Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease and Stroke

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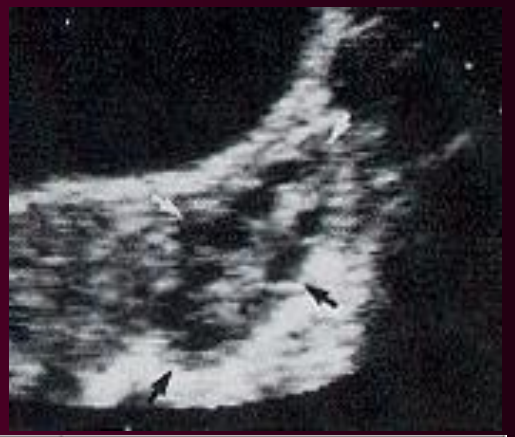
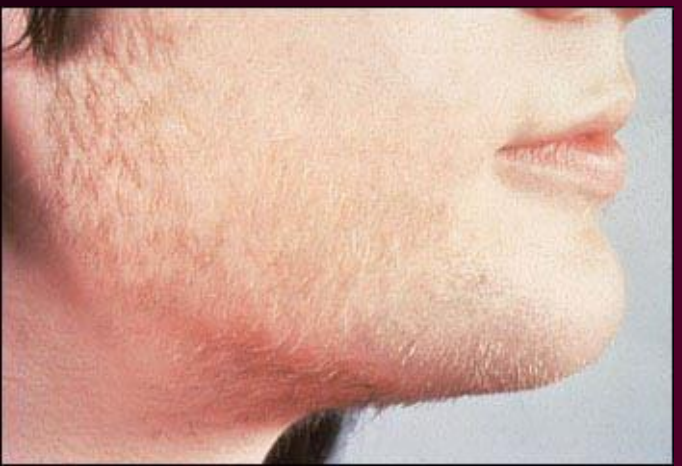
PCOS: Diagnostic Features

- Hyperandrogenism (symptoms) and/or hyperandrogenemia (↑ androgen levels)
- Oligo- or anovulation
- Polycystic ovarian morphology
- Exclusion of other disorders





	NIH	Rotterdam			
Hyperandrogenemia or Hyperandrogenism	■	■		■	■
Ovulatory Dysfunction	■	■	■		■
Polycystic Ovarian Morphology			■	■	■

Clinical Features & Complications

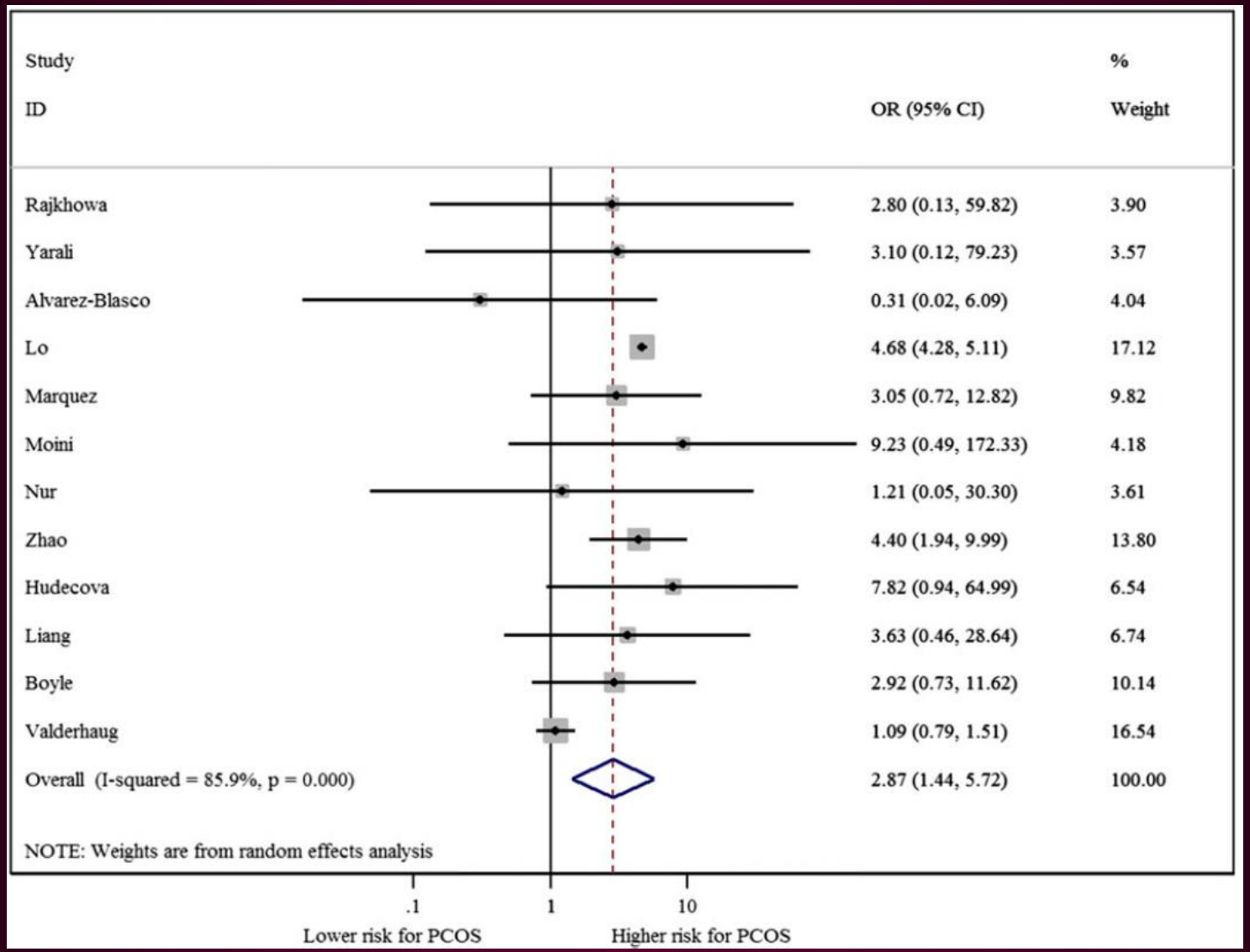
- Infertility, gestational diabetes, preeclampsia
- Endometrial hyperplasia and cancer
- Depression, anxiety, social isolation
- Insulin resistance, obesity, sleep apnea, hepatic steatosis
- Type 2 diabetes
- ↑ Cardiovascular risk factors (e.g., dyslipidemia)
  - Possibly ↑ CV events
- Which cause PCOS and which are caused by PCOS?
  - Genetic studies can help

PCOS, Impaired Glucose Tolerance & Type 2 Diabetes

- Systematic review and meta-regression
- 40 studies, most low quality
- 15 studies: increased prevalence of IGT (OR 3.3, 95% CI 2.2-4.9)
- 12 studies: increased prevalence of T2D (OR 2.9, 95% CI 1.4-5.7)
  - 7 studies where PCOS and controls were BMI matched: OR 1.13 (95% CI 0.83-1.54)

