

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 | | | | |

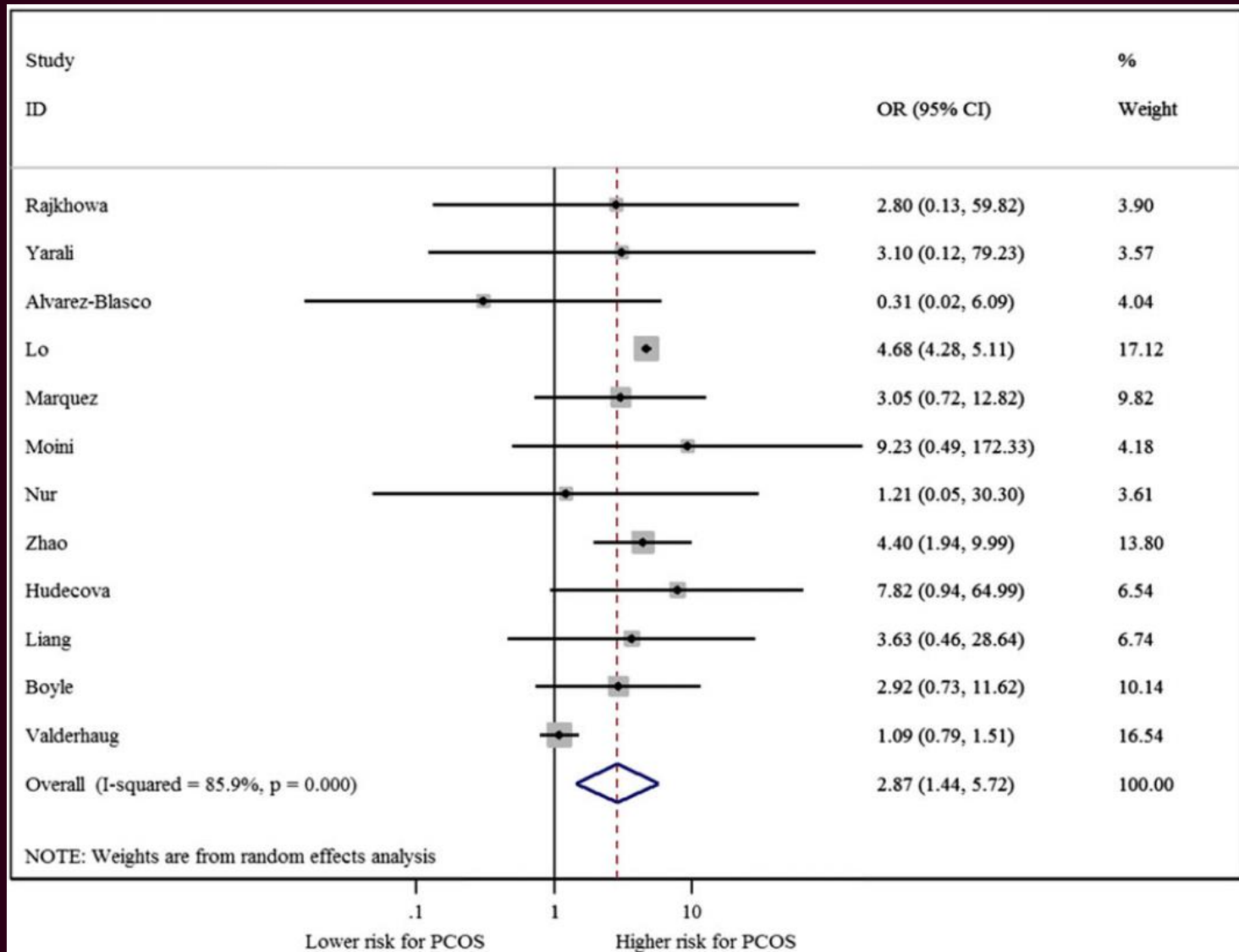
Clinical Features & Complications

- 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

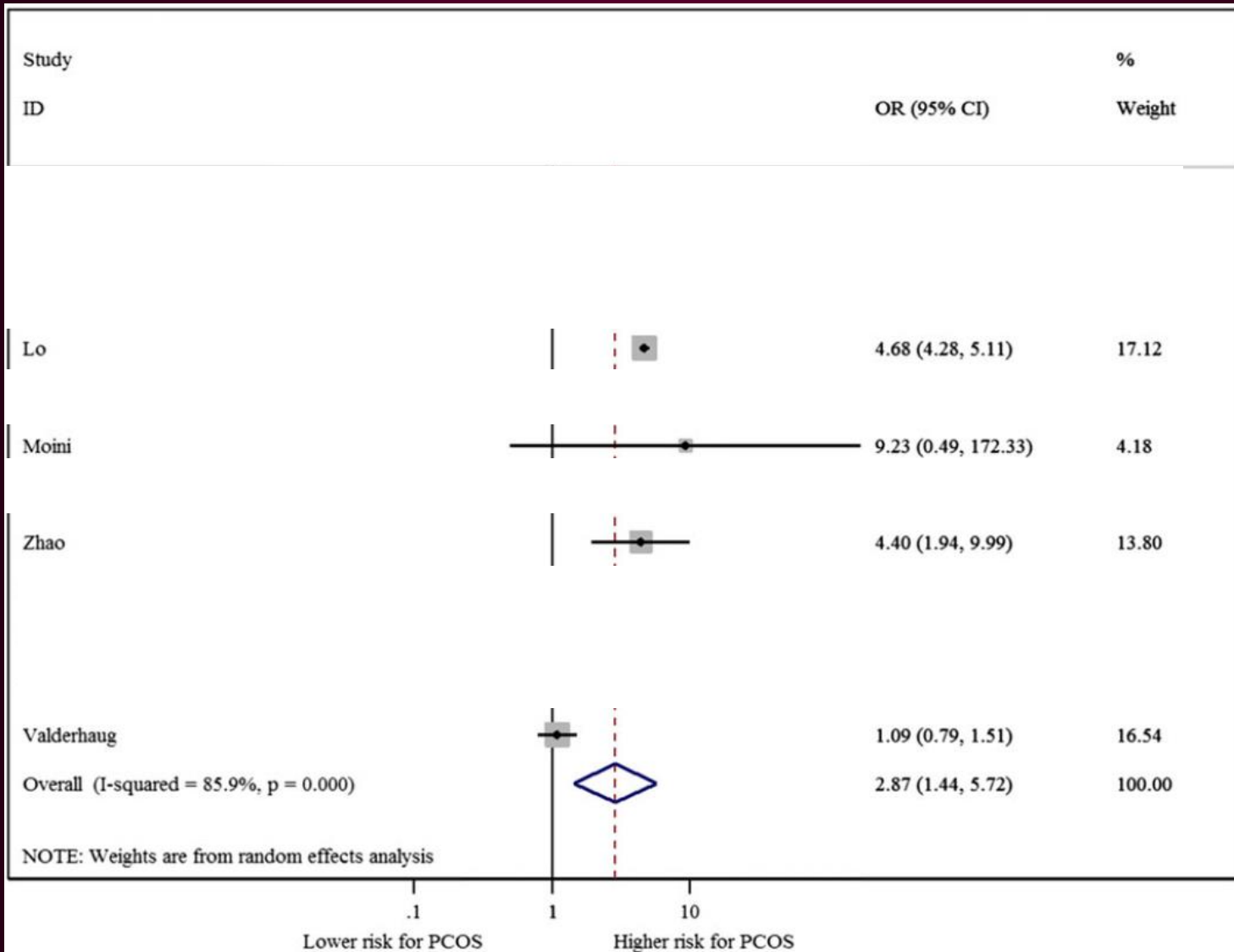
PCOS, Impaired Glucose Tolerance & Type 2 Diabetes

- 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)

