Inflammatory Bowel Disease
A selected overview

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Medical Director, Digestive Health Services Ltd

Medical Advisor, Christchurch Crohn's and Colitis Support Group

Who am I?

- Gastroenterologist with a passion for IBD
- Born and bred in Christchurch
- House Surgeon Nelson / Christchurch
- Gastroenterology Registrar, Christchurch
- PhD “Aspects of IBD in Canterbury”
- IBD Fellow, Box Hill Hospital, Melbourne
- IBD Researcher, Christchurch
- Nutrition Support Fellowship, St Mark’s, London

Acknowledgements

- Brian Poole
- Pharmaco / Ferring
  - Distributers of Pentasa

Conflicts of Interest

- I have received support to present research at international meetings from
  - Ferring/Pharmaco
  - Pharmatel Fresenius Kabi
  - Schering Plough
  - Abbott
  - Orphan

IBD – a selected overview

- IBD in NZ
  - A New Epidemic?
- What Causes IBD?
  - Insights from your backyard
- Drug Treatment of IBD
  - The battle to get and keep you well
- Diet and IBD
  - Are you what you eat?

IBD in New Zealand

A new epidemic?

canterbury medical research foundation

Department Of Gastroenterology, Christchurch Hospital

University of Otago
Te Whare Wānanga o Otāgo

Overview

- What is IBD
- Things that can get mixed up with IBD
- IBD International
- IBD in NZ (the past)
- IBD in NZ (now)
- What does the future hold?

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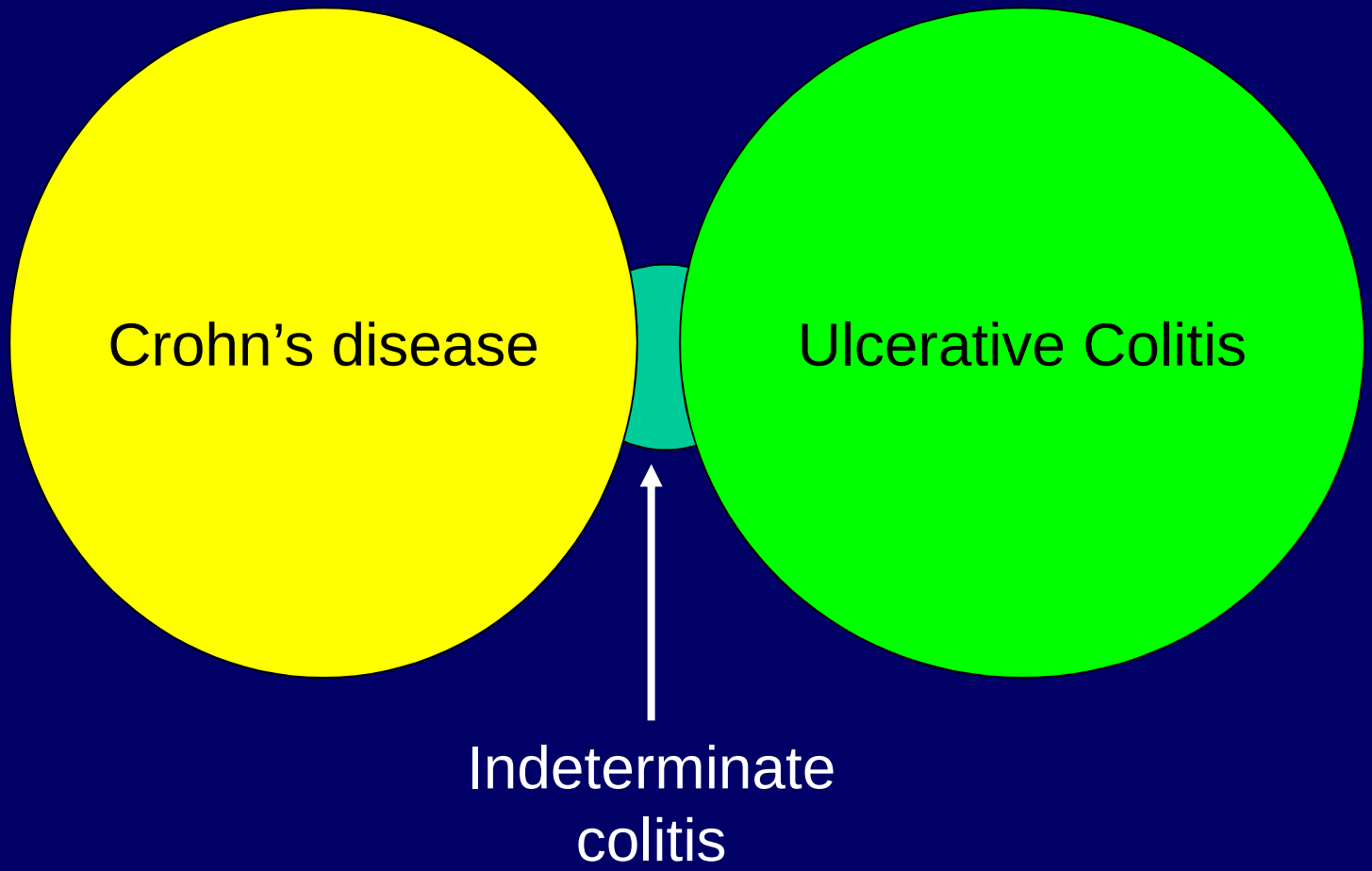
Inflammatory Bowel Disease



The Gastrointestinal Tract

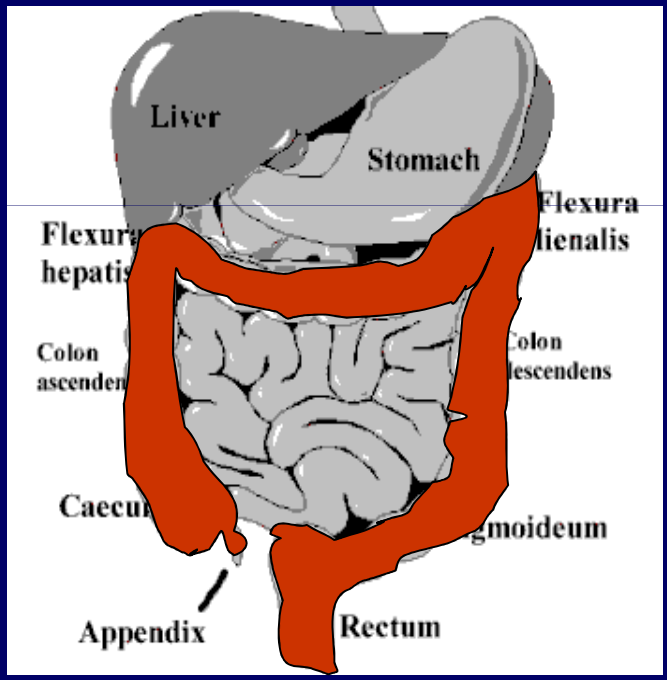
Crohn's disease

Any part of the GI tract

Patchy inflammation

Inflammation affects full thickness of intestine

Perianal disease



Ulcerative Colitis

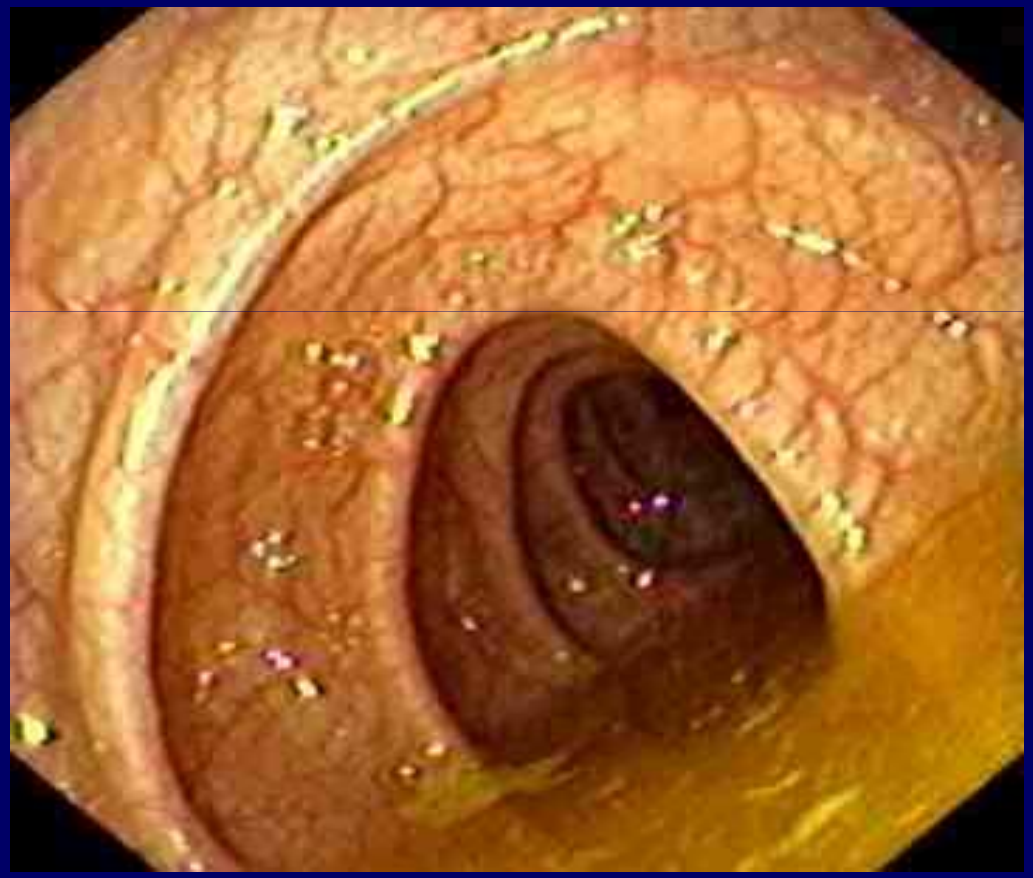
Colon only

Continuous inflammation

Inflammation starts at the bottom and moves proximally

Inflammation affects inner lining of bowel only (mucosa)

Normal Colon



Inflammatory Bowel Disease

Abdominal Pain

Diarrhoea

Rectal Bleeding

Weight Loss

Medication/ Surgery

Colorectal Cancer

Normal v IBD

Overview

- What is IBD
- Things that can get mixed up with IBD
- IBD International
- IBD in NZ (the past)
- IBD in NZ (now)
- What does the future hold?