Kakoly NS, et al. *Hum Reprod Update* 2018;24:455-67

PCOS & Type 2 Diabetes



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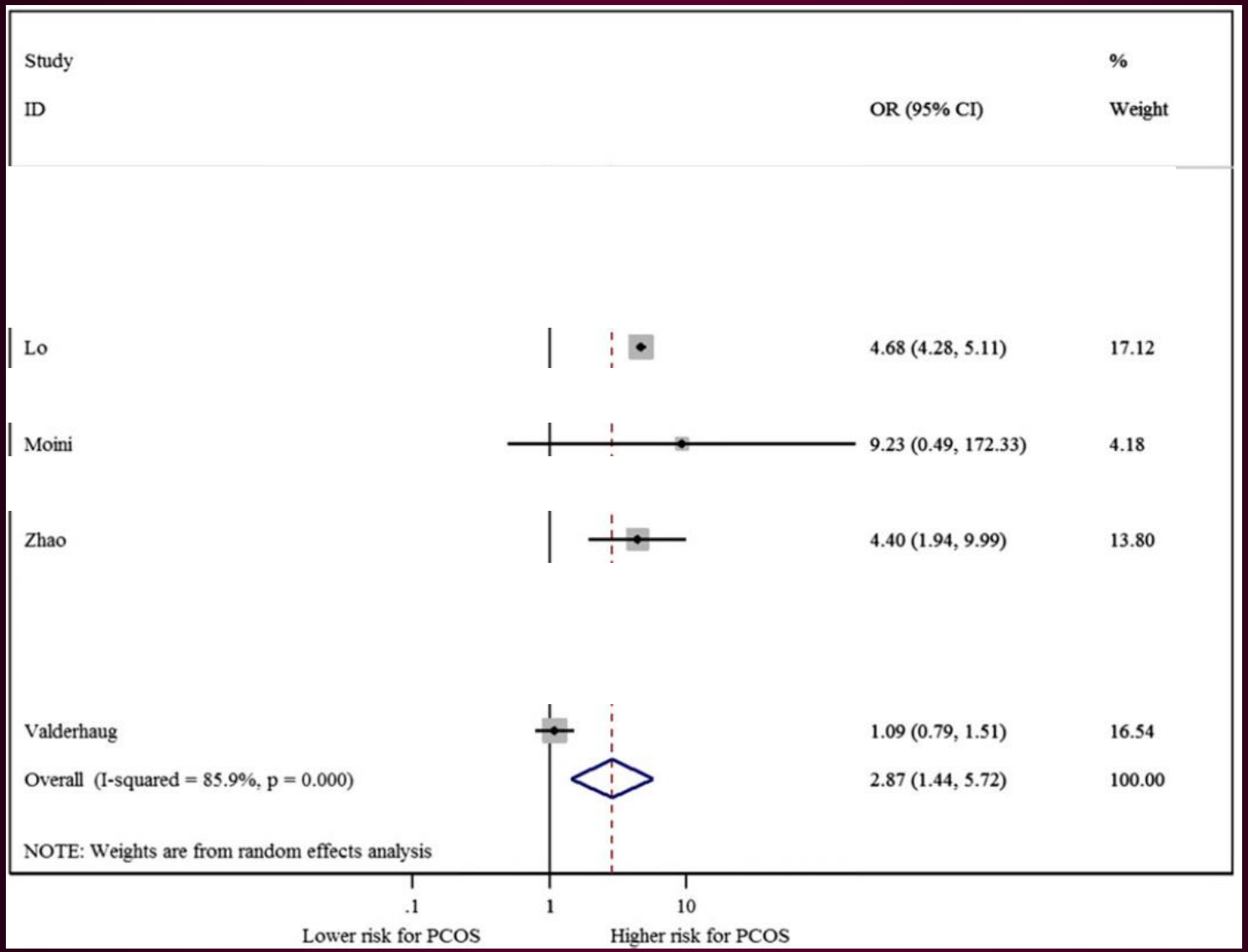
PCOS & Type 2 Diabetes



Largest studies had mixed results

Kakoly NS, et al. *Hum Reprod Update* 2018;24:455-67

PCOS & CVD: Meta-analyses

- CVD: OR 1.30 (95% CI 1.09-1.56)
  - CHD: OR 1.44 (95% CI 1.13-1.84)
  - MI: OR 1.01 (95% CI 0.68-1.51)
- Stroke: OR 1.36 (95% CI 1.09-1.70)
- Risk estimates attenuate with BMI adjustment
- Meta-analyses heavily influenced by large cohort studies examining irregular menses (not necessarily PCOS)

Zhou Y, et al. *Gynecol Endocrinol* 2017; 33:904-910

Zhao L, et al. *Oncotarget* 2016;7:33715-33721

PCOS: Familial Aggregation

- Several studies have demonstrated clustering of PCOS in families
  - 25-40% of first-degree female relatives affected
- Inherited nature of
  - PCOS
  - Component phenotypes
    - Hyperandrogenemia
    - PCO
    - Insulin-related traits
- Twin study suggested heritability of 70%

Vink JM, et al. *J Clin Endocrinol Metab* 2006;91;2100-4.

Genetics 101: Genetic Markers

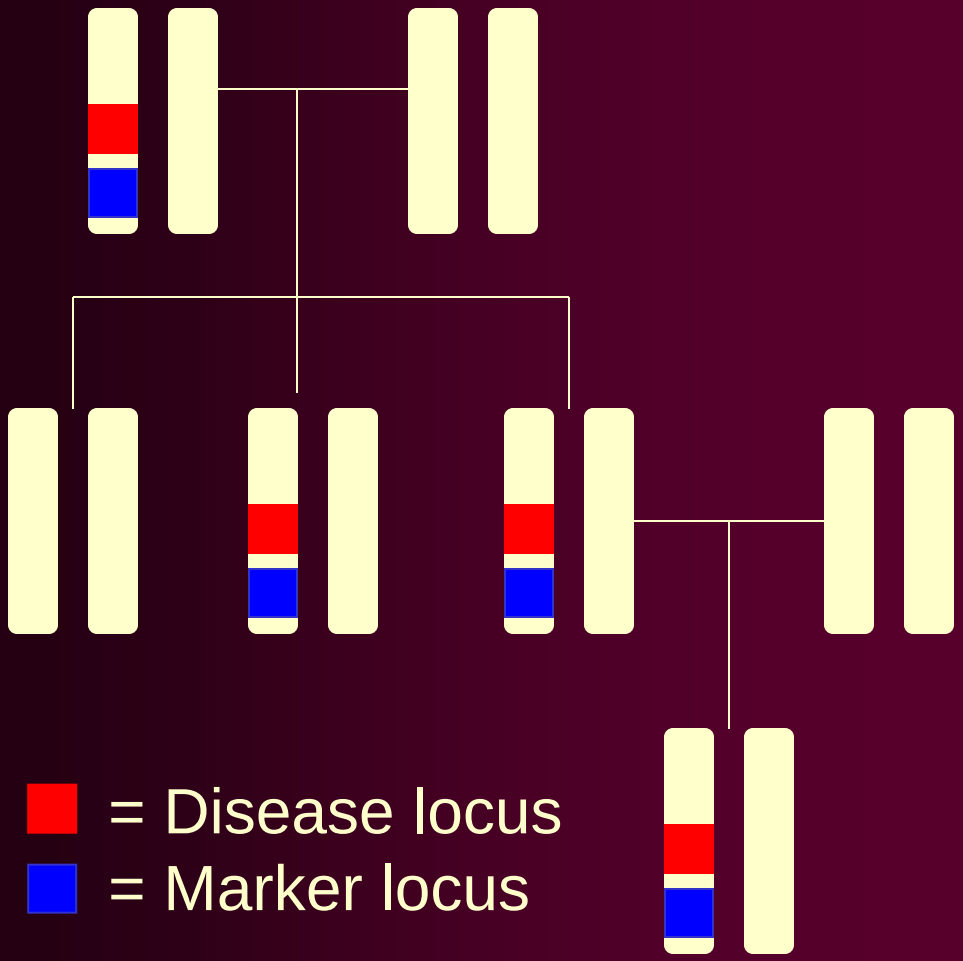
- Single nucleotide polymorphism (SNP)

AAGC**T**T → AAGC**G**T

TTCGAA → TTCGCA

- Haplotype

How do we use markers to track down disease genes?



- Two variants located near each other tend to be inherited together as a unit (unlikely to be separated by recombination during meiosis)
- Allows the use of chromosomal markers (SNPs), which are **known** (thanks to the Human Genome Project)
- To track down disease-causing variants (**unknown**).