PCOS & Type 2 Diabetes



PCOS & Type 2 Diabetes



Largest studies had mixed results

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)

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%

Genetics 101: Genetic Markers

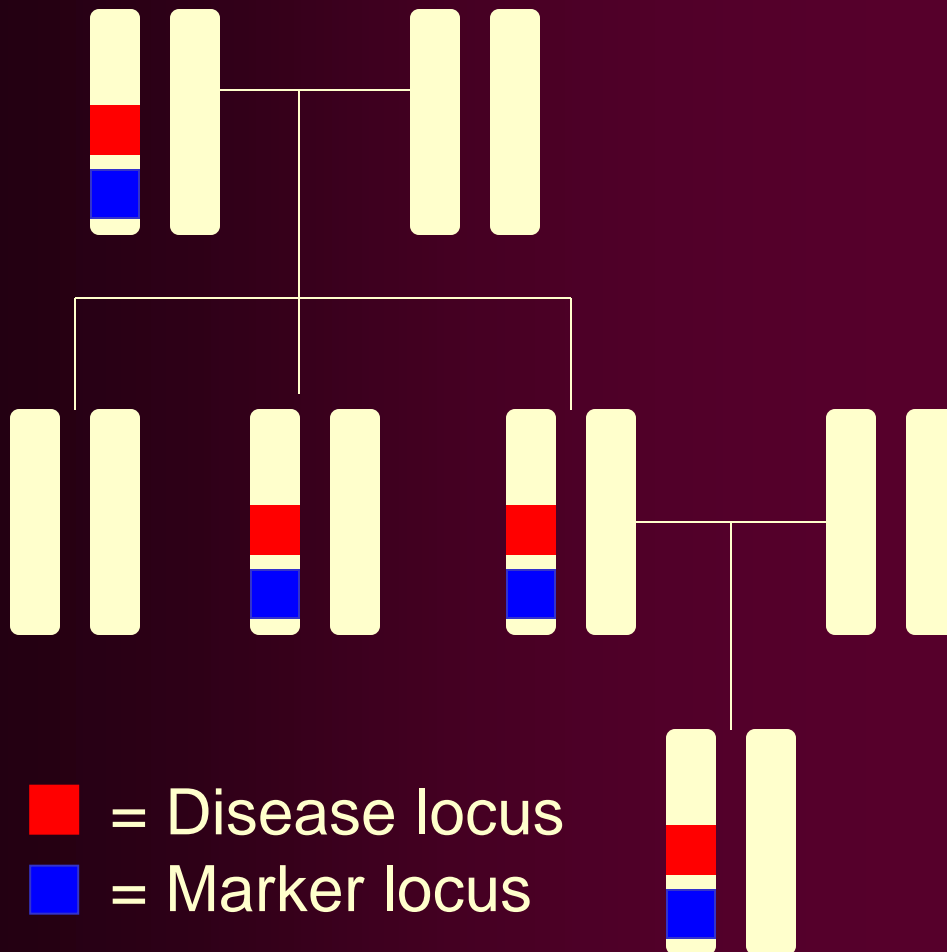
- Single nucleotide polymorphism (SNP)