IBD Differential Diagnosis

Other causes of GI Sx

- Irritable Bowel Syndrome (IBS)
- Colorectal Cancer
- Diverticular disease
- Microscopic colitis
- Coeliac disease

Other causes of Inflammation

- Infective gastroenteritis
- Drugs (NSAIDS)
- IBD
  - Crohn's disease
  - Ulcerative colitis

Overview

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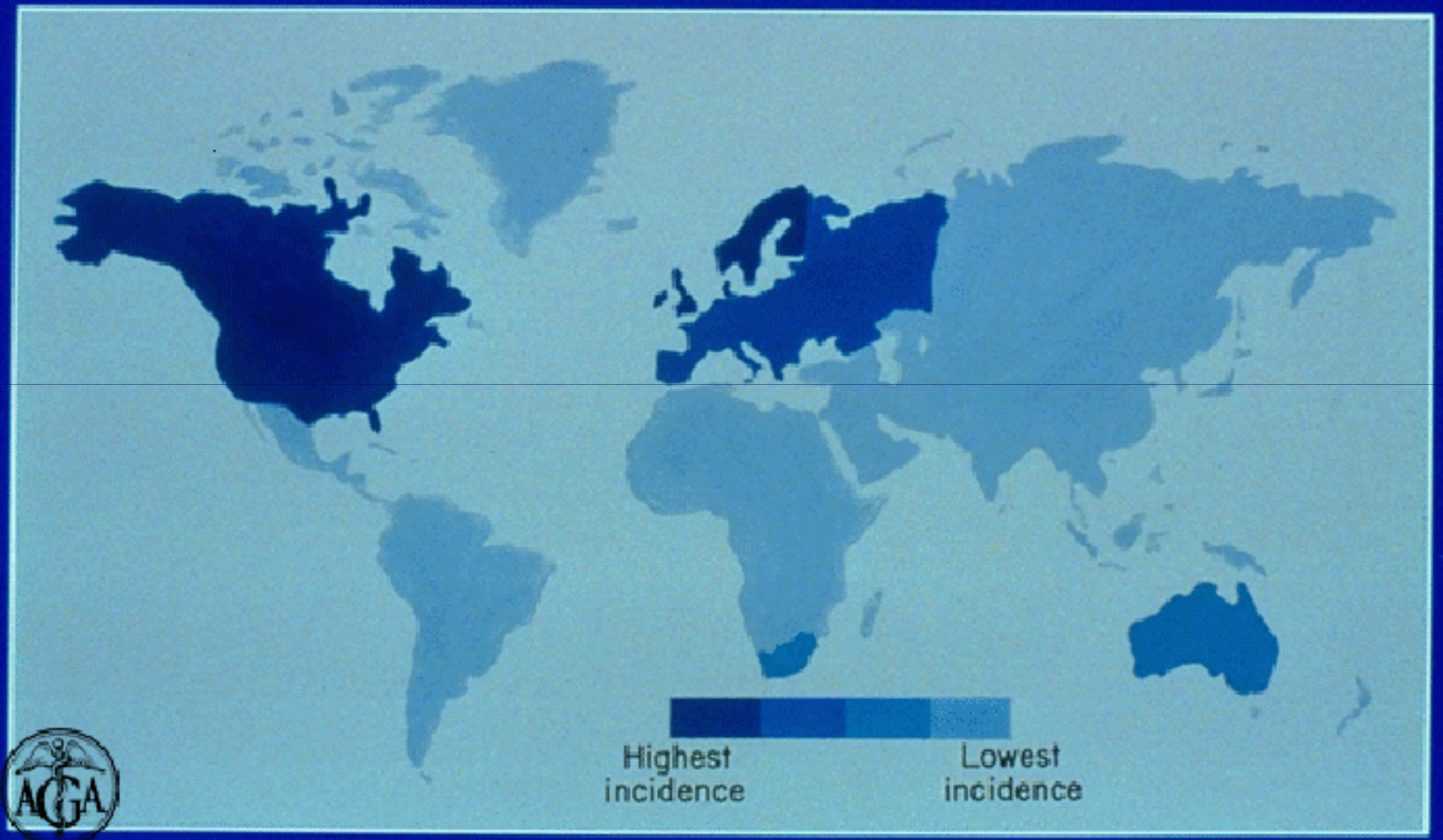
GEOGRAPHIC DISTRIBUTION OF IBD



Introduction
IBD epidemiology

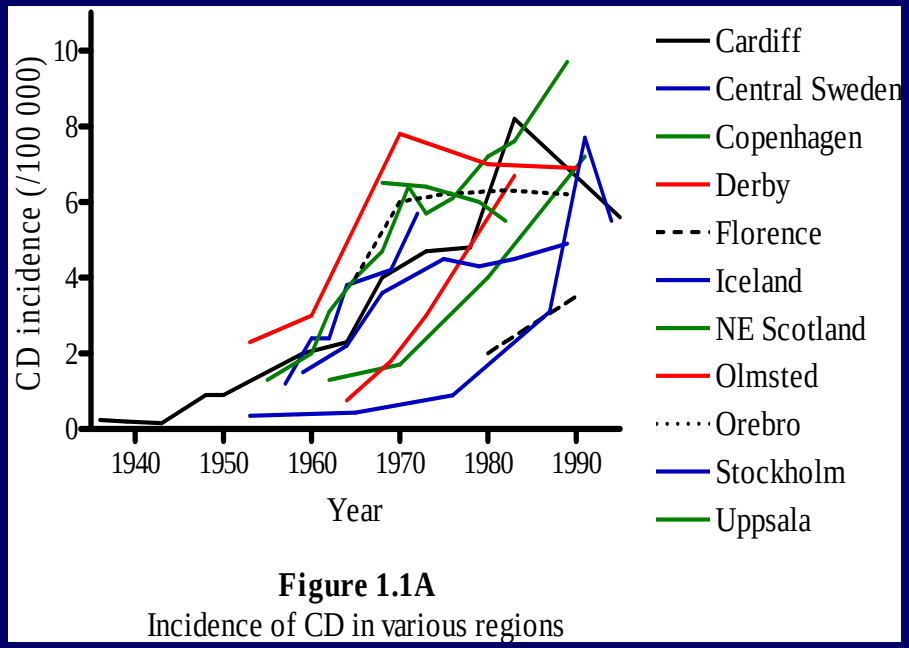


Figure 1.1A
Incidence of CD in various regions

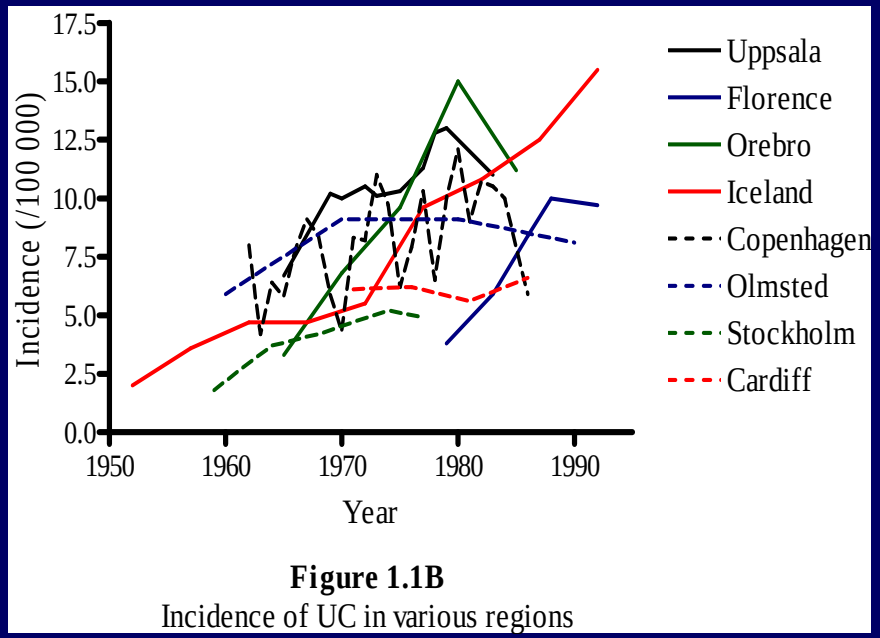


Figure 1.1B
Incidence of UC in various regions

The incidence of IBD has risen rapidly over the last 50 years

Overview

- What is IBD
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- IBD in NZ (the past)
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Epidemiological studies of IBD in New Zealand

- Wigley, *et al.*, 1962 **Wellington**
- Eason, *et al.*, 1982 **Auckland**
- Schlup, *et al*., 1986 **Otago**

Epidemiological studies of IBD in New Zealand

Wellington	Auckland	Otago
1962	1982	1986

UC is about as common as other places

CD is less common than other places

Very few Maori / Pacific Island people have IBD

Introduction
the reality in Christchurch

- clinics full of IBD patients
- most clinically difficult group of patients
- ↑ use of expensive tests/therapies
- CD >> UC
- little understanding of aetiology

How common is IBD in Canterbury?

