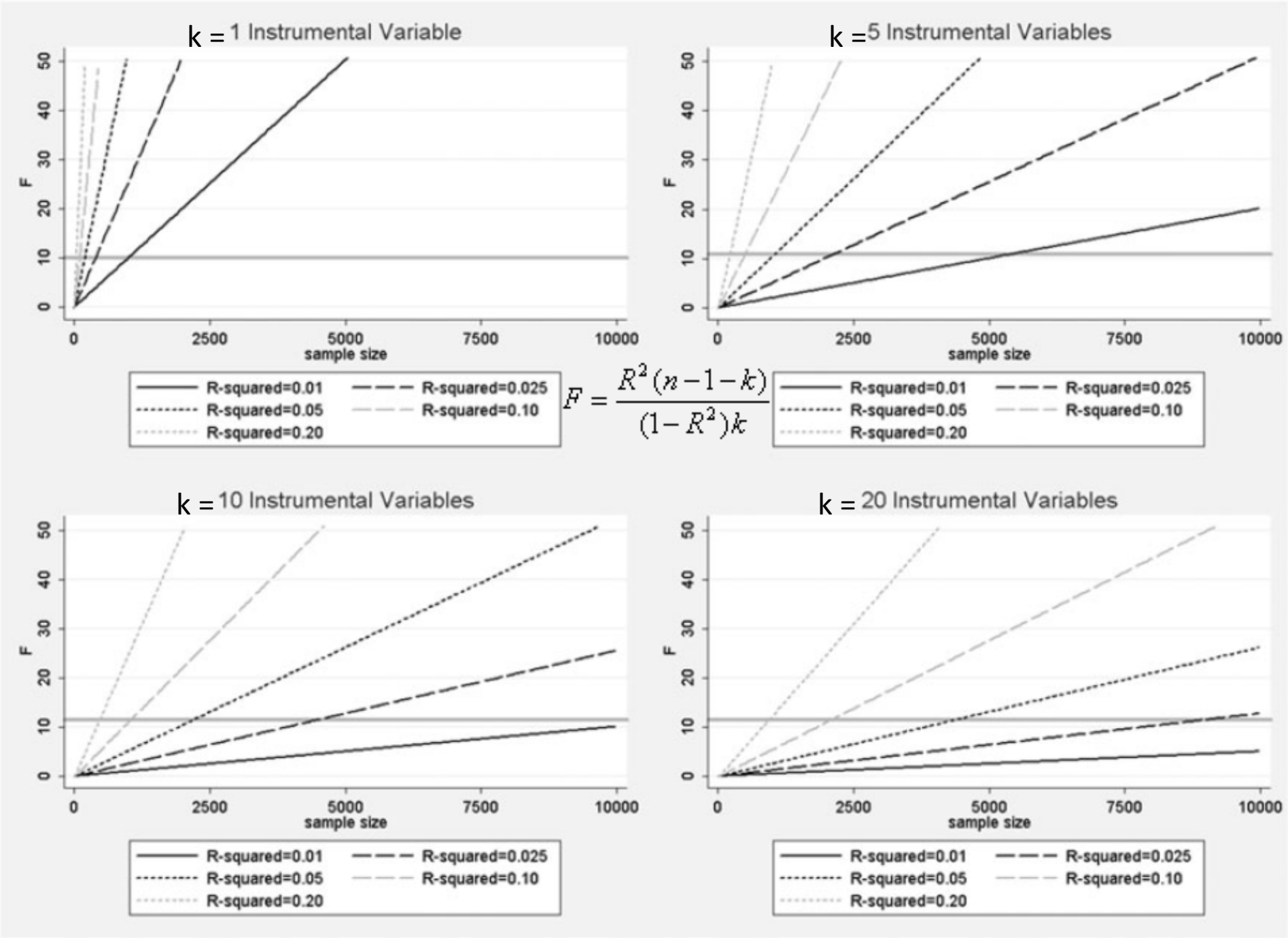
Well-powered studies will typically need to be quite large for modest effects



