PIPADOR REVISION

MRCOG Part 1 Revision Notes

Multifactorial Inheritance

GENETICS • LECTURE 80

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 80: Multifactorial Inheritance

Genetics • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

POPULATION	RELATIVES / RISK	GENES	ENVIRONMENT / PREVENTION	COUNSELLING

LEARNING OBJECTIVES — tick off as you go

- ☐ Define polygenic and multifactorial traits; explain the liability–threshold model.
- ☐ Know what raises recurrence risk, including the Carter effect.
- ☐ Quote recurrence risks for the common obstetric conditions.
- ☐ Explain heritability, twin/family studies, GWAS and polygenic risk scores.
- ☐ Apply to counselling and prevention (folic acid, diabetes control, smoking).

1 Concepts

IN ONE LINE: *Many genes of small effect + environment. Continuous traits (height, BP) form a bell curve; 'yes/no' diseases appear when total LIABILITY crosses a THRESHOLD.*

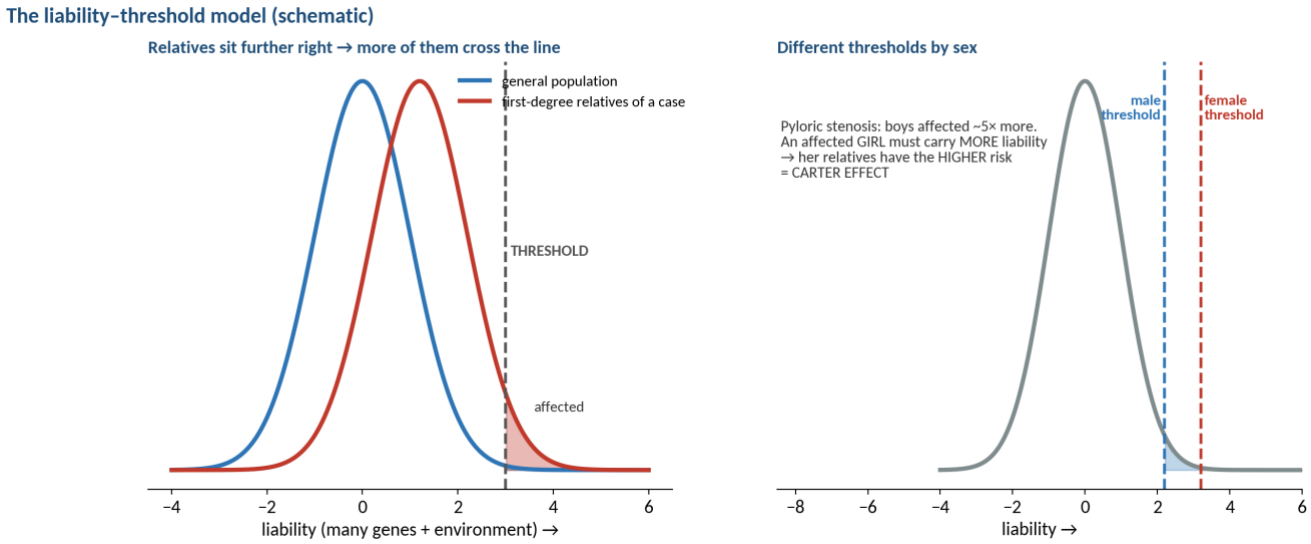


Figure 1. Liability–threshold model and the Carter effect.