- Try to find every person living in Canterbury ever diagnosed with IBD

= Prevalence

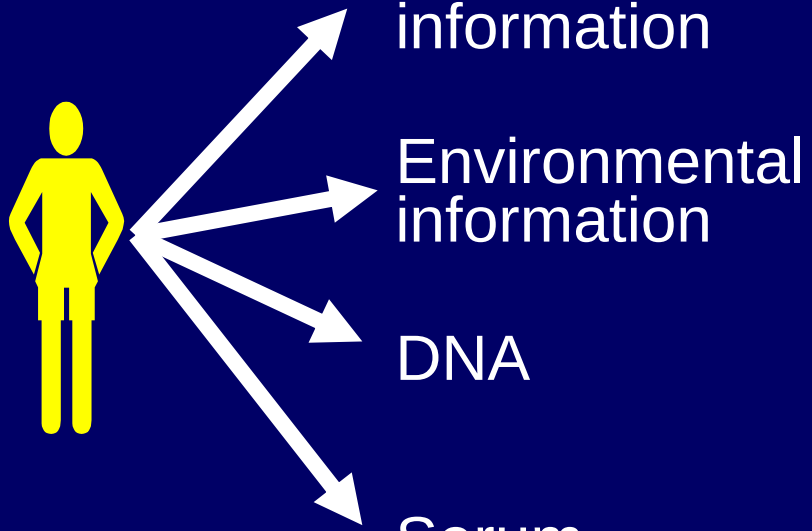
- Try to find every person living in Canterbury diagnosed with IBD in 2004

= Incidence

Methods

Case recruitment and prevalence study

- Outpatient clinics
- Inpatients
- Support Groups
- Advertising
- Direct Mail



The Canterbury IBD Study

Epidemiology

Genetic studies

Environmental risk factors

Drug studies

Role of microbes

Effect on people

Canterbury

464 700 people (2005)

75% live in Christchurch

10% of NZ population

Centralised health services

Good public/private health relationships

Canterbury, New Zealand

Incidence of IBD in Canterbury (2004)

CD 16.5 / 100 000

- Previous highest published 14.6/100 000 (Manitoba, Canada - 1994)

UC 7.6 / 100 000

- About average compared to other populations

Worldwide incidence of CD

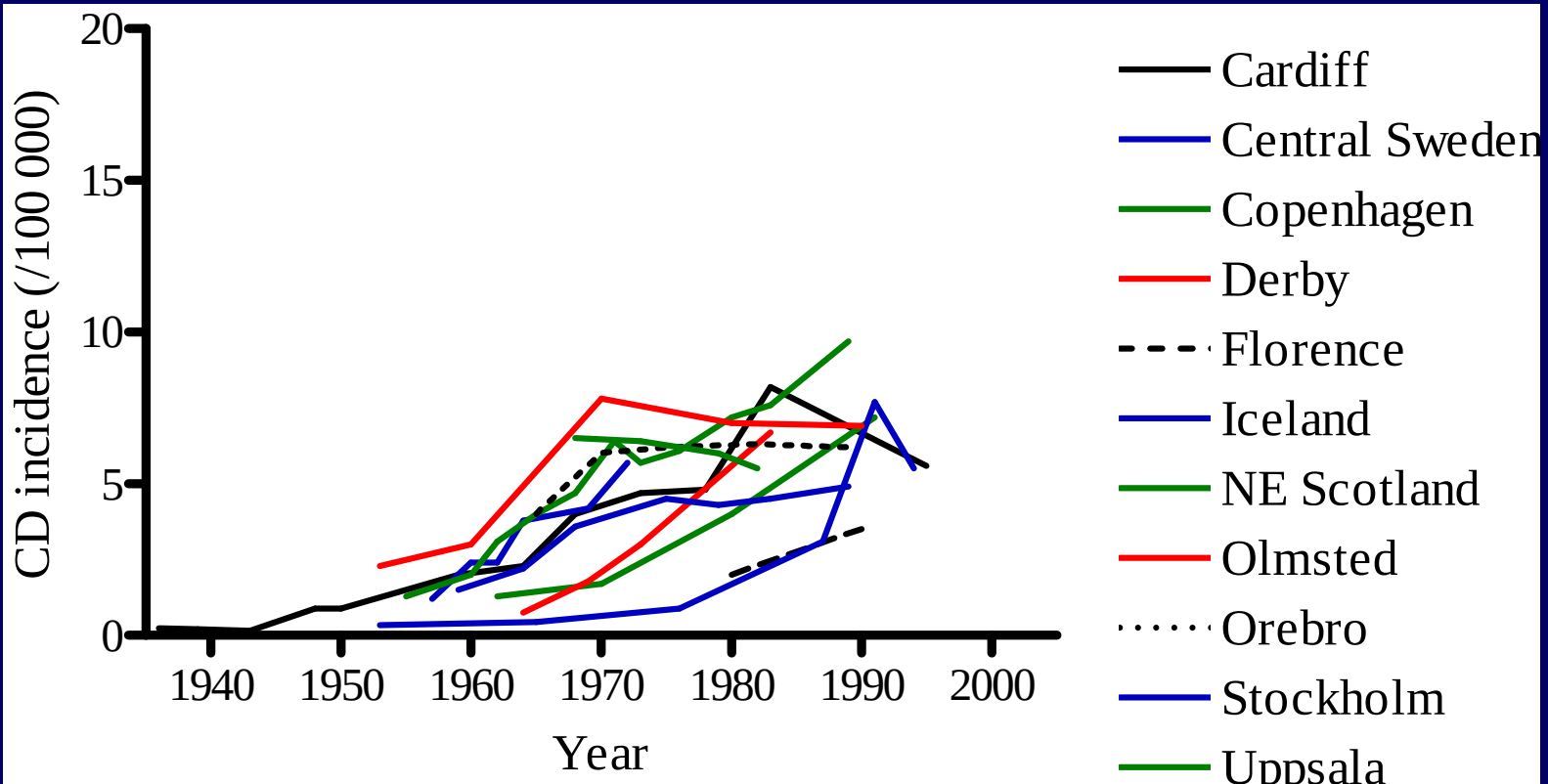


Figure 1.1A
Incidence of CD in various regions

Worldwide incidence of UC

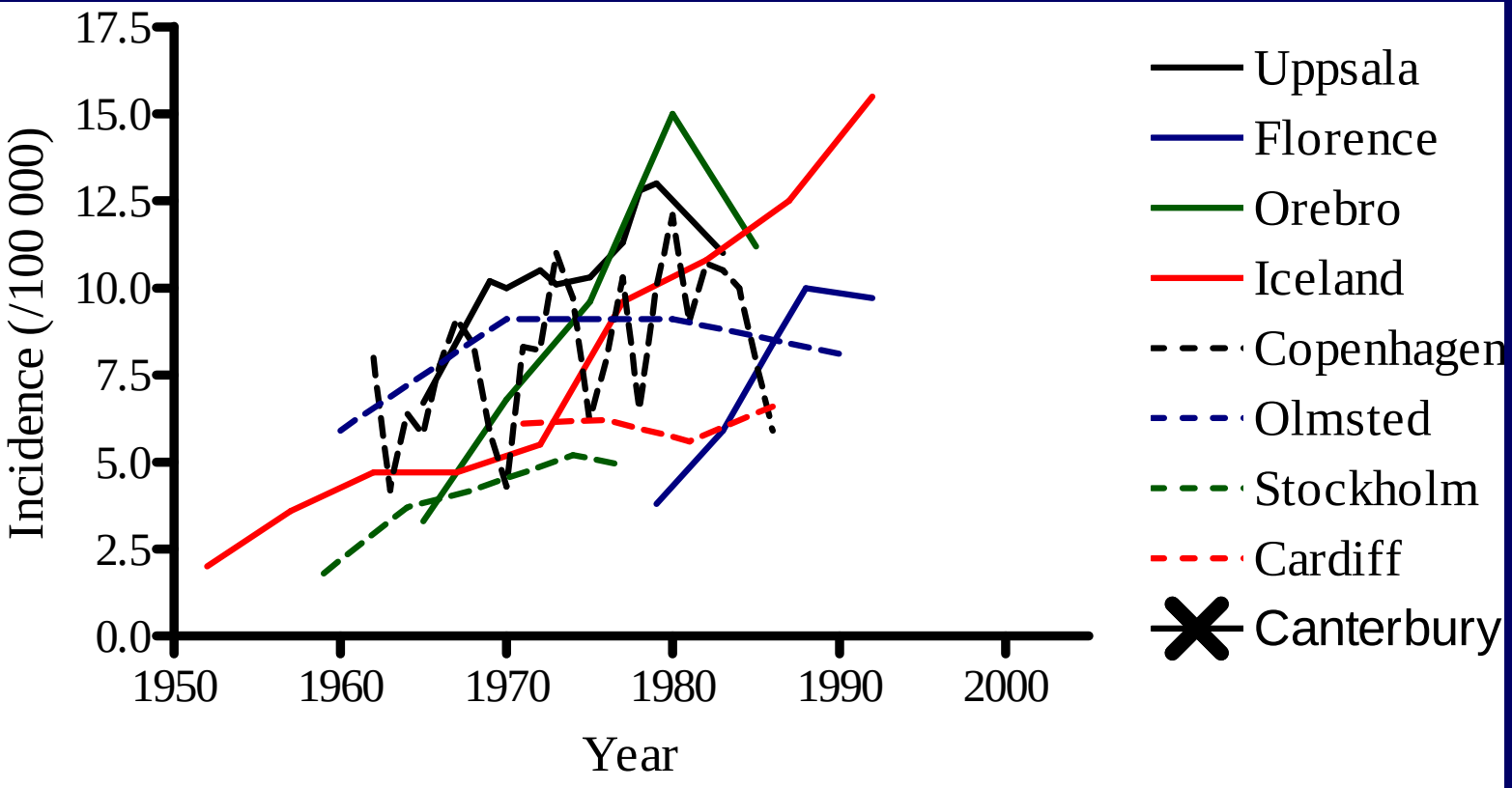


Figure 1.1B
Incidence of UC in various regions

Prevalence of IBD in Canterbury

Crohn's disease 715	
Ulcerative colitis 680	
IBD total 1420	

Prevalence of IBD in Canterbury

Crohn's disease 715	155 / 100 000
Ulcerative colitis 680	145 / 100 000
IBD total 1420	308 / 100 000

Location	Year	CD	UC
Canada (Mannitoba)	1984	199	170
Canterbury (NZ)	**2004**	**155**	**145**
Britain (Aberdeen)	1988	147	-
Sweden (Orebro)	1987	136	234
USA (Minnesota)	1991	133	229
Germany (Tubingen)	1994	55	25
Denmark (Copenhagen)	1987	54	161
Hungary (Veszprem)	2001	53	143
Israel (Jews – southern)	1992	51	-
Netherlands (Leiden)	1983	48	-
Italy (Florence)	1992	40	121
Faroe Islands	1988	32	157
Iceland (Nation-wide)	1979	10	122
Spain (Granada)	1989	9	21
Puerto Rico (South-west)	2000	6	13
India (Punjab)	2000	-	44

World-wide prevalence of IBD

(/100 000 population)