- 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 | <i>LHCGR</i> | rs13405728 | 7.55 x 10 ⁻²¹ |
| 2p16.3 | <i>FSHR</i> | rs2268361 | 9.89 x 10 ⁻¹³ |
| 2p21 | <i>THADA</i> | rs13429458 | 1.73 x 10 ⁻²³ |
| 9q33.3 | <i>DENND1A</i> | rs2479106 | 8.12 x 10 ⁻⁹ |
| 9q22.32 | <i>C9orf3</i> | rs4385527 | 5.87 x 10 ⁻⁹ |
| | | rs3802457 | 5.28 x 10 ⁻¹⁴ |
| 11q22.1 | <i>YAP1</i> | rs1894116 | 1.08 x 10 ⁻²² |
| 12q14.3 | <i>HMGA2</i> | rs2272046 | 1.95 x 10 ⁻²¹ |
| 12q13.2 | <i>RAB5B/SUOX</i> | rs705702 | 8.64 x 10 ⁻²⁶ |
| 16q12.1 | <i>TOX3</i> | rs4784165 | 3.64 x 10 ⁻¹¹ |
| 19p13.3 | <i>INSR</i> | rs2059807 | 1.09 x 10 ⁻⁸ |
| 20q13.2 | <i>SUMO1P1</i> | rs6022786 | 1.83 x 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
Tugce Karaderi⁵, Thomas M
Corrine K. Welt¹¹, Evanthia
Yi Zhang^{16,17}, Roland G. Jar
Network[#], Elisabet Stener-V

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

ng¹, Ji Young Lee¹, Ryan Sisk¹,
ilia M. Lindgren^{5,10},
podarzi¹⁴, Ricardo Azziz¹⁵,
eproductive Medicine

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OPEN

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

Felix R. Day¹, David A. Hind
Andrew Bjornes⁵, Linda Bro
Guillaume Laval¹⁰, Iain Mat
Robert A. Scott¹, Patrick Sul
Corrine Welt¹⁴, Kari Stefans

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

ir⁴, Richa Saxena⁵,
ie A. Lawlor^{8,9},
ndy Meun¹², Susan Ring^{8,9},
Unnur Thorsteinsdottir^{4,13},
B. Perry^{1,*}

Updated PCOS GWAS loci

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



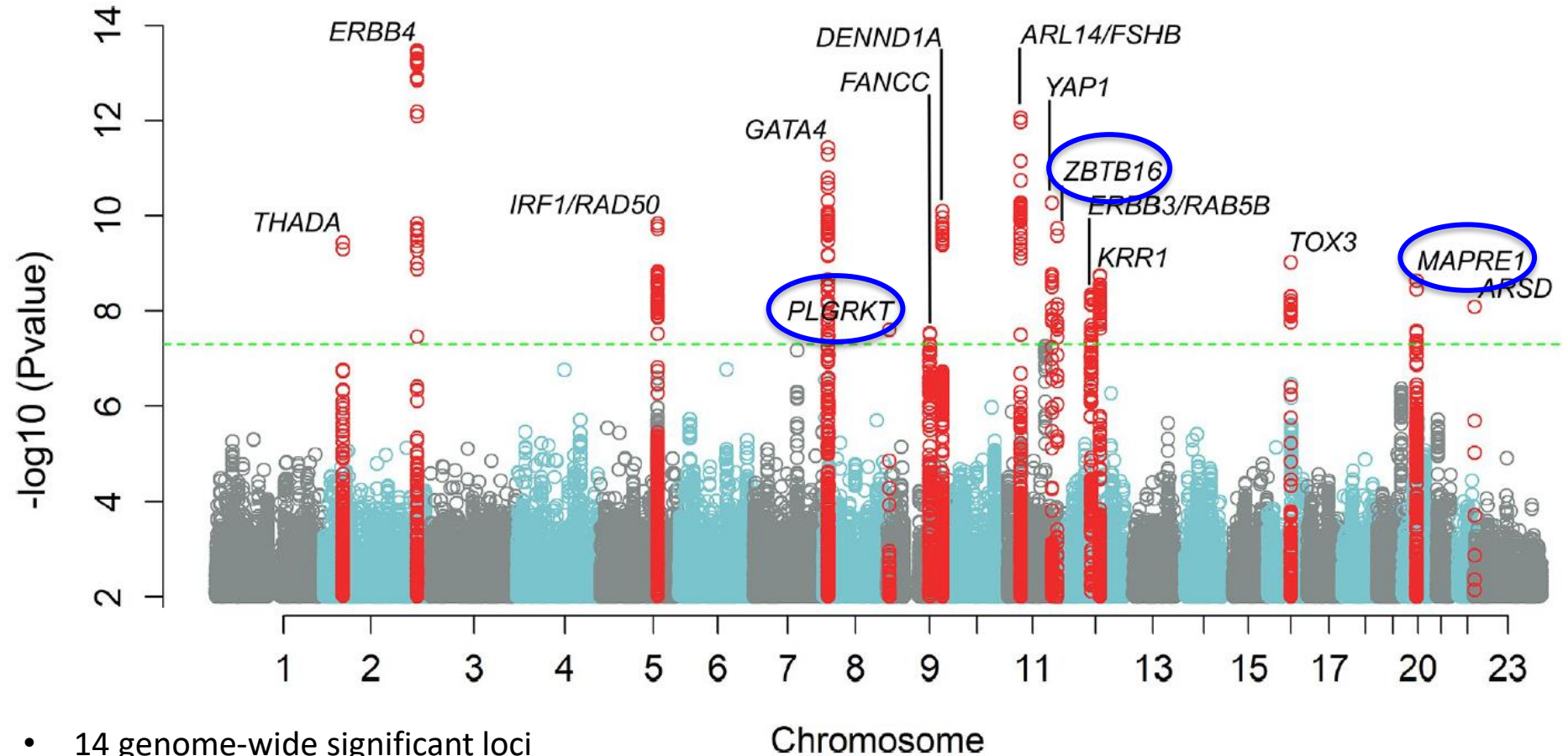
| POPULATION | CASES | CONTROLS | DIAGNOSTIC CRITERIA |
|--------------|---------------|----------------|---------------------|
| 23andMe | 5,184 | 82,759 | Self-reported |
| deCODE | 1,410 | 7,050 | Rotterdam/NIH |
| Rotterdam | 1,184 | 5,799 | Rotterdam/NIH |
| Chicago | 984 | 2,963 | NIH |
| Oxford | 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