2 Recurrence Risk

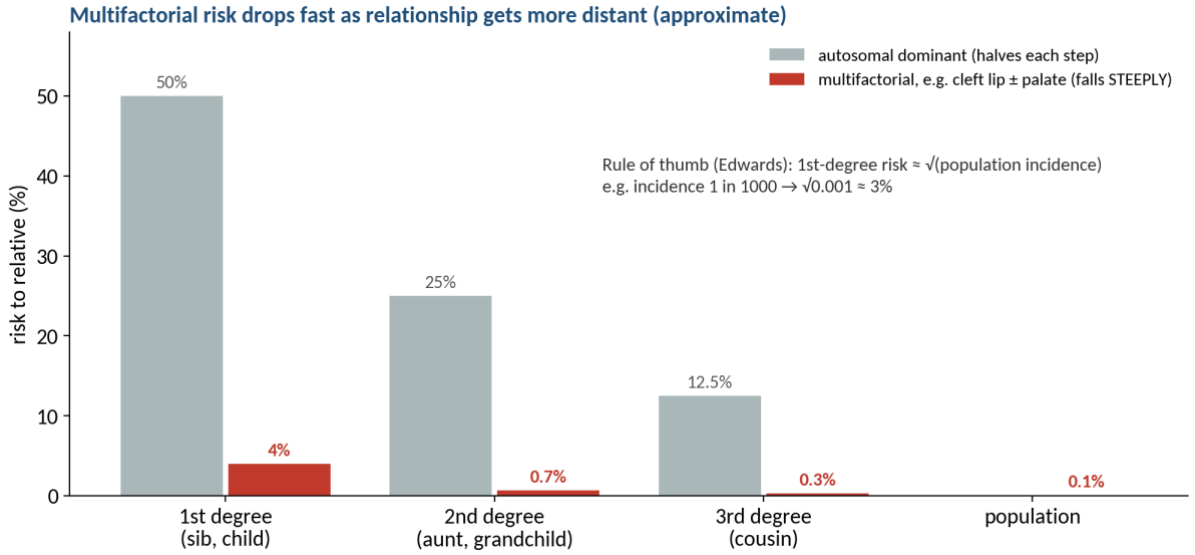


Figure 2. Risk falls steeply with distance.

Risk is HIGHER when…	Why
More relatives affected	Family carries more liability (e.g. NTD: ~4% after one, ~10% after two)
Index case is more SEVERE	e.g. bilateral cleft lip + palate > unilateral cleft lip
Index case is the LESS-affected sex	Carter effect — needed more liability to be affected
Relative is CLOSE	Shares more genes; falls sharply 1st → 2nd → 3rd degree
Consanguinity	Modest increase (shared alleles) — much smaller effect than in AR disease

MNEMONIC / MEMORY HOOK

'Square-root rule' — risk to a first-degree relative ≈ √(population incidence): 1 in 1000 → ~3%. Works best for highly heritable conditions.

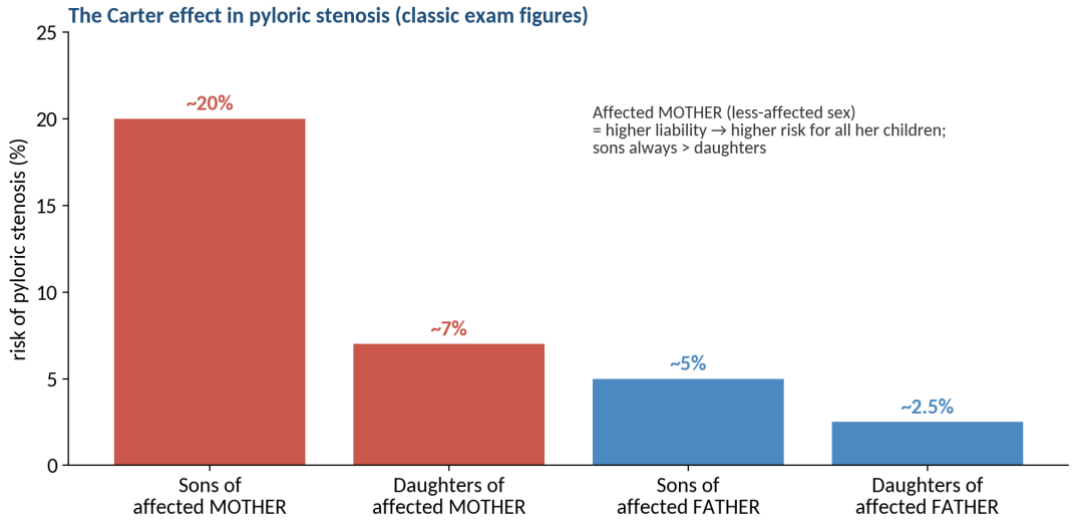


Figure 3. Carter effect — pyloric stenosis.