CD age of diagnosis

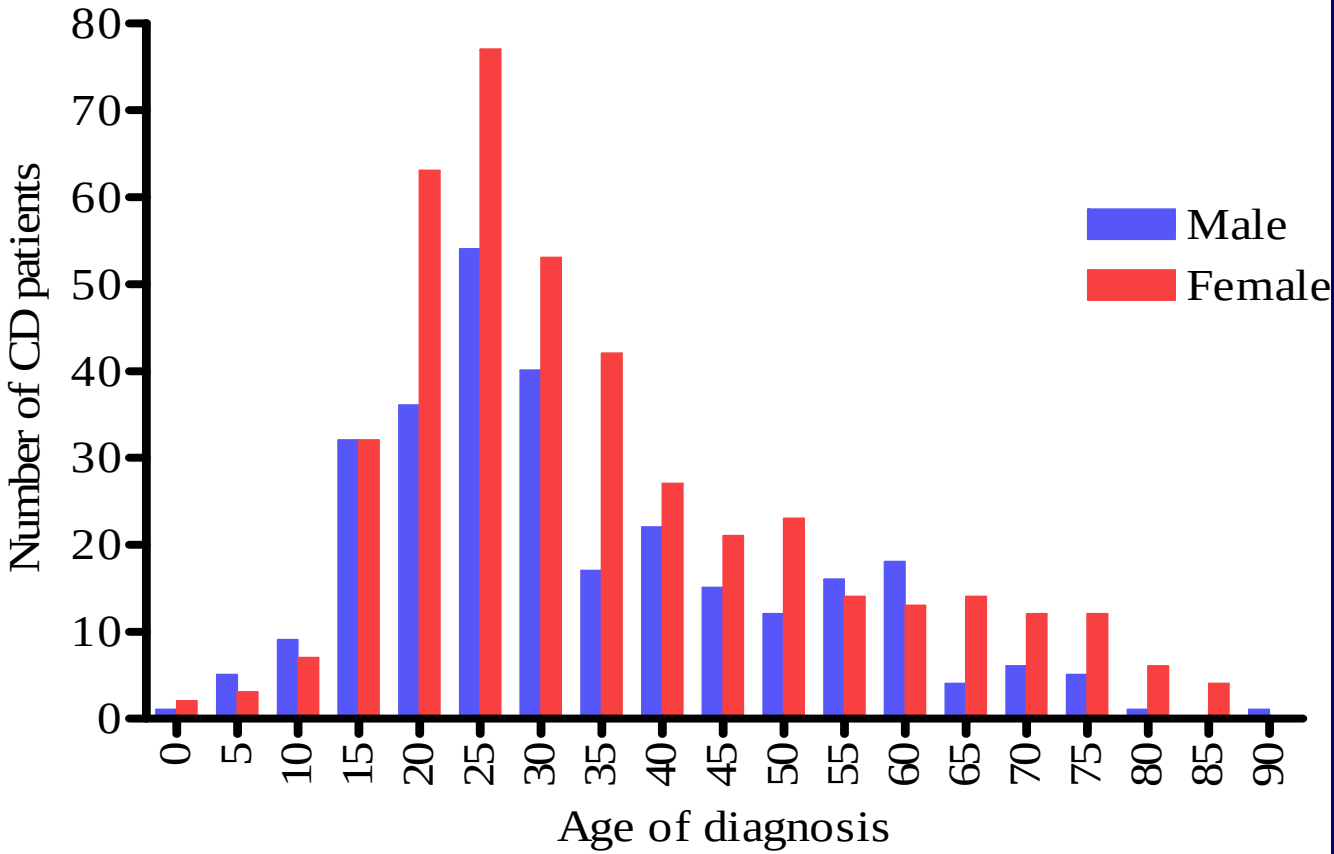


Figure 2.5A
CD age of diagnosis by sex

UC age of diagnosis

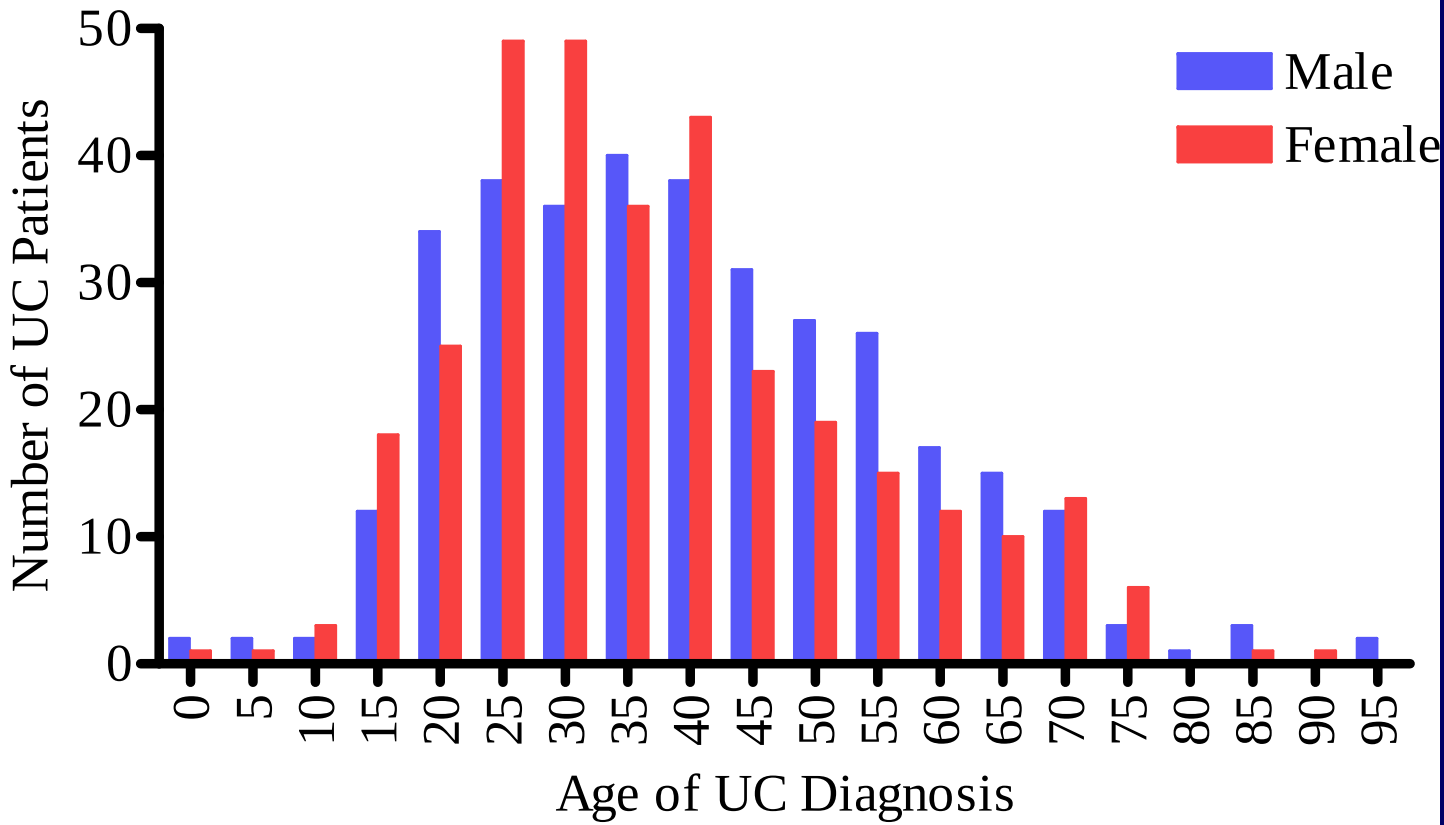
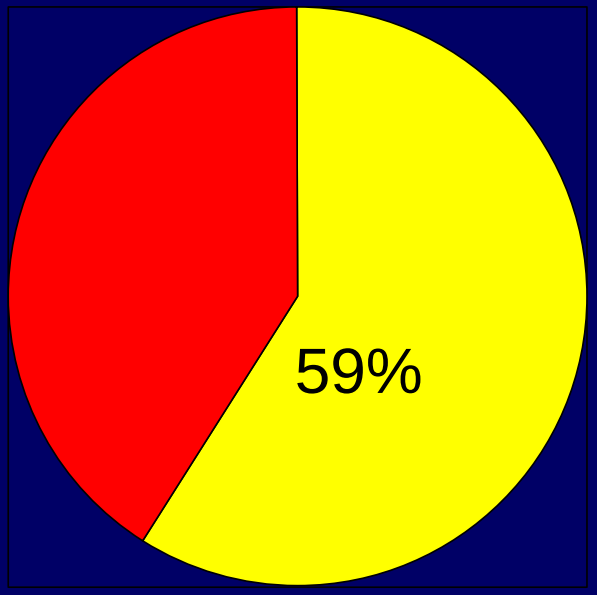


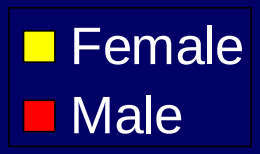
Figure 2.5B
UC Age of Diagnosis by Sex

IBD gender split

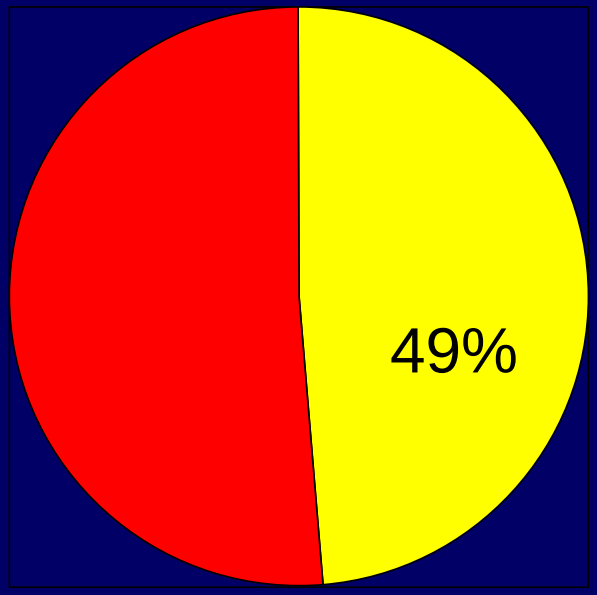
Crohn's disease



***p* = 0.042**



Ulcerative colitis



***p* = ns**

How common is IBD in Canterbury?