Genome-Wide Association Study

- Formerly impractical
- Millions of SNPs in the human genome
- Genotyping ~500,000 SNPs can capture the information of 80% of all SNPs (Europeans)
- How can this be?
  - Advances in technology, drops in cost
  - Haplotypes/linkage disequilibrium

Chinese PCOS GWAS: 11 Loci

Chr.	Nearest Gene	GWAS Index SNP	Discovery P value
2p16.3	*LHCGR*	rs13405728	7.55×10^{-21}
2p16.3	*FSHR*	rs2268361	9.89×10^{-13}
2p21	*THADA*	rs13429458	1.73×10^{-23}
9q33.3	*DENND1A*	rs2479106	8.12×10^{-9}
9q22.32	*C9orf3*	rs4385527	5.87×10^{-9}
		rs3802457	5.28×10^{-14}
11q22.1	*YAP1*	rs1894116	1.08×10^{-22}
12q14.3	*HMGA2*	rs2272046	1.95×10^{-21}
12q13.2	*RAB5B/SUOX*	rs705702	8.64×10^{-26}
16q12.1	*TOX3*	rs4784165	3.64×10^{-11}
19p13.3	*INSR*	rs2059807	1.09×10^{-8}
20q13.2	*SUMO1P1*	rs6022786	1.83×10^{-9}

Chen Z-J, et al. *Nat Genet.* 2011;43:55–9
Shi Y, et al. *Nat Genet* 2012:44;1020-5.

2015: GWAS in Europeans

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DOI: 10.1038/ncomms8502 OPEN

Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations

M. Geoffrey Hayes[1,2,3,*], Ma… …ng[1], Ji Young Lee[1], Ryan Sisk[1], Tugce Karaderi[5], Thomas M… …cilia M. Lindgren[5,10], Corrine K. Welt[11], Evanthia … …podarzi[14], Ricardo Azziz[15], Yi Zhang[16,17], Roland G. Jar… …eproductive Medicine Network[#], Elisabet Stener-V…

Total: 3,000 PCOS (NIH criteria) 5,330 controls

Received 17 Feb 2015 | Accepted 24 Aug 2015 | Published 29 Sep 2015

DOI: 10.1038/ncomms9464 OPEN

Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome

Felix R. Day[1], David A. Hind… …ir[4], Richa Saxena[5], Andrew Bjonnes[5], Linda Bro… …bie A. Lawlor[8,9], Guillaume Laval[10], Iain Matl… …ndy Meun[12], Susan Ring[8,9], Robert A. Scott[1], Patrick Sul… …Unnur Thorsteinsdottir[4,13], Corrine Welt[14], Kari Stefans… …3. Perry[1,*]

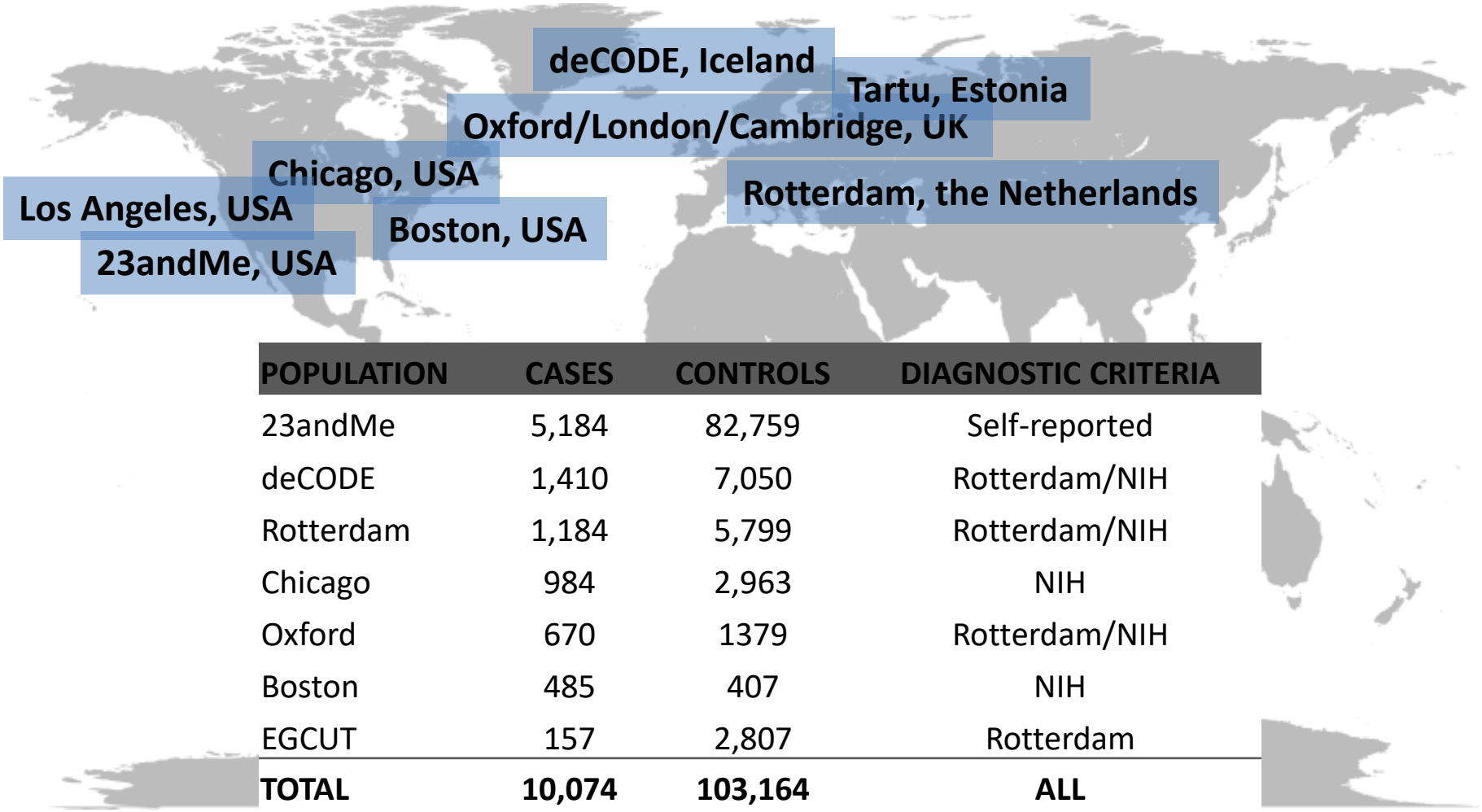
Total: 7,229 PCOS (various criteria) 181,645 controls

Updated PCOS GWAS loci

Chr.	Nearest Gene	GWAS Index SNP	Discovery P value	Discovery Population	Replication Population
2p16.3	*LHCGR*	rs13405728	7.55×10^{-21}	CHN	EUR, IND, ARB, EGY
2p16.3	*FSHR*	rs2268361	9.89×10^{-13}	CHN	EUR, ARB, CHN
2p21	*THADA*	rs13429458	1.73×10^{-23}	CHN	EUR, CHN
2q34	*ERBB4*	rs1351592	1.2×10^{-12}	EUR	
5q31.1	*RAD50*	rs13164856	3.5×10^{-9}	EUR	
8p32.1	*GATA4*	rs804279	8.0×10^{-10}	EUR	
9q33.3	*DENND1A*	rs2479106	8.12×10^{-9}	CHN	EUR
9q22.32	*C9orf3*	rs4385527	5.87×10^{-9}	CHN	CHN, EUR
		rs10993397	4.6×10^{-13}	EUR	
11p14.1	*FSHB*	rs11031006	1.9×10^{-8}	EUR	EUR, CHN
11q22.1	*YAP1*	rs1894116	1.08×10^{-22}	CHN	EUR, CHN
		rs11225154	7.6×10^{-11}	EUR	CHN
12q14.3	*HMGA2*	rs2272046	1.95×10^{-21}	CHN	EUR
12q13.2	*RAB5B/SUOX*	rs705702	8.64×10^{-26}	CHN	EUR
12q21.2	*KRR1*	rs1275468	1.9×10^{-8}	EUR	
16q12.1	*TOX3*	rs4784165	3.64×10^{-11}	CHN	EUR
19p13.3	*INSR*	rs2059807	1.09×10^{-8}	CHN	EUR
20q13.2	*SUMO1P1*	rs6022786	1.83×10^{-9}	CHN	

Populations: CHN= Han Chinese, EUR= Caucasians of European descent, IND= Indians from India, ARB= Arabic women in Bahrain, EGY= Egyptian. *Successful replication was considered on a locus-wide basis (not direct replication of the GWAS index SNP) in direct follow up studies of GWAS publications with $P<0.05$.