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?

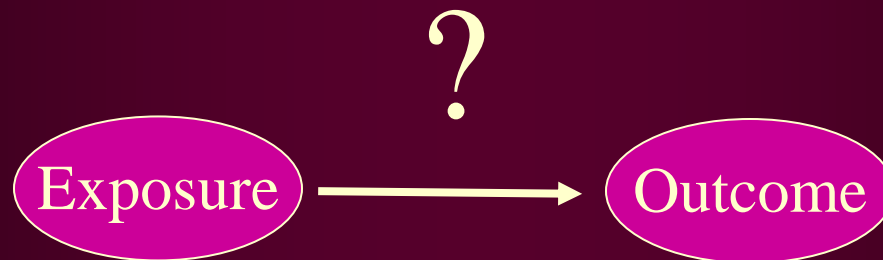
Neuroendocrine and metabolic dysregulation in PCOS

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

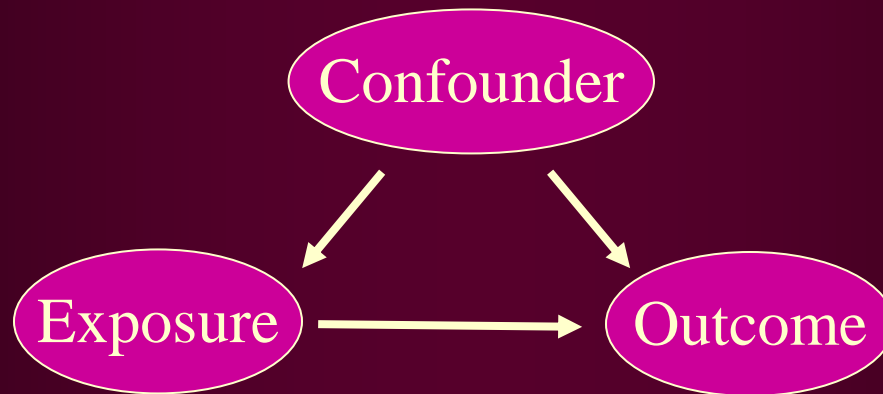
GWAS and Mendelian randomization (MR)