- In 2004, Canterbury had the highest rate of newly diagnosed CD ever recorded
- There is more CD than UC in Canterbury
- Women are more likely than men to get CD
- People are often diagnosed when young
- IBD - uncommon in Maori / rare in Pacific Islanders
- More medical services will be needed to treat people with IBD

IBD in New Zealand
a new epidemic?

ep·i·dem·ic(p -d m k) or **ep·i·dem·i·cal**(- -k l)

adj.

- Spreading rapidly and extensively by infection and affecting many individuals in an area or a population at the same time, as of a disease or illness.

n.

- An outbreak or unusually high occurrence of a disease or illness in a population or area.

The American Heritage® Stedman's Medical Dictionary
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What causes IBD?

Insights from your backyard

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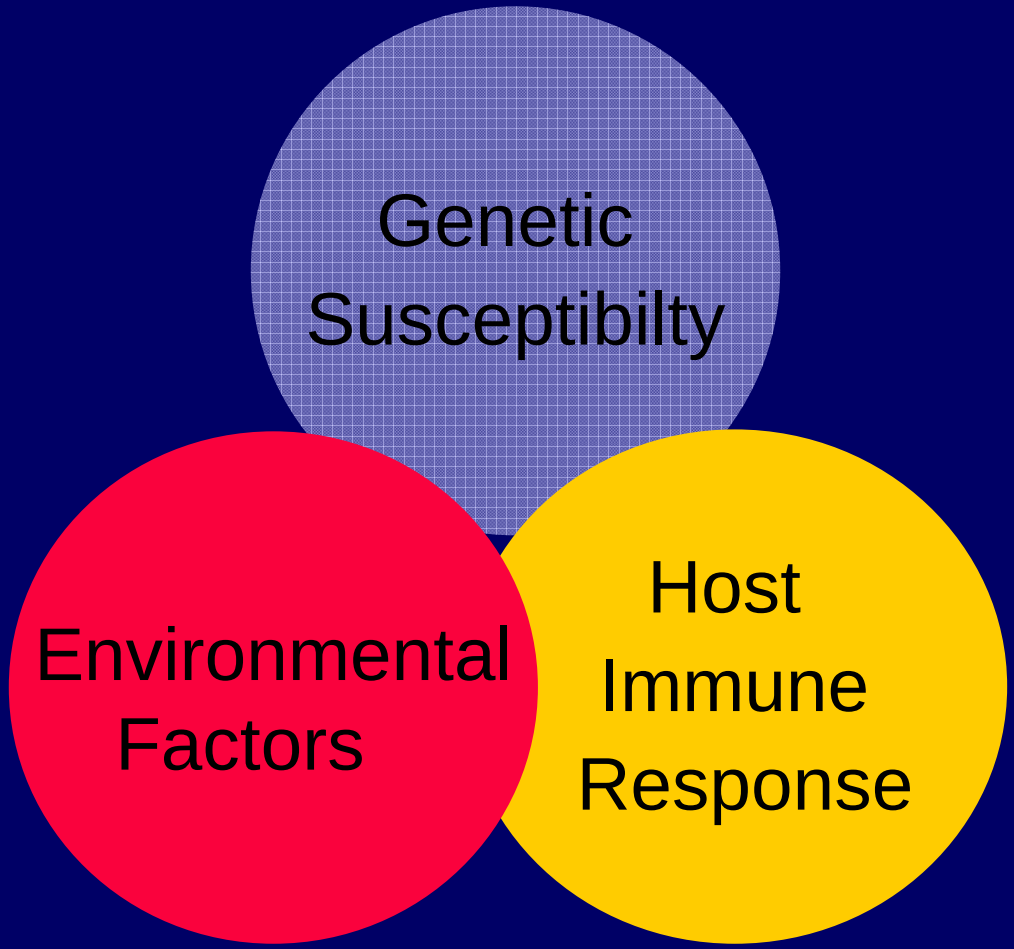
What causes IBD?

Insights from your backyard

- Genes
- The “coal face”
- The environment – the forgotten factor

Current concepts of IBD



IBD and Genes

Genes

If you have IBD, you are 3-10x more likely than someone without IBD to have an affected first degree relative

Are

If you are an identical twin with Crohn's disease, your twin has a 50% chance of having Crohn's disease as well

Important

How much genetic information does each of us contain?

- 60,000 genes in the human genome
- 2 metres of DNA in every cell
- many aspects of bodily function require multiple genes

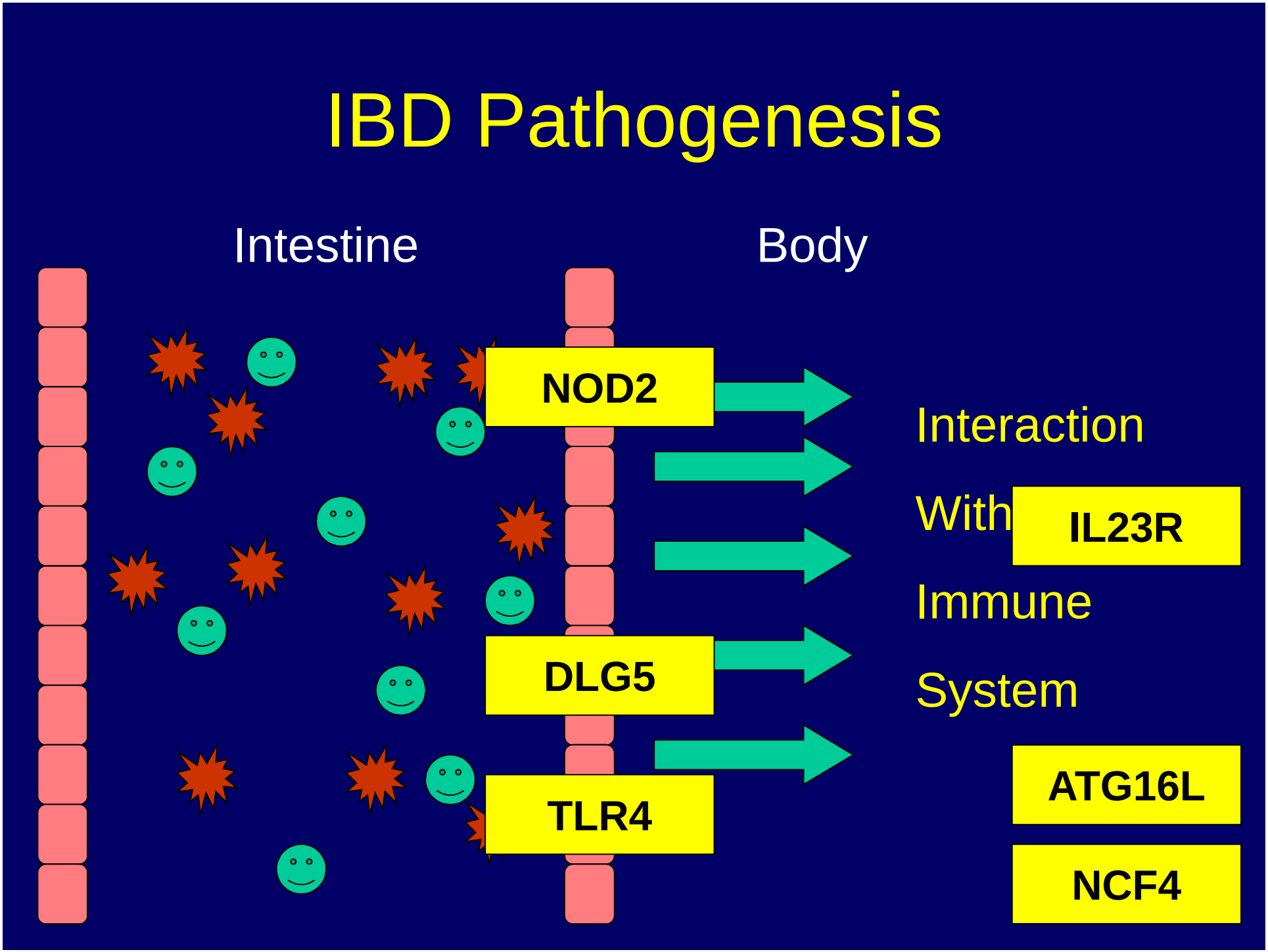
So what are genes?

- Our individual blueprint
- The instructions needed to make proteins
  - Building blocks
  - Enzymes
  - Receptors
  - Cytokines
  - ……

IBD and Bacteria

- Immune system identifies and eliminates foreign organisms and particles
- We are 1% human, 99% bacterial!
- Symbiotic relationship (immune tolerance)
- Dysregulation exacerbates inflammation

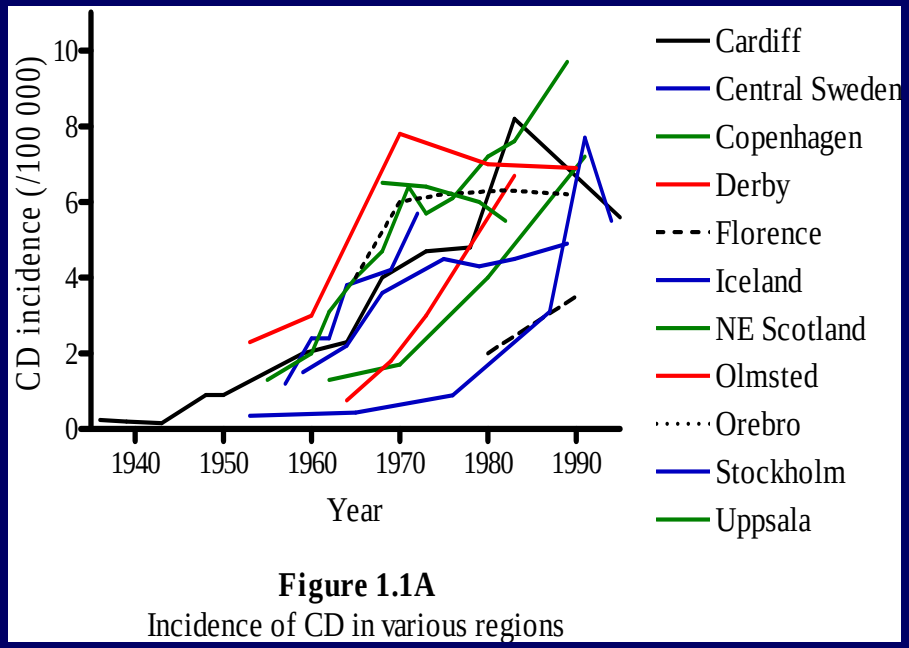
IBD Pathogenesis



NOD2 mutations occur more frequently in some types of CD…

- Stricture (narrowing) **2x ↑**
- Ileal disease location **3x ↑**
- Bowel resection surgery **4x ↑**
- Relative with IBD **1.5x ↑**
- Diagnosed <17 years **2x ↑**