PCOS Consortium



POPULATION	CASES	CONTROLS	DIAGNOSTIC CRITERIA
23andMe	5,184	82,759	Self-reported
deCODE	1,410	7,050	Rotterdam/NIH
Rotterdam	1,184	5,799	Rotterdam/NIH
Chicago	984	2,963	NIH
Oxford	670	1379	Rotterdam/NIH
Boston	485	407	NIH
EGCUT	157	2,807	Rotterdam
TOTAL	**10,074**	**103,164**	**ALL**

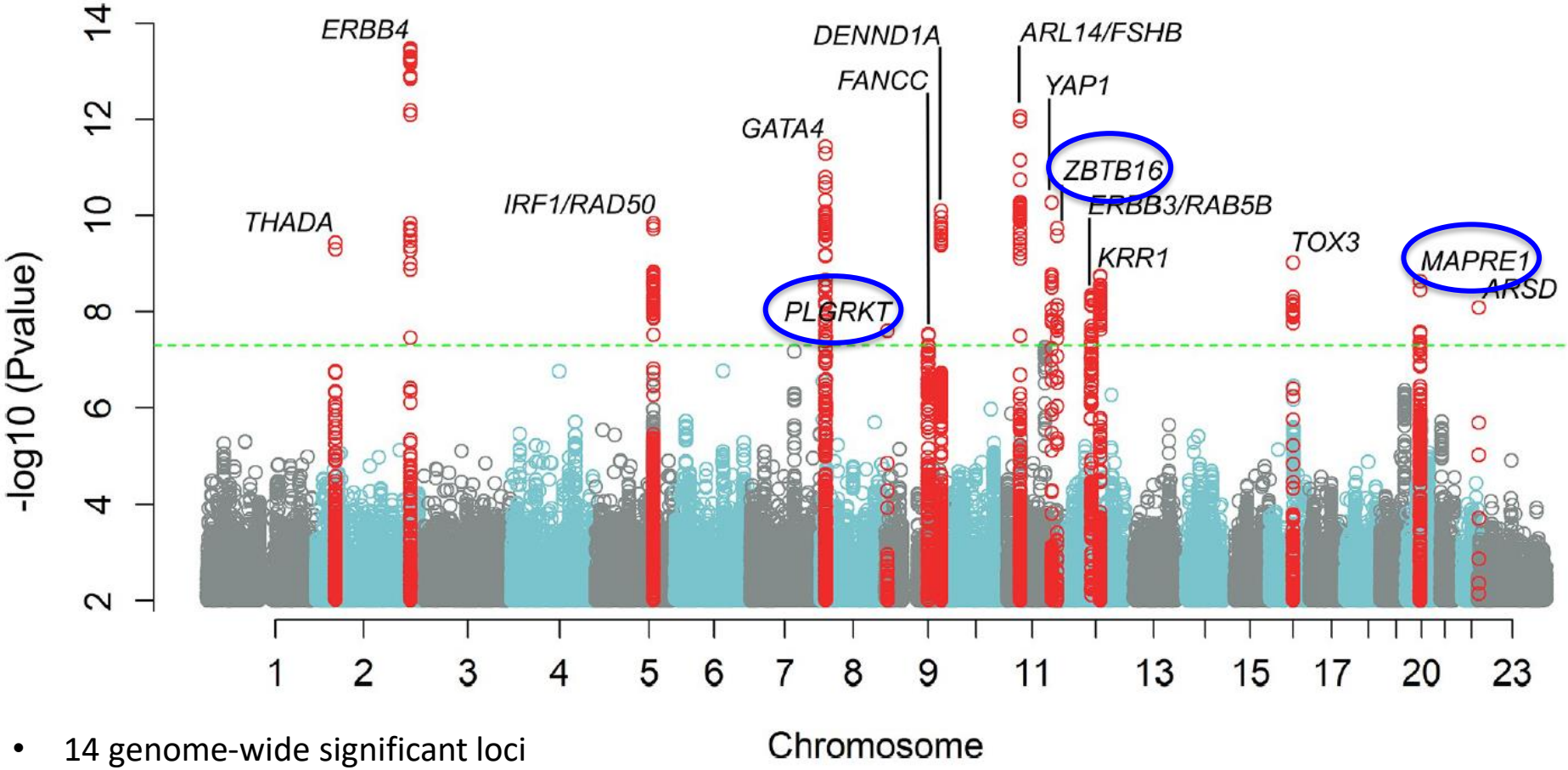
Day F, Karaderi T, Jones MR, Meun C, He C, Drong A, Kraft P, Lin N, Huang H, Broer L *et al.* Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. *PLoS Genet* 2018:14:e1007813

Methods (Highlights)

- Imputation using the 1000 Genomes Database (March 2012 v3)
- Over 10 million SNPs meta-analyzed
  - Variants present in >2 studies and present in >50% of effective sample size

Day F, et al. *PLoS Genet* 2018:14:e1007813

PCOS European GWAS Meta-analysis



- 14 genome-wide significant loci
- 11 known loci
  - 3 more Chinese loci genome-wide significant in European GWAS - ***DENND1A, ERBB3/RAB5B, TOX3***
- 3 novel loci – ***MAPRE1, ZBTB16, PLGRKT***

MAPRE1 microtubule associated protein RP/EB family member 1. EB1 interacts with the low-density lipoprotein receptor related protein 1 (LRP1), which controls adipogenesis.

ZBTB16 zinc finger and BTB domain containing 16. Transcription factor. Involved in cell cycle progression.

PLGRKT plasminogen receptor with a C-terminal lysine. Role in macrophage migration.

Lessons from GWAS

- Method of diagnosis does not matter: identifies the same loci
- Many shared loci across different regions of the world
- Signals are non-coding: will take years to dissect function
- What can we learn about PCOS from genetics before full functional characterization of the loci?

Neuroendocrine and metabolic dysregulation in PCOS

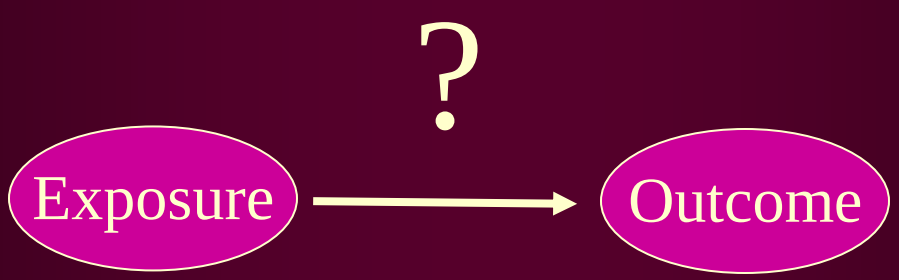
Examine function of genes in the associated loci (with caution)

- *FSHR, LHCGR* and *FSHB:* Gonadotropin action/secretion
- *GATA4:* Response to gonadotropins/gonadal development
- *ERBB3/ERBB4:* EGFR signaling/LH-induced steroidogenesis
- *DENND1A:* Regulation of ovarian steroidogenesis
- *INSR, THADA, HMGA2:* Glucose homeostasis

Day F, et al. *PLoS Genet* 2018:14:e1007813

GWAS and Mendelian randomization (MR)

- GWAS has given us tools to examine causal associations between risk factors and outcomes for which epidemiological studies suggest a causal relationship