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



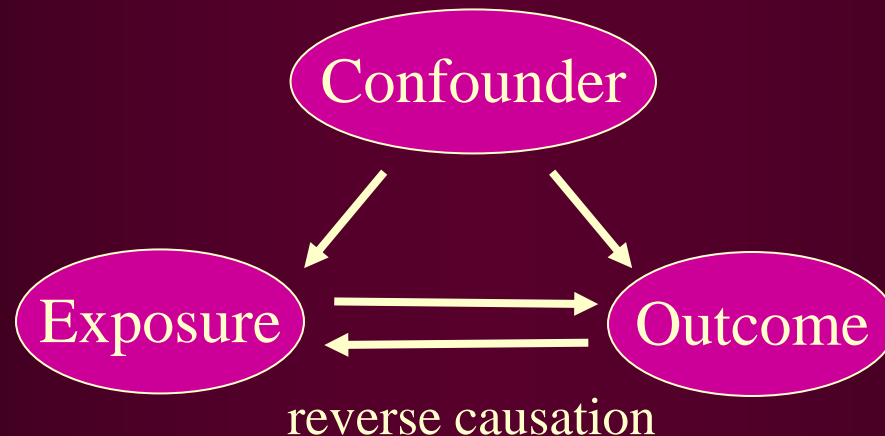
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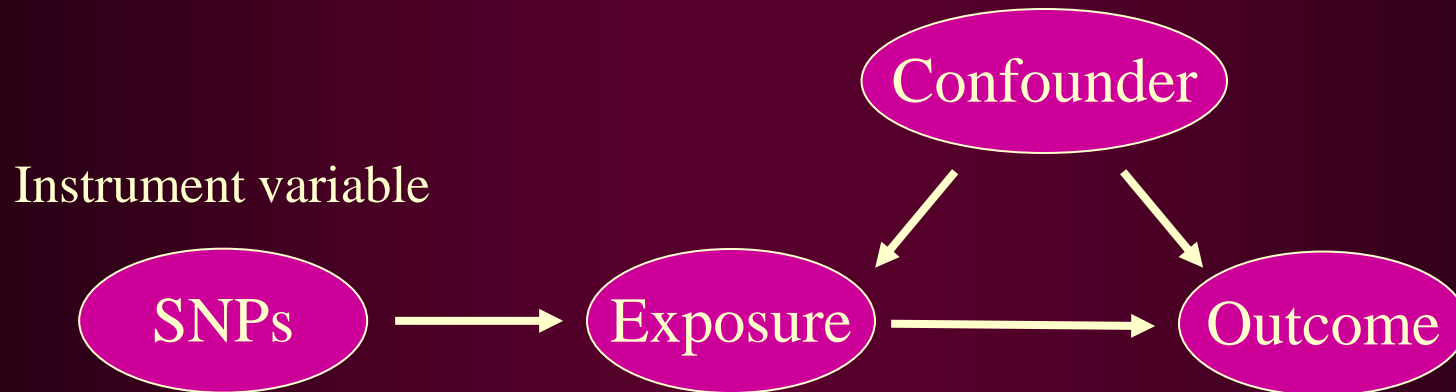
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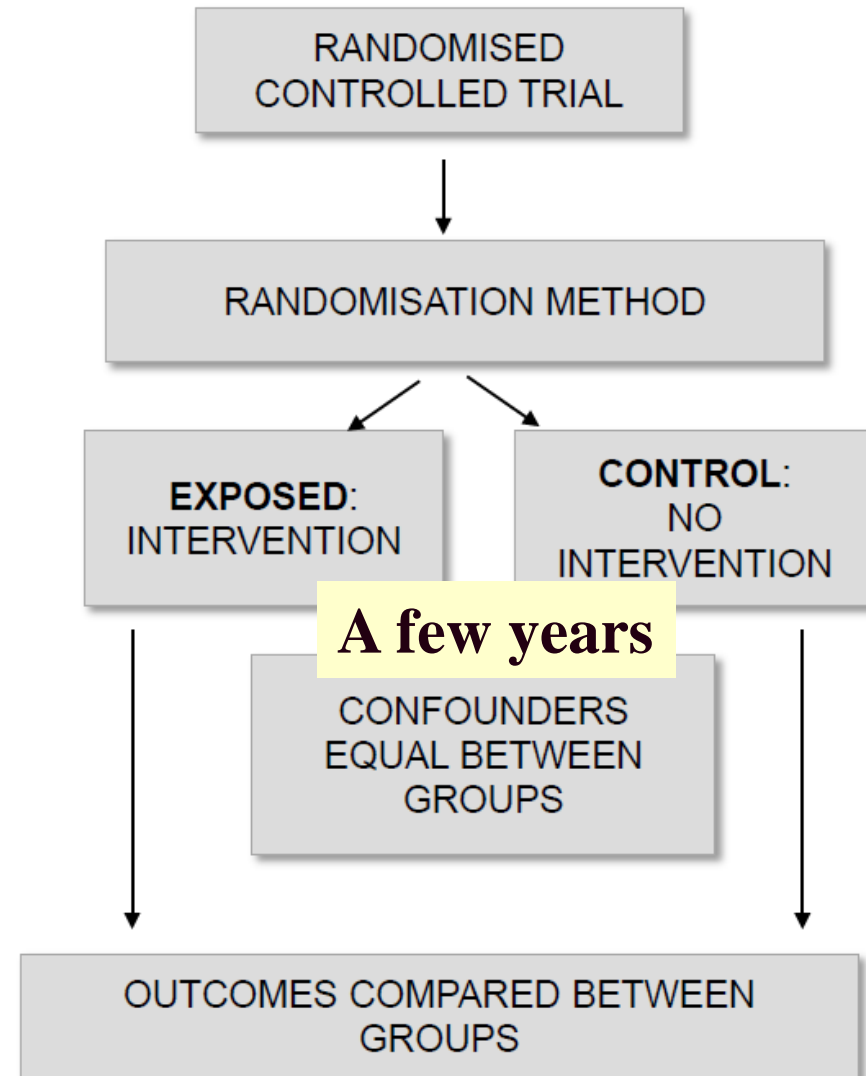
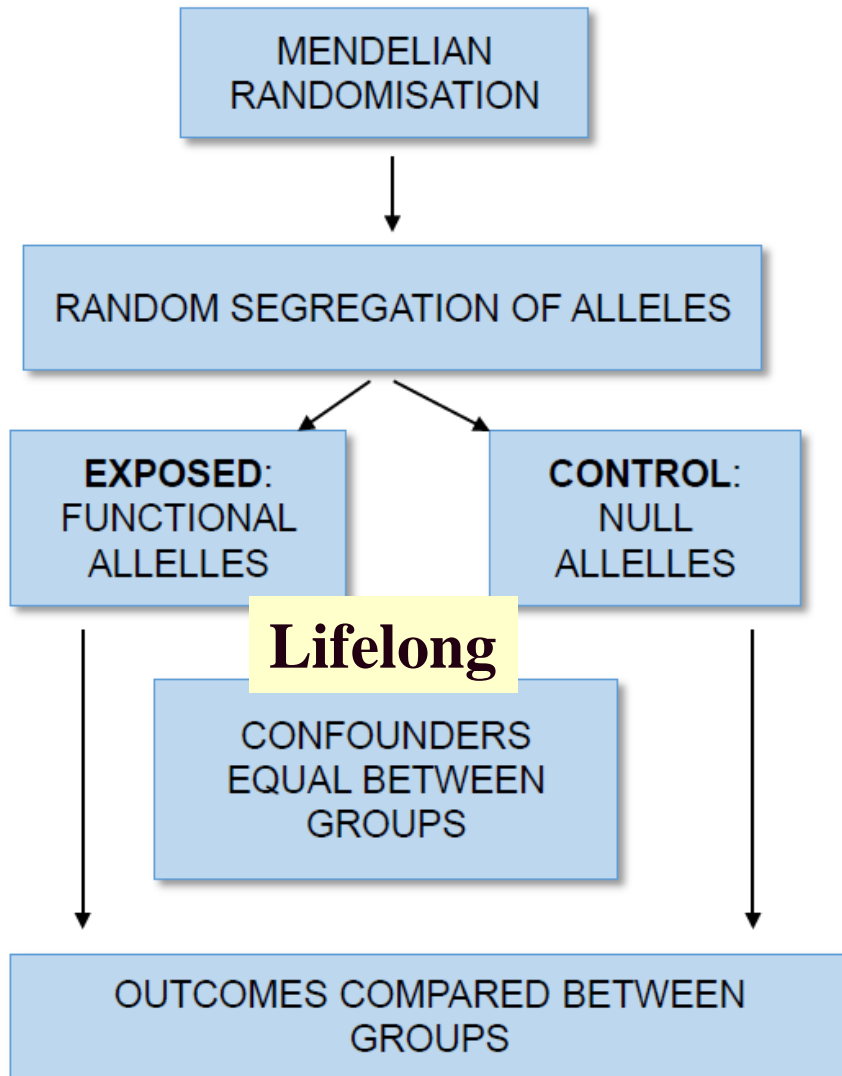
GWAS and Mendelian randomization (MR)