Introduction
IBD epidemiology



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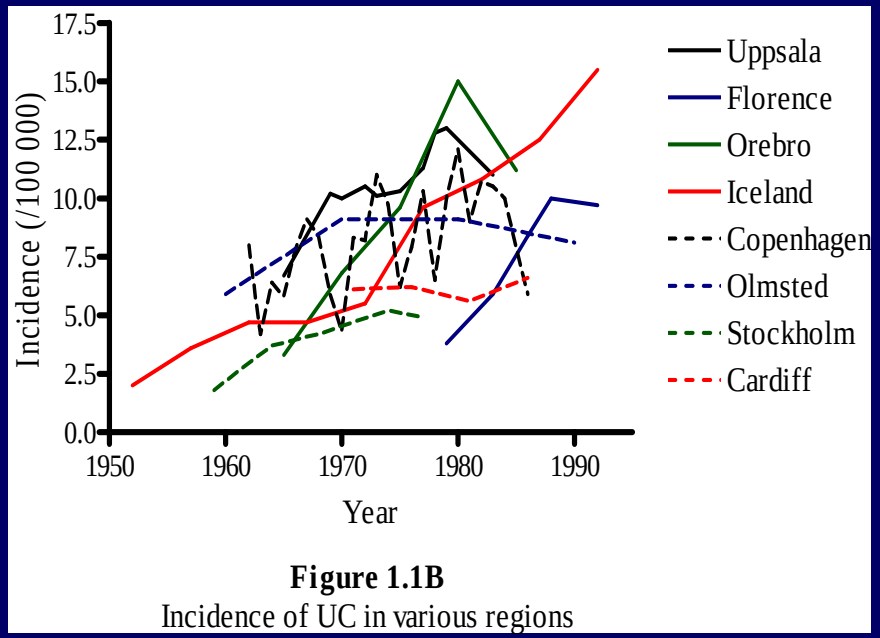


Figure 1.1B
Incidence of UC in various regions

The incidence of IBD has risen rapidly over the last 50 years

The environment and IBD

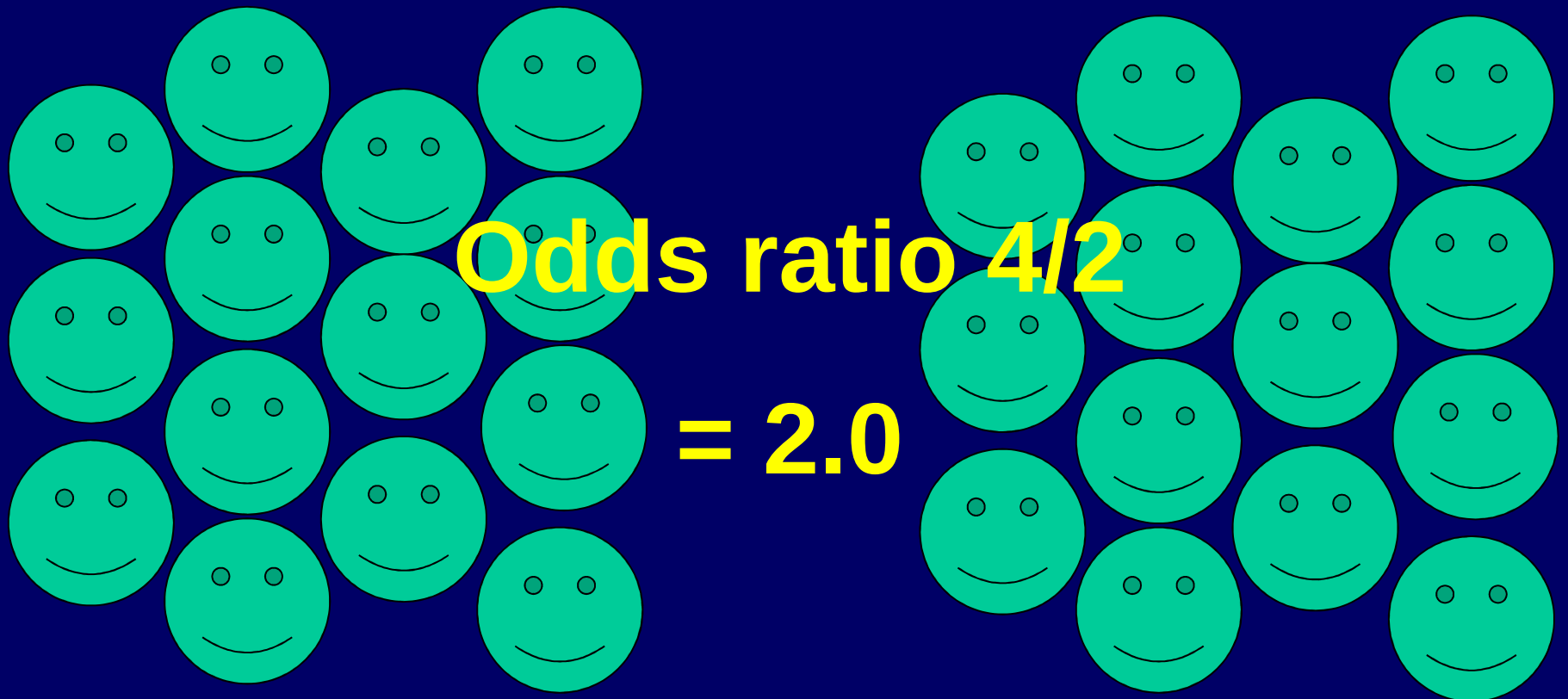
- Genes cannot explain the rapid increase in IBD
- Rapid changes in disease incidence

=

Changes in environmental factors

“Genes may load the gun, but the environment pulls the trigger”