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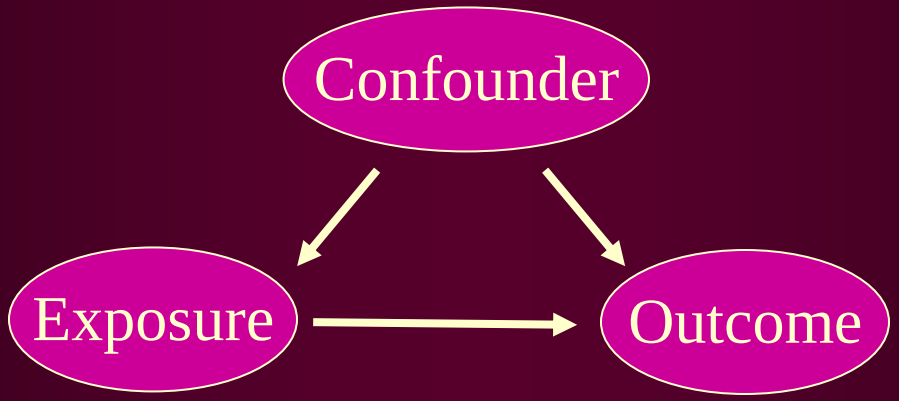

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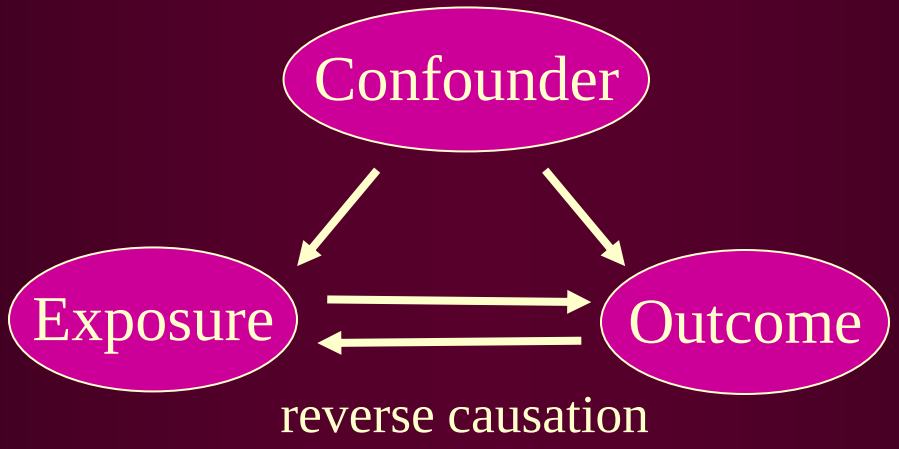

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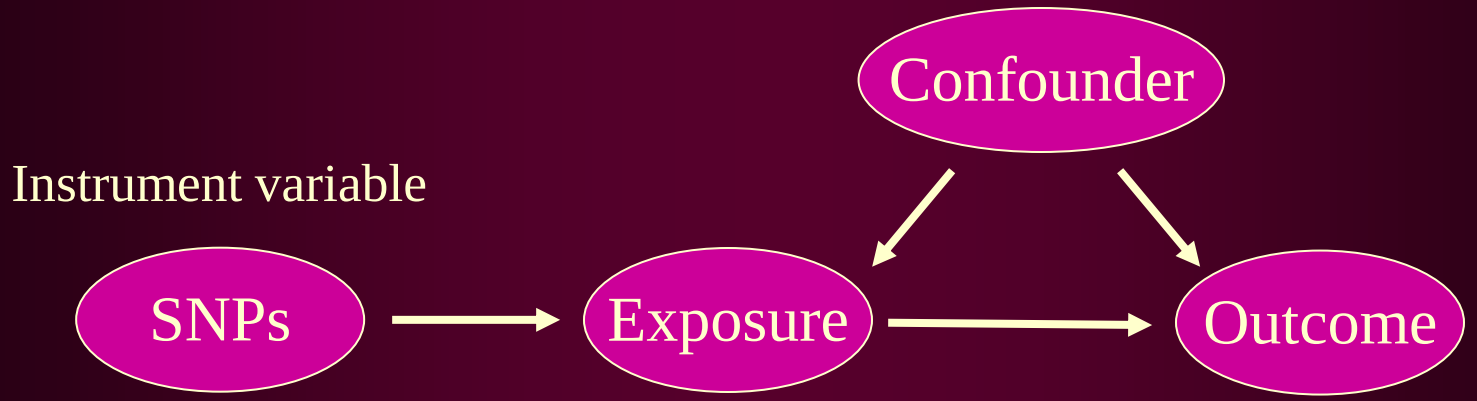
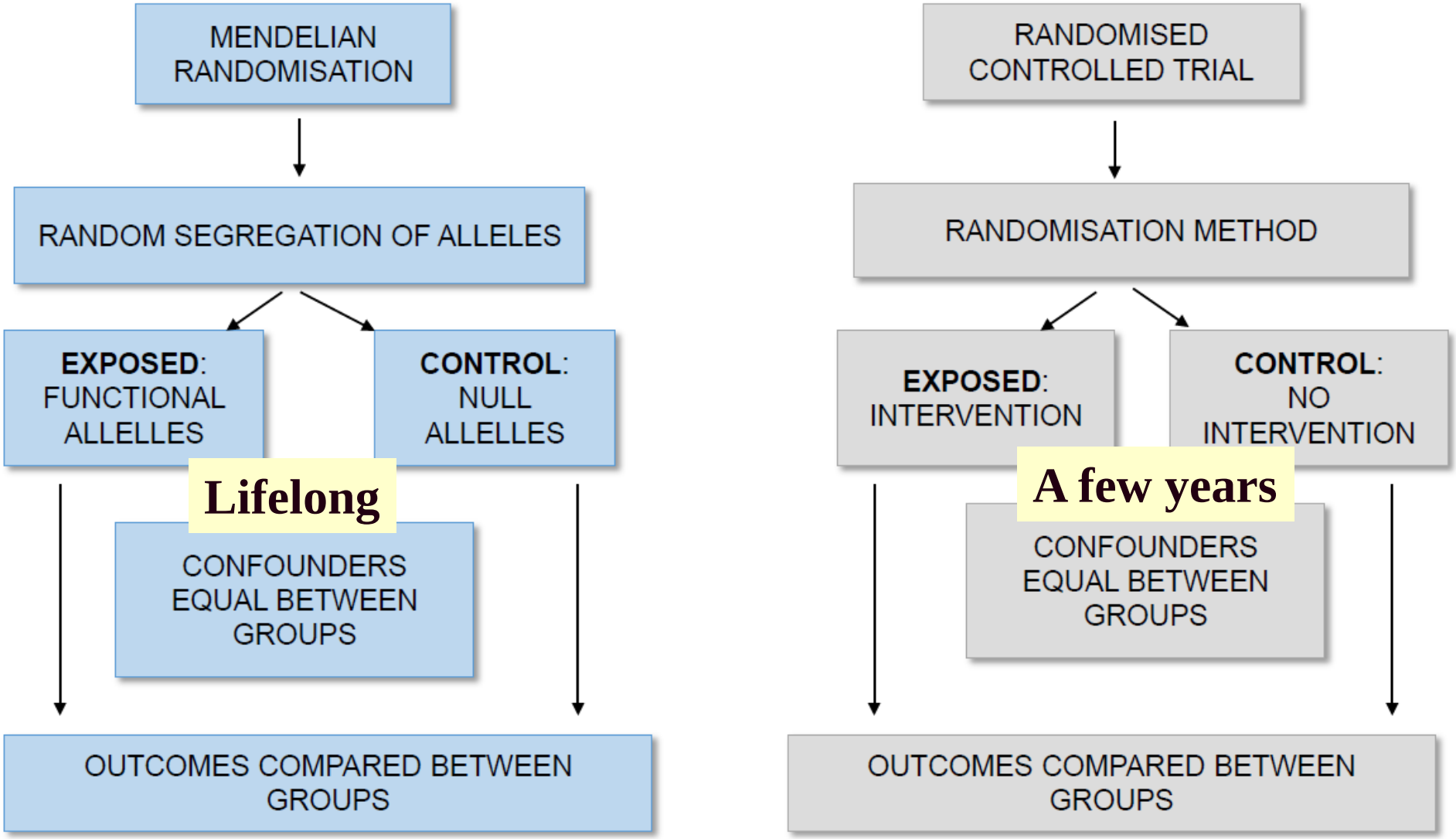
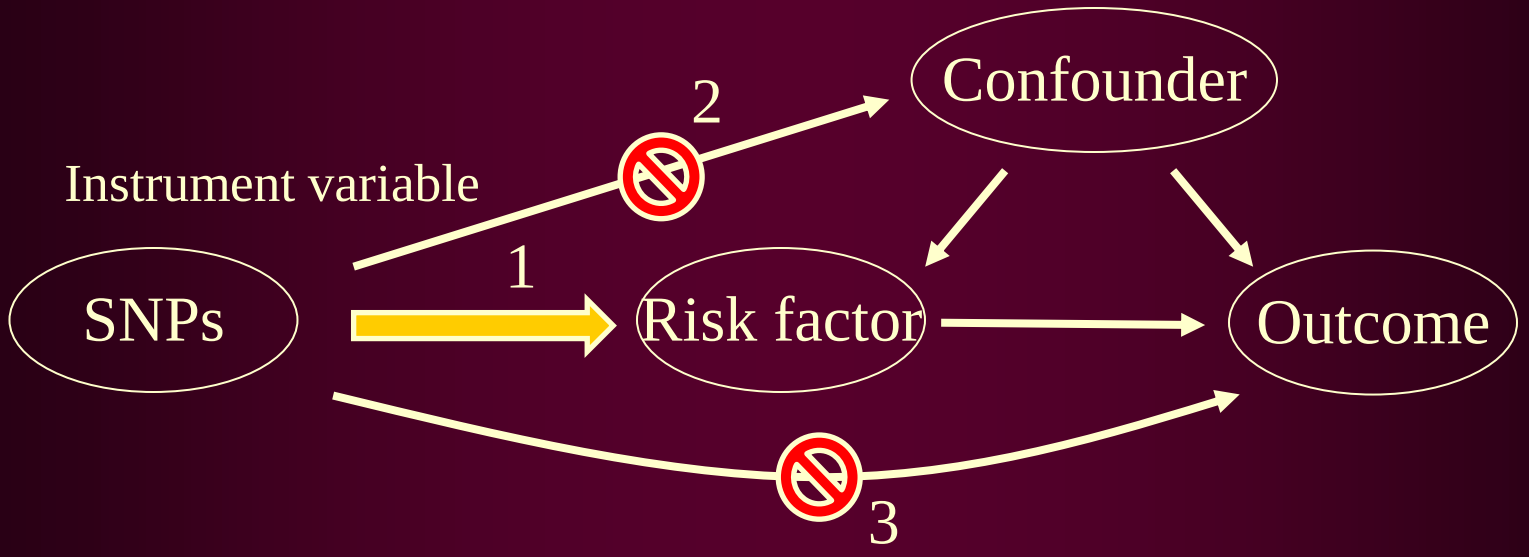