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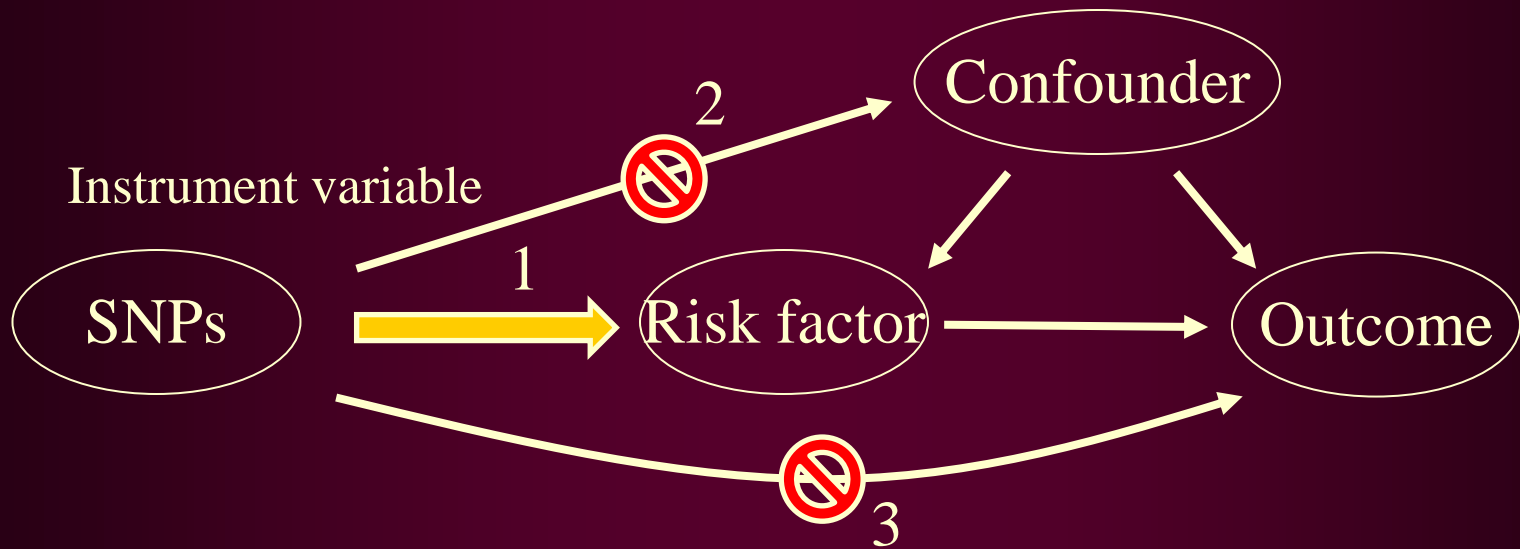