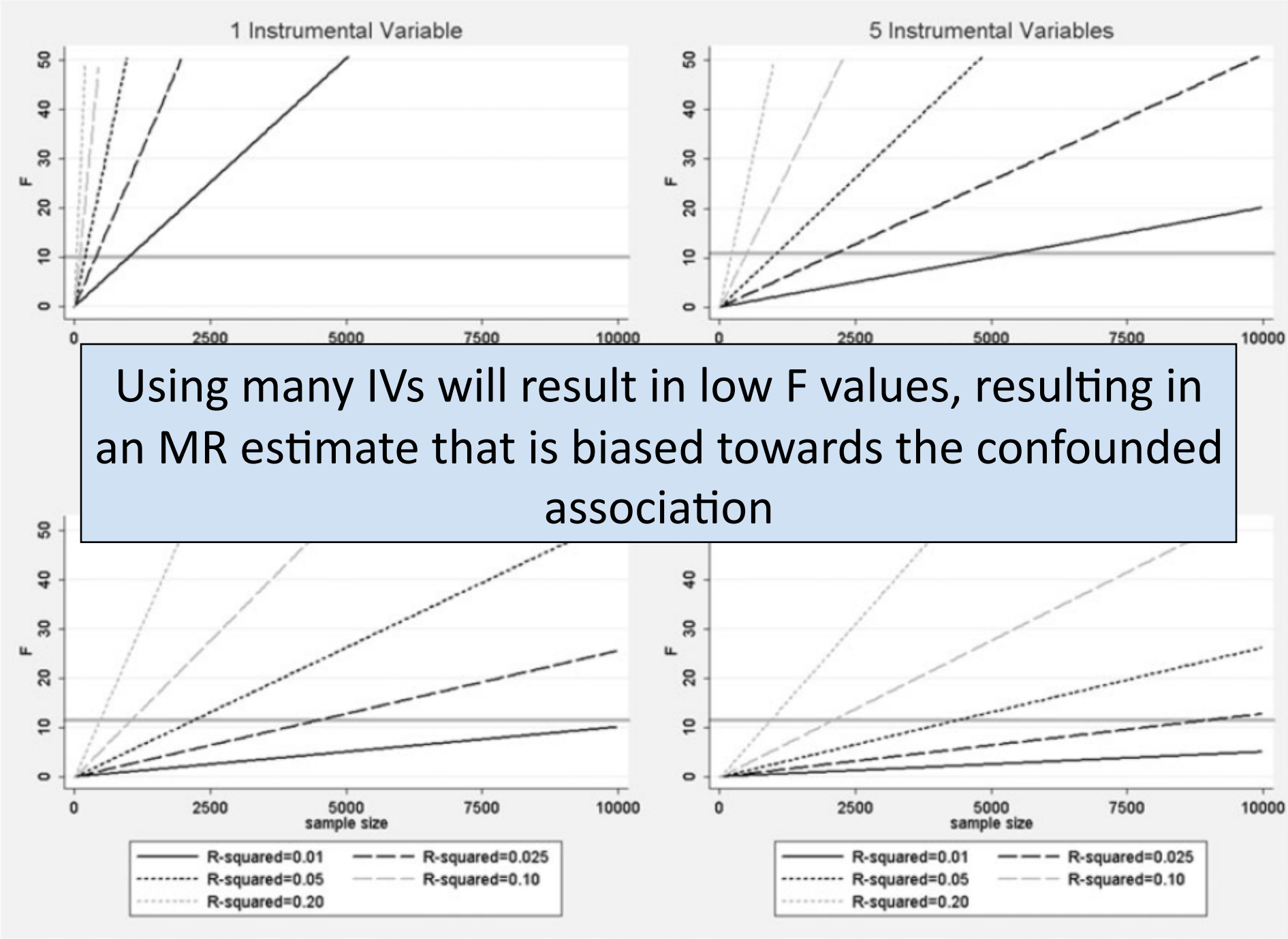
Multi-IV MR

- Multiple IVs in the 2SLS regression
- R^2 as summary measure of the effects of Gs on X
- If n and β_{xy} are held constant, R^2 determines power





$$F = \frac{R^2(n-1-k)}{(1-R^2)k}$$

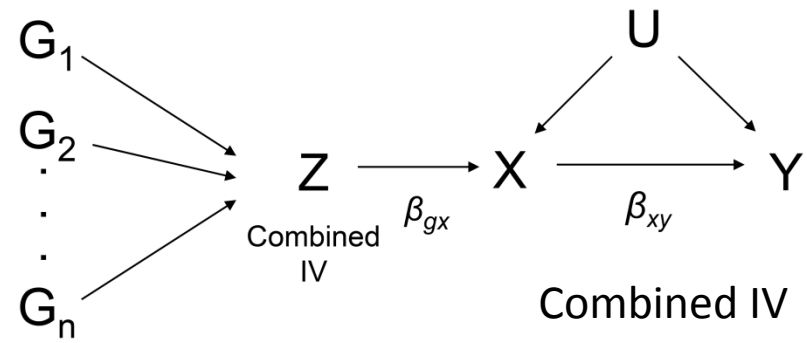


Using many IVs will result in low F values, resulting in an MR estimate that is biased towards the confounded association