Causality: genetically predicted effect exposure on the outcome

Mendelian randomization and RCTs



Requirements for valid MR analysis



1. Instrument variable must strongly represent risk factor
2. Instrument variable must not be associated with confounders
3. Instrument variable must act only through the risk factor

Mendelian randomization in PCOS

Table 3 | Mendelian randomization analyses for PCOS risk.

Trait	23andMe study		Rotterdam study		Combined		
	Effect*	*P*-values	Effect*	*P*-values	Effect*	*P*-values†	$P_{heterogeneity}$
BMI	2.05 (1.63–2.57)	5.6E − 10	1.20 (0.71–2.03)	0.49	1.90 (1.55–2.34)	2.5E − 09	0.07
Age at menopause	1.60 (1.35–1.91)	1.3E − 07	1.57 (1.02–2.43)	0.04	1.60 (1.35–1.91)	1.5E − 08	0.94
SHBG	0.86 (0.79–0.95)	0.002	0.81 (0.64–1.03)	0.08	0.86 (0.78–0.93)	5.4E − 04	0.62
Insulin resistance	1.11 (1.04–1.19)	0.003	1.16 (0.99–1.36)	0.06	1.11 (1.05–1.19)	5.6E − 04	0.59
DHEAS	1.11 (0.99–1.23)	0.06	—	—	—	—	—
HDL cholesterol	0.37 (0.13–1.11)	0.08	—	—	—	—	—
Insulin secretion	*Higher risk*	0.19	—	—	—	—	—
Birth weight	*Higher risk*	0.22	—	—	—	—	—
Age at menarche‡	0.91 (0.79–1.06)	0.23	—	—	—	—	—
Diastolic BP	1.01 (0.99–1.03)	0.24	—	—	—	—	—
LDL cholesterol	1.04 (0.94–1.16)	0.43	—	—	—	—	—
Adult height	*Lower risk*	0.51	—	—	—	—	—
Triglycerides	1.03 (0.90–1.18)	0.65	—	—	—	—	—
Systolic BP	1.05 (0.82–1.34)	0.68	—	—	—	—	—
Total cholesterol	0.98 (0.88–1.09)	0.71	—	—	—	—	—

BMI, body mass index; BP, blood pressure; DHEAS, dehydroepiandrosterone sulphate; HDL, high-density lipoprotein; LDL, low-protein lipoprotein; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin.
*Effect estimates are odds ratios for PCOS per 1 s.d. increase (based on s.d. from the genome-wide studies, approximated in the case of SHBG and DHEAS, as the discovery analysis used natural log units) in the candidate trait. For some traits, insufficient reported data were available to calculate an effect estimate, and in these cases only the direction of effect on PCOS risk is stated.
†Associations are displayed that passed the multiple test corrected *P*-value threshold (0.05/15 = 0.0033).
‡Any SNPs reported at genome-wide significance for adult BMI were omitted from this score.

- Mendelian randomization suggests ↑ BMI, ↑ age at menopause, ↓ SHBG, ↑ insulin resistance are causal for PCOS

Day FR, et al. *Nat Comm* 2015;6:8464

Mendelian randomization in PCOS

Potential Risk factor	IVW method[1]		
	Beta	SE	P-value
Body mass index	0.72	0.072	1.56×10^{-23}
Fasting insulin levels*	0.03	0.007	1.73×10^{-5}
Male pattern balding	0.05	0.017	0.0034
Menopause	0.1	0.022	1.31×10^{-5}
Depression	0.77	0.213	0.00029