Causality: genetically predicted effect exposure on the outcome

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 | <i>Higher risk</i> | 0.19 | — | — | — | — | — |
| Birth weight | <i>Higher risk</i> | 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 | <i>Lower risk</i> | 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-density 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

Mendelian randomization in PCOS

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

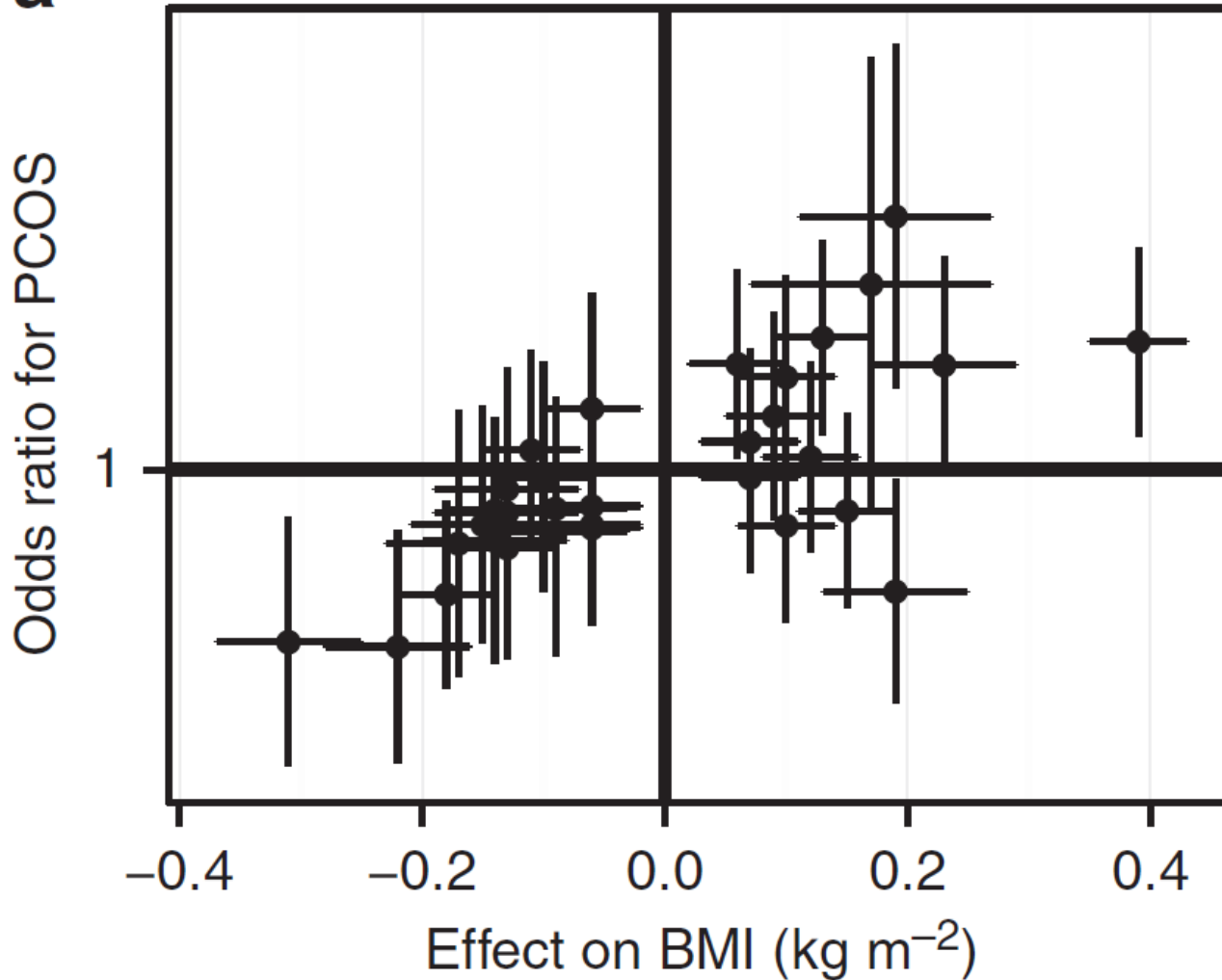
*Loci used were initially reported in an analysis of fasting insulin adjusted for BMI.