3 Conditions in O&G

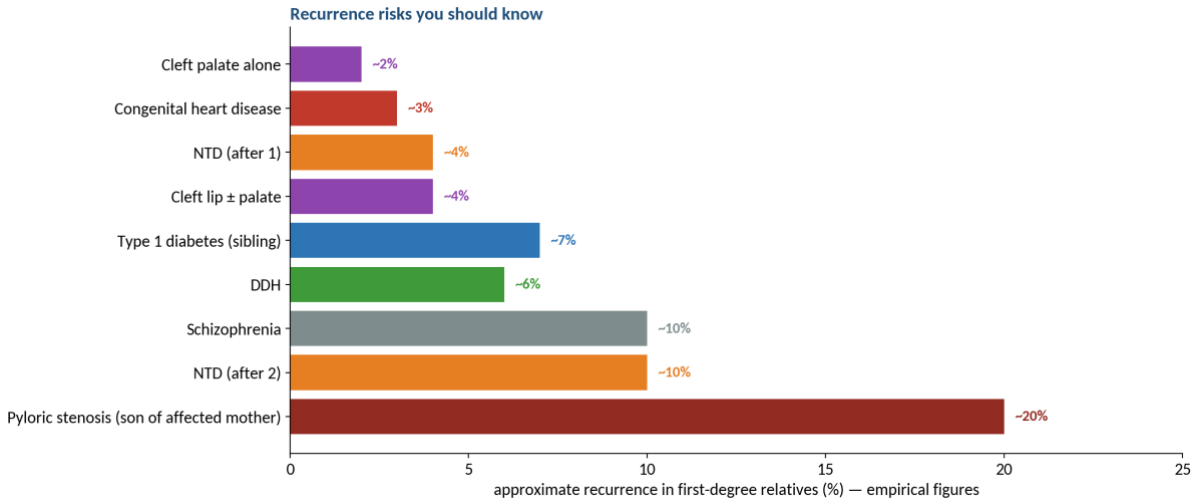


Figure 4. Recurrence risks.

Condition	Points
Neural tube defects	~1 in 1000 UK; folate-sensitive. Folic acid 400 µg to 12 weeks; 5 mg if previous NTD/family history, diabetes, BMI ≥ 30, antiepileptics, sickle/thalassaemia. Folate supports one-carbon metabolism (DNA synthesis, methylation; MTHFR variants)
Cleft lip ± palate / CP	Different mechanisms — CL±P ~4% recurrence, CP ~2%; smoking, alcohol, antiepileptics; exclude syndromes (Van der Woude, 22q11.2)
Congenital heart disease	~8 per 1000; ~2–3% after one child, ~5–10% after two; higher if MOTHER affected; pre-existing diabetes
Pyloric stenosis	Boys ~5×; Carter effect (figure 3)
DDH	Girls, breech, first-born, family history, oligohydramnios
Type 1 diabetes	Population ~0.4%; sib ~6–7%; father affected ~6% > mother ~2–3%; MZ twin ~30–50%; HLA-DR3/DR4
Type 2 diabetes, hypertension, pre-eclampsia, asthma	Strong family + lifestyle components — risks vary widely