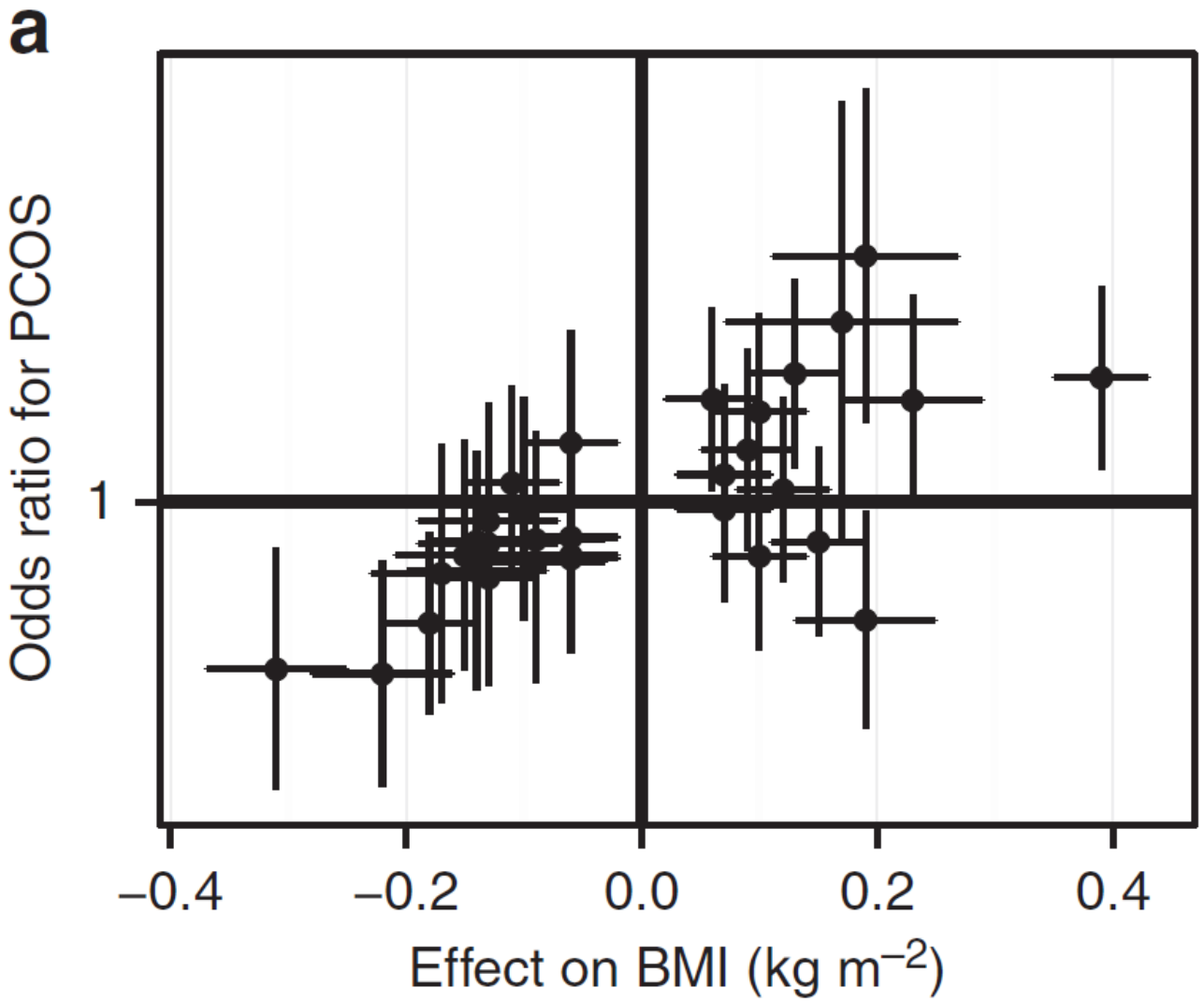
*Loci used were initially reported in an analysis of fasting insulin adjusted for BMI.

[1]IVW = inverse weighted variant,

- Male pattern balding suggested as a male phenotype for PCOS years ago, now appears to have a genetic basis
- Long-standing association between depression and PCOS, now appears that depression may be causal

Day F, et al. *PLoS Genet* 2018:14:e1007813

Mendelian randomization in PCOS



Obesity causes PCOS

Same result in several MR studies

Day FR, et al. *Nat Comm* 2015;6:8464

Obesity and PCOS

- Does PCOS lead to obesity?
- 2685 individuals from population cohort (MESA)
- 16 PCOS SNPs used for instrument variable
- Two-sample MR
  - SNP → PCOS effects from Day 2018
  - SNP → BMI in MESA
- No causal effect of PCOS on BMI

Brower MA, et al. *Hum Reprod* 2019;34:127-136

Obesity and PCOS

- Increasing BMI appears to be causal for PCOS but having PCOS does not appear to affect BMI.
- Highlights the potential utility of weight management (lifestyle or drug) in the prevention and treatment of PCOS
- Useful to future drug development efforts

Brower MA, et al. *Hum Reprod* 2019;34:127-136

MR: PCOS and adverse cardiometabolic outcomes

- European instrument variable: 14 genome-wide significant SNPs from Day 2018 (10,074 ccases, 103,164 controls)

Table 1—PCOS SNPs used to construct the main instrument variable in Europeans

Chr:position	SNP	Effect allele	Other allele	EAF	β	SE	Nearest gene	*P*	*F* statistic
2:43561780	rs7563201	A	G	0.451	−0.108	0.017	*THADA*	3.68E−10	39.50
2:213391766	rs2178575	A	G	0.151	0.166	0.022	*ERBB4*	3.34E−14	57.66
5:131813204	rs13164856	T	C	0.729	0.124	0.019	*IRF1/RAD50*	1.45E−10	40.95
8:11623889	rs804279	A	T	0.262	0.128	0.018	*GATA4/NEIL2*	3.76E−12	48.09
9:5440589	rs10739076	A	C	0.308	0.110	0.020	*PLGRKT*	2.51E−08	31.01
9:97723266	rs7864171	A	G	0.428	−0.093	0.017	*C9orf3*	2.95E−08	30.84
9:126619233	rs9696009	A	G	0.068	0.202	0.031	*DENND1A*	7.96E−11	42.19
11:30226356	rs11031005	T	C	0.854	−0.159	0.022	*ARL14EP/FSHB*	8.66E−13	51.03
11:102043240	rs11225154	A	G	0.094	0.179	0.027	*YAP1*	5.44E−11	43.16
11:113949232	rs1784692	T	C	0.824	0.144	0.023	*ZBTB16*	1.88E−10	40.49
12:56477694	rs2271194	A	T	0.416	0.097	0.017	*ERBB3/RAB5B*	4.57E−09	34.22
12:75941042	rs1795379	T	C	0.240	−0.117	0.020	*KRR1*	1.81E−09	36.25
16:52375777	rs8043701	A	T	0.815	−0.127	0.021	*TOX3*	9.61E−10	37.46
2:49247832	rs2349415	T	C	0.343	0.076	0.017	*FSHR*	9.59E−06	19.65

F statistic 39.5 (*F* statistic > 10 indicates strong instrument)

Zhu T, et al. *Diabetes* 2021;70:627-37

MR: PCOS and adverse cardiometabolic outcomes

- East Asian instrument variable: 13 genome-wide significant SNPs from Chen 2011 (4,082 cases, 6,687 controls) and Shi 2012 (10,480 cases, 10,579 controls)

Table 2—PCOS SNPs used to construct the main instrument variable in East Asians

Chr:position	SNP	Effect allele	Other allele	EAF	β	SE	Nearest gene	*P*	*F* statistic
2:43638838	rs13429458	A	C	0.81	0.401	0.040	*THADA*	1.73E−23	99.75
2:48978159	rs13405728	A	G	0.754	0.343	0.037	*LHCGR*	7.55E−21	87.72
2:49201612	rs2268361	C	T	0.504	0.139	0.020	*FSHR*	9.89E−13	50.87
2:49247832	rs2349415	T	C	0.181	0.174	0.025	*FSHR*	2.35E−12	49.17
9:97648587	rs4385527	G	A	0.781	0.174	0.030	*C9orf3*	5.87E−09	33.88
9:97741336	rs3802457	G	A	0.904	0.261	0.035	*C9orf3*	5.28E−14	56.62
9:126525212	rs2479106	G	A	0.222	0.293	0.033	*DENND1A*	8.12E−19	78.47
11:102070639	rs1894116	G	A	0.194	0.239	0.024	*YAP1*	1.08E−22	96.12
12:56390636	rs705702	G	A	0.245	0.239	0.023	*RAB5B/SUOX*	8.64E−26	110.25
12:66224461	rs2272046	A	C	0.907	0.357	0.038	*HMGA2*	1.95E−21	90.4
16:52347819	rs4784165	G	T	0.325	0.140	0.021	*TOX3*	3.64E−11	43.8
19:7166109	rs2059807	G	A	0.301	0.131	0.023	*INSR*	1.09E−08	32.67
20:52447303	rs6022786	A	G	0.339	0.122	0.020	*SUMO1P1*	1.83E−09	36.15

Chr, chromosome; EAF, effect allele frequency.