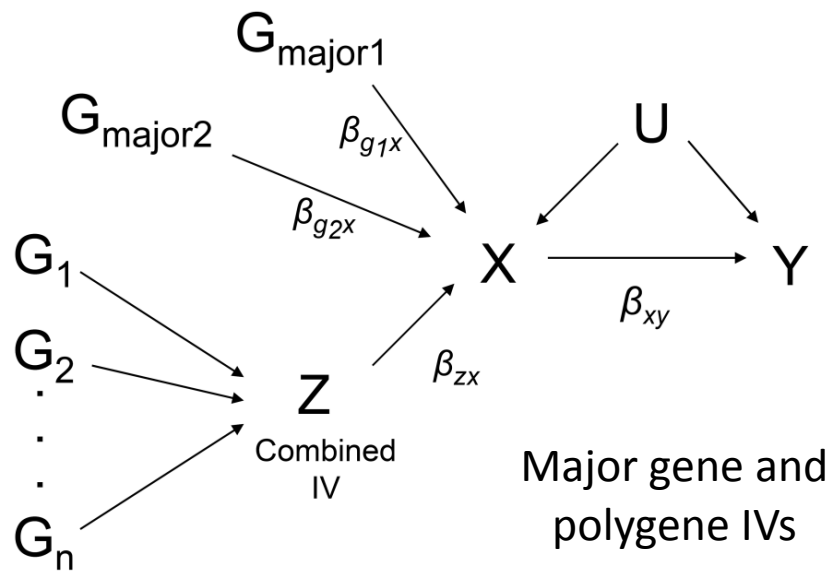
Reducing the number of IVs

- Combined IVs could take several forms:
  - allele count
  - weighted allele count
  - major gene/polygene

- **<u>Goal:</u>** maximize R^2, while maintaining acceptable F values



Combined IV



Major gene and polygene IVs

A continuum of effects

No. of variants IV(s)	β_{gx}	R^2	F	Power Estimates β_{xy} 0.1	0.3	0.5
A continuum of effects (n=1,000)						
5 variants						
5 IVs	**0.189**	0.055	11.6	0.10	0.61	0.93
Allele count	**0.189**	0.045	47.2	0.09	0.56	0.89
Weighted count	**0.189**	0.051	53.5	0.11	0.58	0.92
10 variants						
10 IVs	**0.134**	0.060	6.3	0.11	0.64	0.95
Allele count	**0.134**	0.045	46.5	0.09	0.53	0.90
Weighted count	**0.134**	0.051	53.7	0.11	0.57	0.93
20 variants						
20 IVs	**0.094**	0.069	3.6	0.14	0.71	0.98
Allele count	**0.094**	0.045	47.0	0.10	0.53	0.89
Weighted count	**0.094**	0.051	53.7	0.11	0.58	0.92

- Weighted count outperforms allele count (R^2 and F)
- Model misspecification decreases R^2 and F

Major gene/polygene model

No. of variants IV(s)	β_{gx}	R^2	F	Power Estimates β_{xy} 0.1	0.3	0.5
2 main effects + 8 polygenes (n=500)						
10 variants						
10 IVs	**0.081**	0.118	6.6	0.13	0.67	0.96
Allele count	**0.081**	0.063	33.6	0.07	0.42	0.79
Weighted count	**0.081**	0.102	57.0	0.10	0.60	0.94
2 major IVs + allele count	**0.081**	0.105	19.7	0.11	0.62	0.94

- Major-gene/polygene has slightly higher R^2 than the weighted count, lower F (but acceptable)

- Allows flexibility in model assumptions

Conclusions

- R^2, power are maximized when using one IV per variant. But…
- For fixed R^2, IV strength (F) decreases as # of IV increases

- Constructing optimal IV set is a balancing act:
  - Maximize R^2, power
  - Minimize bias (adequate F values)
- Weighted allele counts may accomplish this

- GWAS-based MR requires careful treatment of weak IV problem

- BUT… with multiple instruments, we have multiple exclusion restrictions