4 Measuring Genetic Contribution

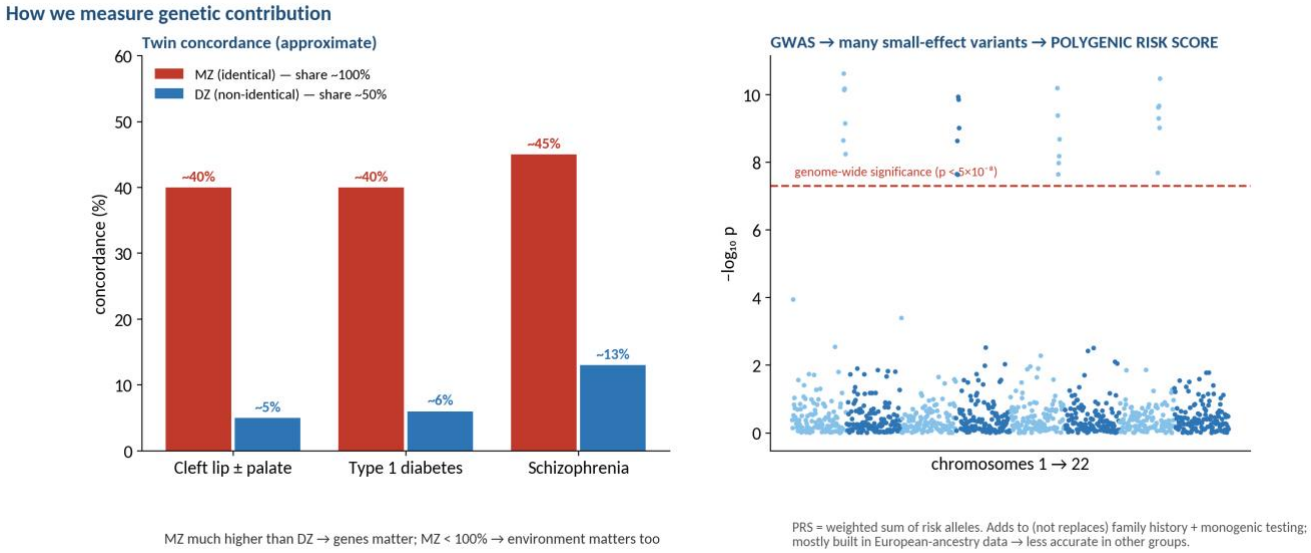


Figure 5. Twins, GWAS and polygenic scores.

Method	What it shows
Heritability (h^2)	Share of variation due to genes in THAT population (0–1): height ~0.8, schizophrenia ~0.8, T2DM ~0.5–0.7 — not 'how genetic' one person is
Family studies (λR)	How much more common in relatives than the population
Twin studies	MZ vs DZ concordance; twins reared apart
Adoption studies	Biological vs adoptive parents → genes vs shared environment
GWAS	Common SNPs of small effect in cases vs controls (linkage studies suit rarer, larger-effect variants)
Polygenic risk score	Weighted sum of risk alleles; refines risk with family history; less accurate outside European ancestry

5 Counselling

EMPIRICAL RISKS

- Come from observed families, not Punnett squares
- Population averages — adjust for family details
- **Most pregnancies after one affected child are unaffected** (~95–97%)
- Check it isn't a Mendelian/syndromic condition in disguise

PRE-CONCEPTION

- **Folic acid** (dose by risk)
- **HbA1c < 48 mmol/mol** in diabetes; 5 mg folic acid
- Stop smoking and alcohol; review antiepileptics
- Detailed anomaly scan ± fetal echo next pregnancy

★ PEARL

Carter effect: affected member of the LESS-affected sex → HIGHER risk to relatives (pyloric stenosis: sons of affected mothers ~20%).

Mendelian risk halves with each degree; multifactorial risk falls far faster.

6 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

√ incidence 1st-degree risk	**~4% / ~10%** NTD after 1 / 2	**~4% / ~2%** CL±P / CP alone	**~3%** CHD after one child
~20% PS: son of affected mum	**~6% vs ~3%** T1DM: father vs mother	**~0.8** h^2 height, schizophrenia	**< 48** HbA1c pre-pregnancy

HIGH-YIELD CHECKLIST

- ☐ Multifactorial = many genes + environment; threshold model.
- ☐ Risk ↑ with number affected, severity, less-affected sex, closeness.
- ☐ Carter effect — pyloric stenosis.
- ☐ 1st-degree risk ≈ √(incidence); falls steeply with distance.
- ☐ NTD 4% → 10%; CL±P 4%; CP 2%; CHD ~3%.
- ☐ T1DM: affected father > mother.
- ☐ Heritability is population-specific; twin + adoption studies.
- ☐ GWAS → PRS; ancestry bias.
- ☐ Empirical risks; exclude Mendelian mimics.
- ☐ Prevention: folic acid, diabetes control, smoking, drugs.

Self-assessment — cover the right-hand column

Question	Answer
What is the threshold model?	Disease appears when total genetic + environmental liability exceeds a threshold
Define the Carter effect.	Higher recurrence when the index case is of the less commonly affected sex
Classic example of the Carter effect?	Pyloric stenosis
Recurrence of NTD after one affected child?	~4% (≈10% after two)
Rule of thumb for 1st-degree multifactorial risk?	√(population incidence)
Which parent with T1DM gives the higher risk?	Father (~6% vs ~2–3%)
Define heritability.	Proportion of trait variance due to genetic variance in a population
What do GWAS find?	Common variants of small effect
Main limitation of current PRS?	Built mostly on European-ancestry data
How does risk change with distance of relationship?	Falls steeply (faster than halving)

7 References

- Turnpenny P, Ellard S. Emery's Elements of Medical Genetics. 16th ed. 2021.
- Harper PS. Practical Genetic Counselling. 8th ed. 2020.
- NICE NG3. Diabetes in pregnancy. 2015 (updated 2020).