F statistic 66.6

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Sources of Data for Outcomes

- Several large consortium GWAS

Table 3—Characteristics of the outcome data sources used for MR analyses

Trait	No. of case subjects	No. of control subjects	Consortium	Population	Year
Diabetes in Asian (all subjects)	77,418	356,122	AGEN	Asian	2020
Female	27,370	135,055	AGEN	Asian	2020
Male	28,027	89,312	AGEN	Asian	2020
Diabetes in European (all subjects)	74,124	824,006	DIAMANTE	European	2018
Female	30,053	434,336	DIAMANTE	European	2018
Male	41,846	383,767	DIAMANTE	European	2018
CHD	122,733	424,528	UKBB plus CARDIoGRAMplusC4D	Majority European	2018
Any stroke	40,585	406,111	MEGASTROKE	European	2018
Any ischemic stroke	34,217	406,111	MEGASTROKE	European	2018
Large artery stroke	4,373	406,111	MEGASTROKE	European	2018
Cardioembolic stroke	7,193	406,111	MEGASTROKE	European	2018
Small vessel stroke	5,386	406,111	MEGASTROKE	European	2018

UKBB: UK Biobank

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MR Analysis

- Two-sample MR
  - SNP effect on PCOS from Day (European) or Chen/Shi (East Asian)
  - SNP effects on outcomes from GWAS for each outcome
- Primary analysis: Inverse variance weighted (IVW)
- Sensitivity analyses
  - MR-Egger to detect pleiotropy
  - MR by weighted median
  - MR using 3 SNPs associated with PCOS by NIH definition (Hayes 2015 GWAS)
  - Exclusion of SNPs associated with BMI, WHR, bioavailable or total testosterone (6 European SNPs, 5 East Asian SNPs)

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MR Results

Trait	IVW	
	OR (95% CI)	*P*
Diabetes in Asian (all)	0.98 (0.96–1.01)	0.13
Female	0.98 (0.95–1.02)	0.33
Male	0.99 (0.95–1.02)	0.45
Diabetes in European (all)	0.97 (0.92–1.01)	0.16
Female	0.95 (0.88–1.02)	0.16
Male	0.98 (0.93–1.03)	0.42
CHD	1.00 (0.96–1.04)	0.88
Any stroke	0.98 (0.93–1.02)	0.33
Any ischemic stroke	0.98 (0.93–1.03)	0.40
Large artery stroke	0.88 (0.78–1.00)	0.06
Cardioembolic stroke	0.92 (0.83–1.02)	0.10
Small vessel stroke	1.10 (0.95–1.27)	0.21

- No evidence of pleiotropy by MR-Egger
- Similar results in the sensitivity analyses

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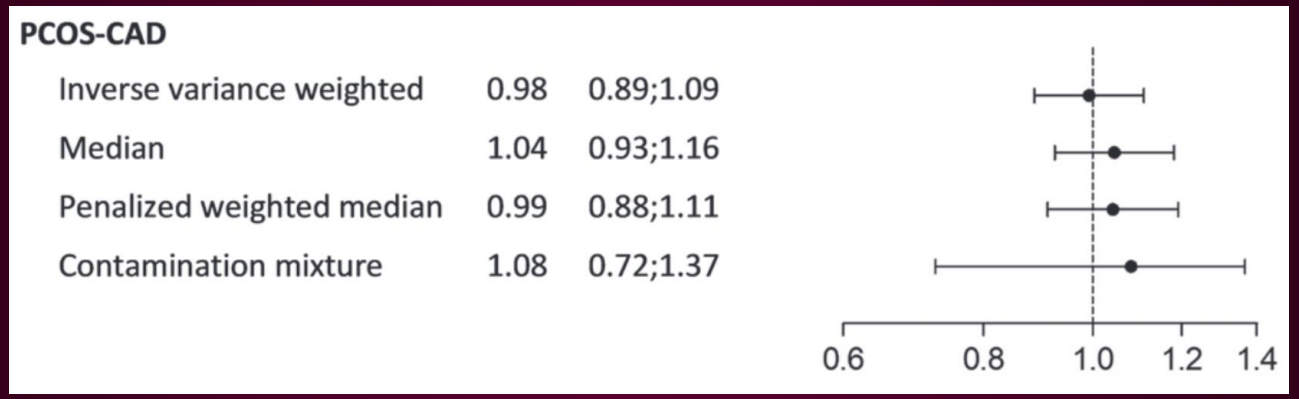
MR PCOS & CHD in Women

- MR conducted in women
- Exposure: PCOS, instrument: 12 SNPs from Day 2018
- Outcome: CAD, from UKBB
  - 8403 cases, 190,435 controls
  - Age 40-69
  - Diagnosis by ICD code or self-report
- No causal effect of PCOS on CAD



Simons P, et al. *Clin Endocrinol* 2022;96:599-604

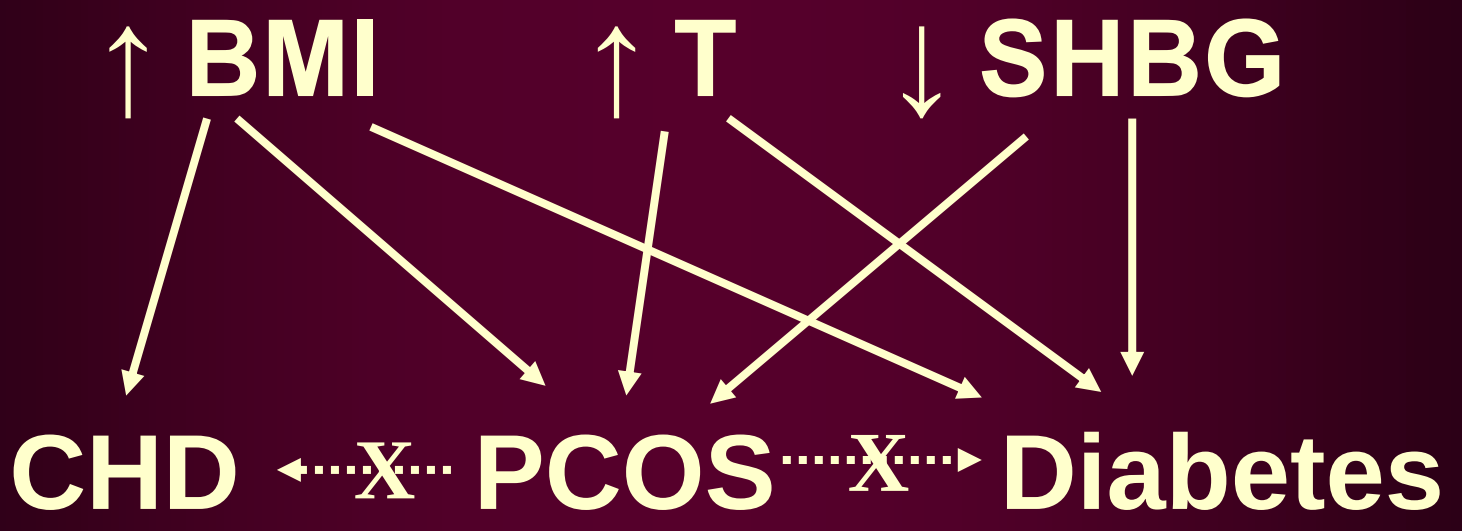
PCOS and adverse cardiometabolic outcomes

- How can we explain the association?
- Synthesis of MR studies
  - ↑ BMI → ↑ T2D (several studies)
  - ↑ BMI → ↑ CHD (several studies)
  - ↑ BMI → ↑ PCOS (several studies)
  - Low sex hormone binding globulin → ↑ T2D (several)
  - Low sex hormone binding globulin → ↑ PCOS (Day et al)
  - ↑ Circulating testosterone → ↑ T2D in women (Ruth et al)
  - ↑ Circulating testosterone → ↑ PCOS (Ruth et al)

Ruth KS, et al. *Nat Med* 2020;26:252-8

PCOS and adverse cardiometabolic outcomes

- Synthesis of MR studies
- PCOS *per se* does not increase risk



Zhu T, et al. *Diabetes* 2021;70:627-37

PCOS and adverse cardiometabolic outcomes

- Caveats
  - MR provides strong evidence, but not proof
  - Additional PCOS SNPs coming soon
  - Most T2D and CVD events in GWAS occurred in older individuals
    - MR studies inconclusive regarding CVD risk at young age
- Potential clinical impact
  - No need to tell all women with PCOS that they are at risk for diabetes and cardiovascular disease
  - Focus prevention efforts on those with risk features (obesity, high circulating testosterone, low SHBG)
    - Metformin vs targeting these risk factors