¹IVW = 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

Mendelian randomization in PCOS

a



**Obesity
causes
PCOS**

Same
result in
several
MR
studies

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



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

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

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

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 | <i>P</i> | <i>F</i> statistic |
|--------------|------------|---------------|--------------|-------|---------|-------|-------------------|----------|--------------------|
| 2:43638838 | rs13429458 | A | C | 0.81 | 0.401 | 0.040 | <i>THADA</i> | 1.73E−23 | 99.75 |
| 2:48978159 | rs13405728 | A | G | 0.754 | 0.343 | 0.037 | <i>LHCGR</i> | 7.55E−21 | 87.72 |
| 2:49201612 | rs2268361 | C | T | 0.504 | 0.139 | 0.020 | <i>FSHR</i> | 9.89E−13 | 50.87 |
| 2:49247832 | rs2349415 | T | C | 0.181 | 0.174 | 0.025 | <i>FSHR</i> | 2.35E−12 | 49.17 |
| 9:97648587 | rs4385527 | G | A | 0.781 | 0.174 | 0.030 | <i>C9orf3</i> | 5.87E−09 | 33.88 |
| 9:97741336 | rs3802457 | G | A | 0.904 | 0.261 | 0.035 | <i>C9orf3</i> | 5.28E−14 | 56.62 |
| 9:126525212 | rs2479106 | G | A | 0.222 | 0.293 | 0.033 | <i>DENND1A</i> | 8.12E−19 | 78.47 |
| 11:102070639 | rs1894116 | G | A | 0.194 | 0.239 | 0.024 | <i>YAP1</i> | 1.08E−22 | 96.12 |
| 12:56390636 | rs705702 | G | A | 0.245 | 0.239 | 0.023 | <i>RAB5B/SUOX</i> | 8.64E−26 | 110.25 |
| 12:66224461 | rs2272046 | A | C | 0.907 | 0.357 | 0.038 | <i>HMGGA2</i> | 1.95E−21 | 90.4 |
| 16:52347819 | rs4784165 | G | T | 0.325 | 0.140 | 0.021 | <i>TOX3</i> | 3.64E−11 | 43.8 |
| 19:7166109 | rs2059807 | G | A | 0.301 | 0.131 | 0.023 | <i>INSR</i> | 1.09E−08 | 32.67 |
| 20:52447303 | rs6022786 | A | G | 0.339 | 0.122 | 0.020 | <i>SUMO1P1</i> | 1.83E−09 | 36.15 |

Chr, chromosome; EAF, effect allele frequency.

F statistic 66.6

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 CARDIo GRAMplusC4D | 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

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)

MR Results

| Trait | IVW | |
|----------------------------|------------------|----------|
| | OR (95% CI) | <i>P</i> |
| 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

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

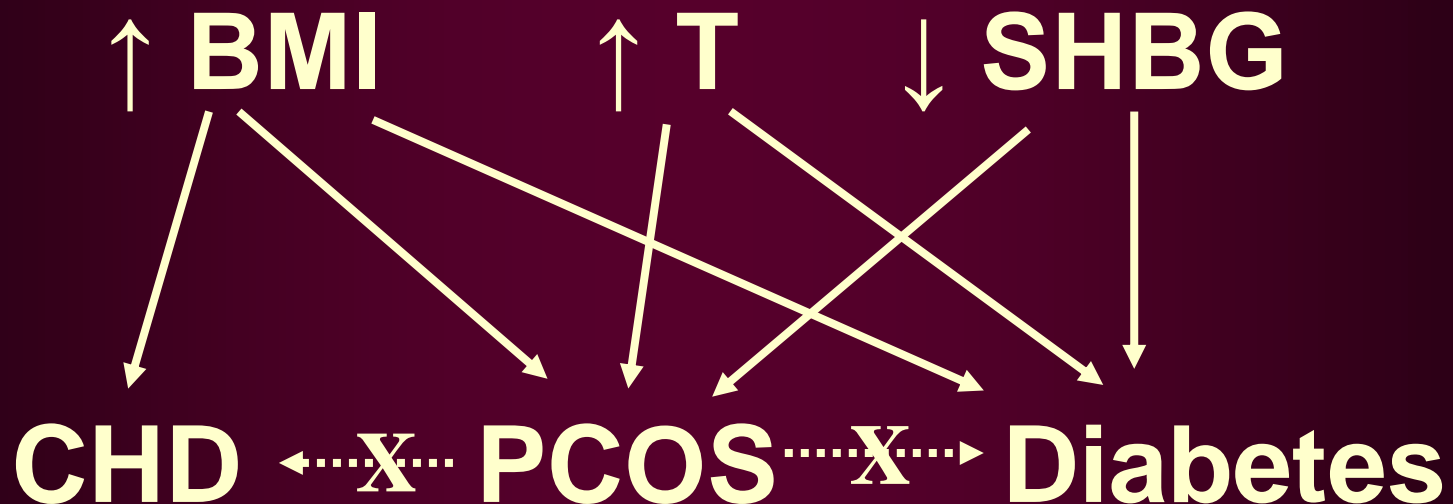


PCOS and adverse cardiometabolic outcomes

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

PCOS and adverse cardiometabolic outcomes

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



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