Case-control study



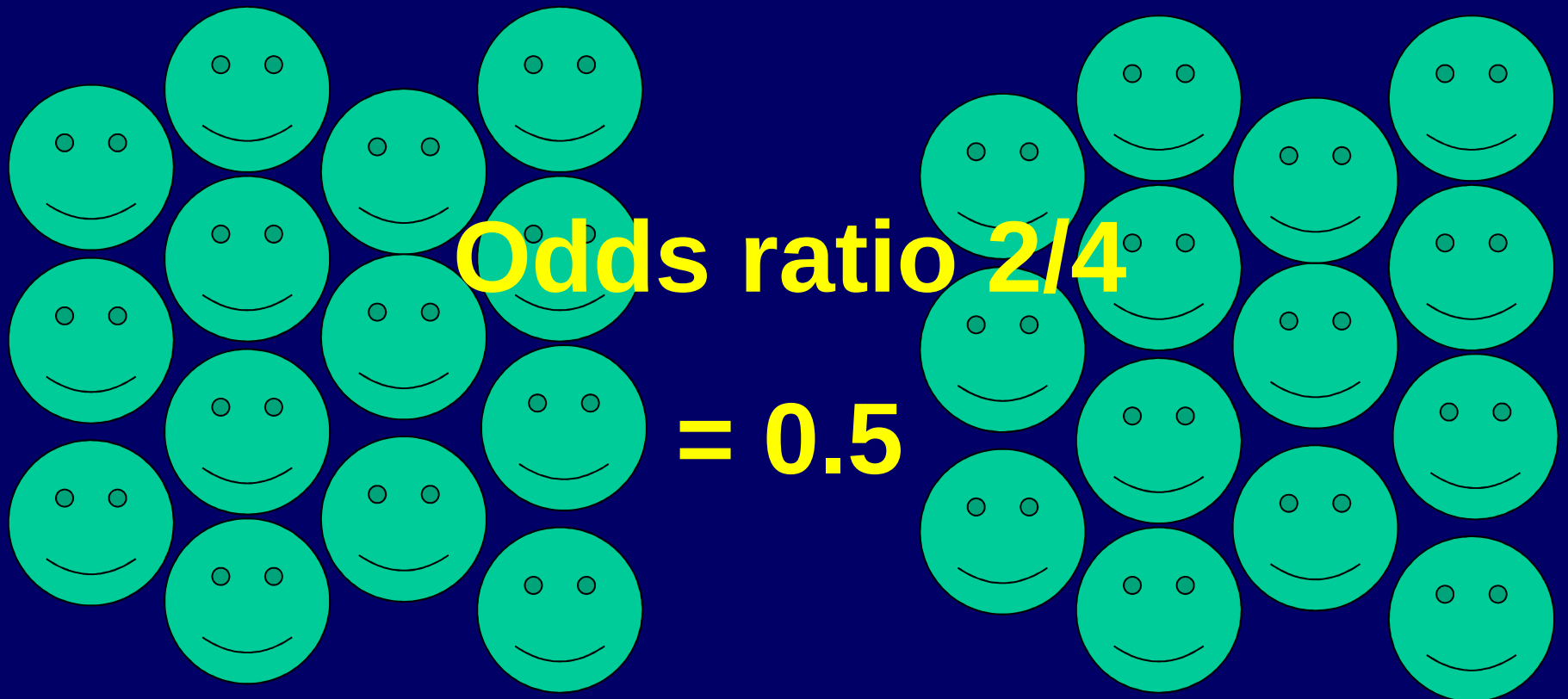
Odds ratio 4/2

= 2.0

People with medical condition

People without medical condition

Case-control study



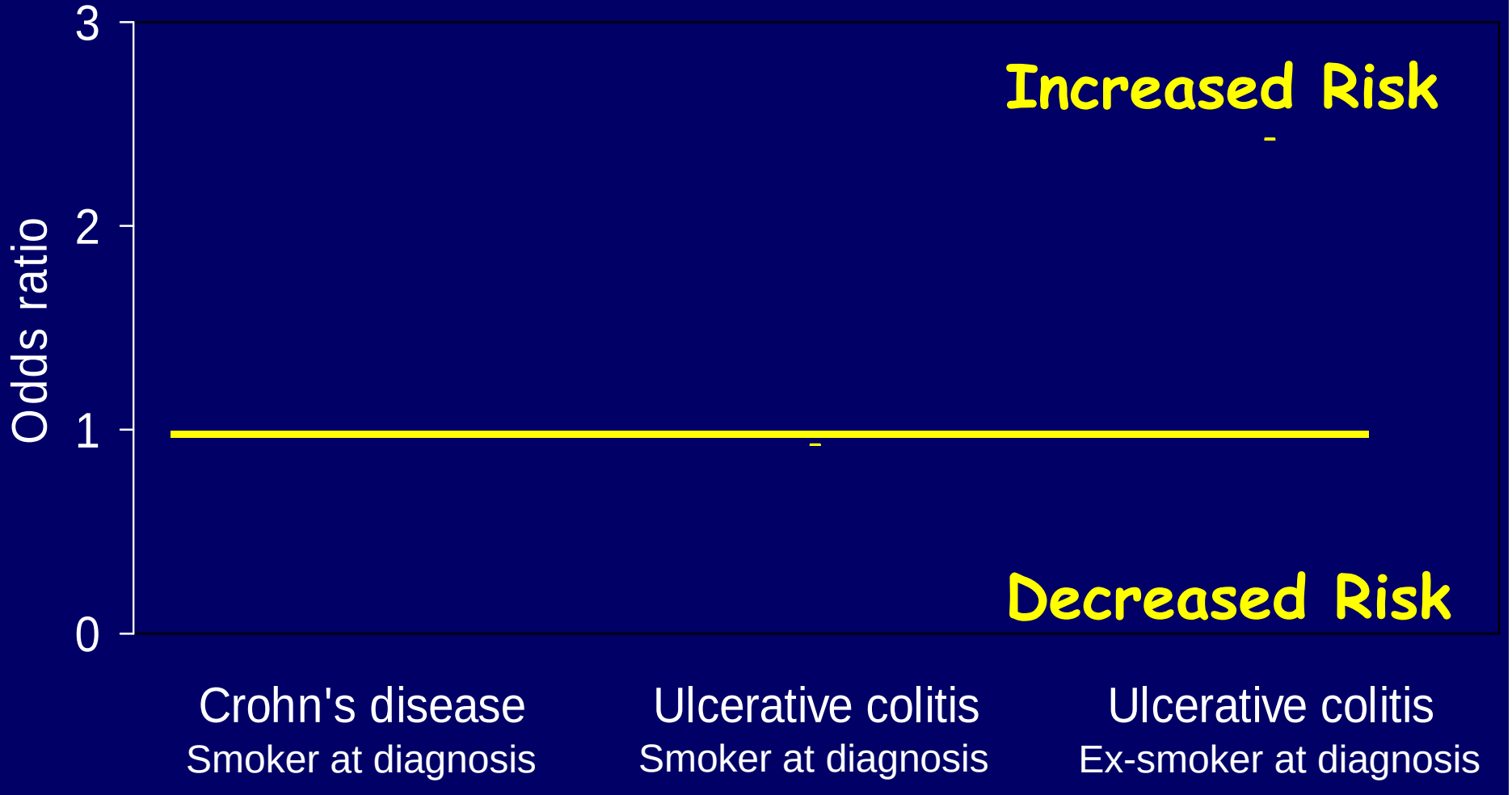
Odds ratio 2/4

= 0.5

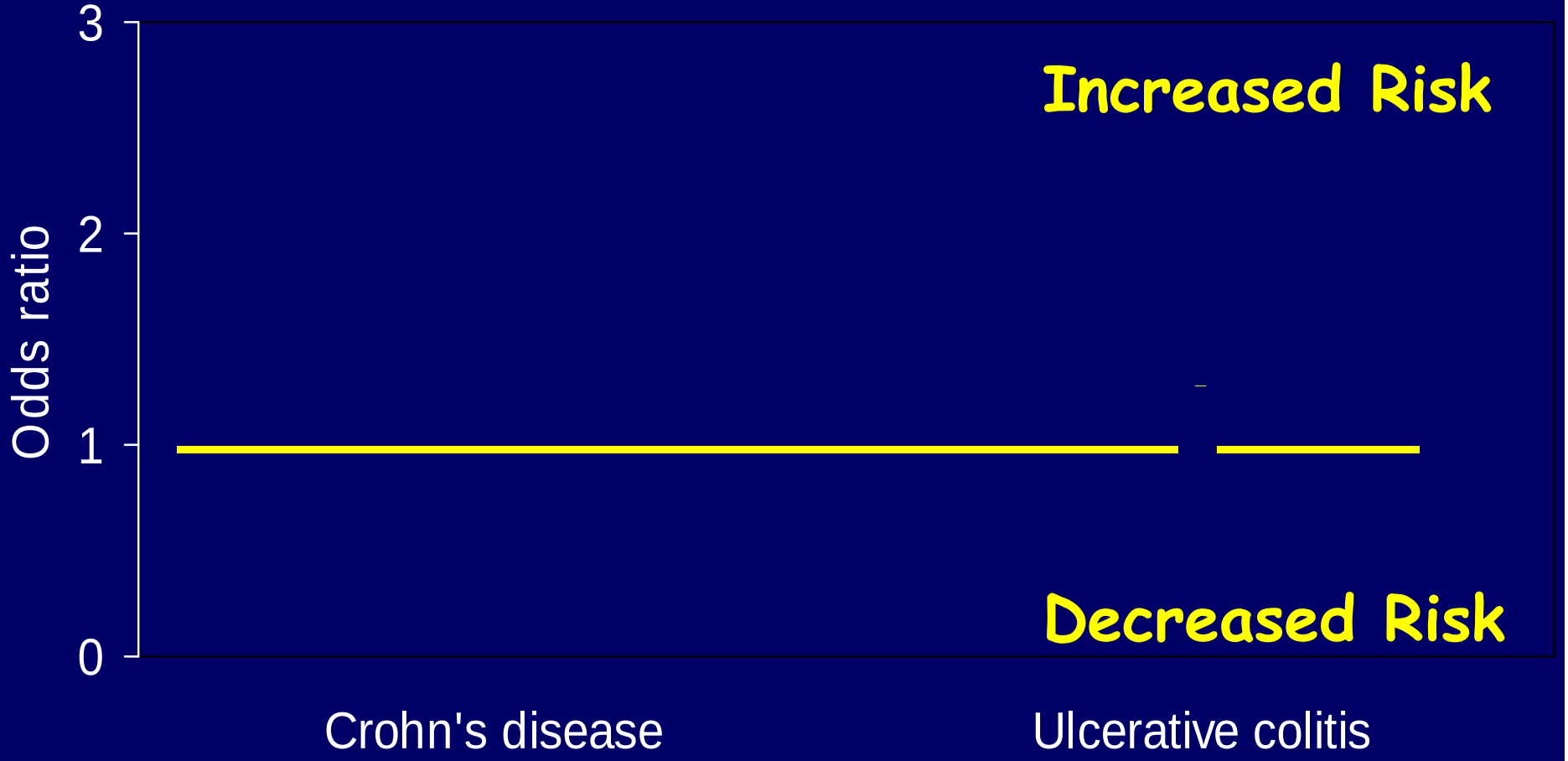
People with medical condition

People without medical condition

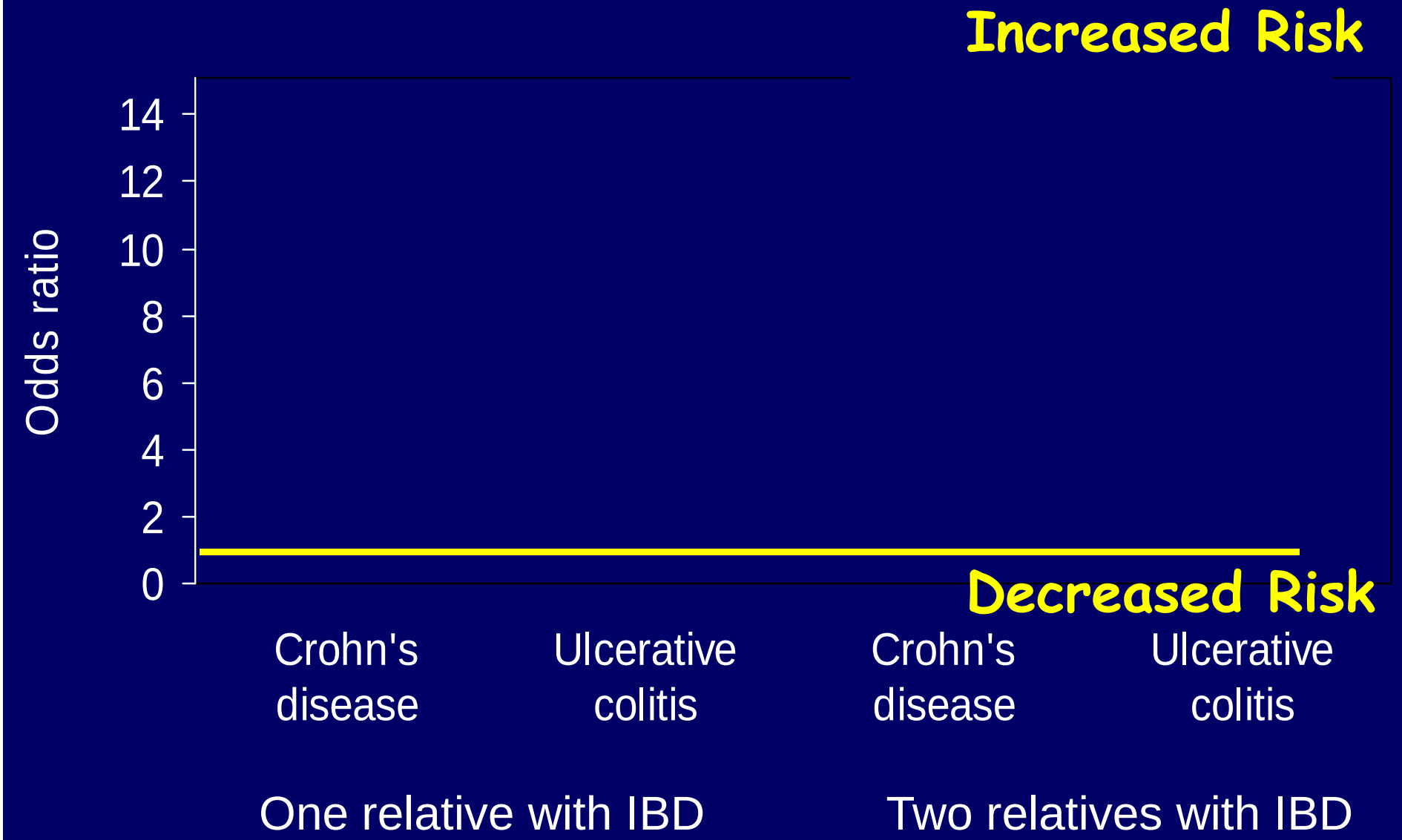
Smoking and IBD



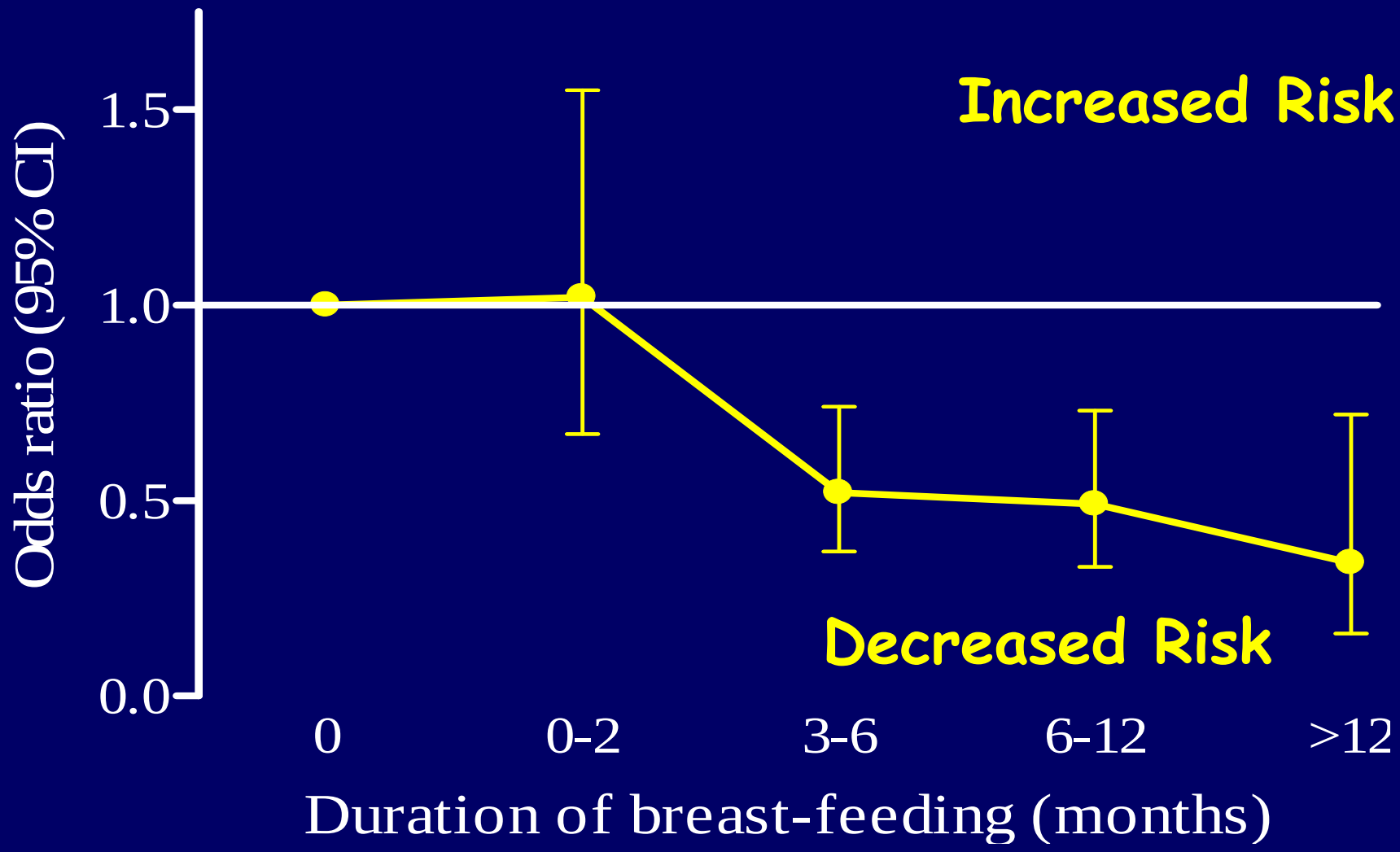
Maternal smoking and IBD



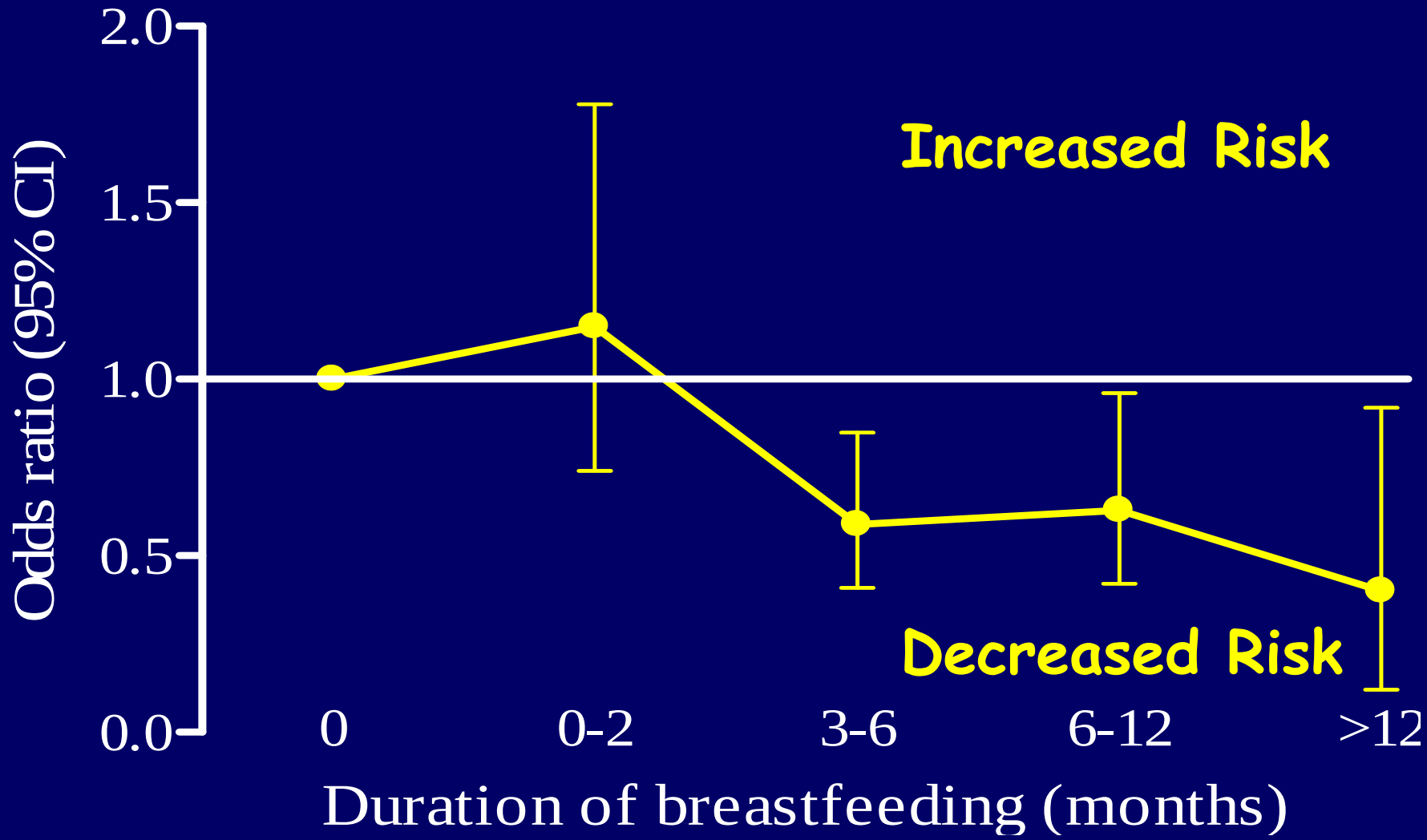
Family history and IBD



Duration of Breastfeeding & risk of CD



Duration of Breastfeeding & risk of UC



Environmental risk factors & CD

Risk Factor	OR	95%CI
One relative IBD	3.0	2.2-4.1
Two relatives IBD	7.0	3.3-15
Smoker at diagnosis	2.0	1.5-2.7
Maternal smoking	1.7	1.2-2.3
Appendicectomy	1.7	1.2-2.0
Tonsillectomy	1.5	1.1-2.0
Breastfed as infant	0.5	0.4-0.7
OCP use	1.8	1.1-3.1
High antibiotic use (adolescence)	2.1	1.3-3.3
Urban living	1.5	1.1-2.1
Childhood vegetable garden	0.5	0.4-0.7
High childhood SES	1.6	1.1-2.2
High recruitment SES	0.5	0.3-0.7

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High recruitment SES	0.5	0.3-0.7

Environmental risk factors & UC

Risk Factor	OR	95%CI
One relative IBD	2.5	1.8-3.5
Two relatives IBD	6.8	3.2-15
Smoker at diagnosis	0.7	0.5-0.9
Ex-smoker at diagnosis	1.8	1.4-2.4
Appendicectomy	0.4	0.3-0.7
Breastfed as infant	0.7	0.5-0.9
High antibiotic use (adolescence)	1.7	1.1-2.8
Childhood vege garden	0.6	0.4-0.9
Childhood SES	1.7	1.2-2.4

Environmental risk factors & UC

Risk Factor	OR	95%CI
One relative IBD	2.5	1.8-3.5
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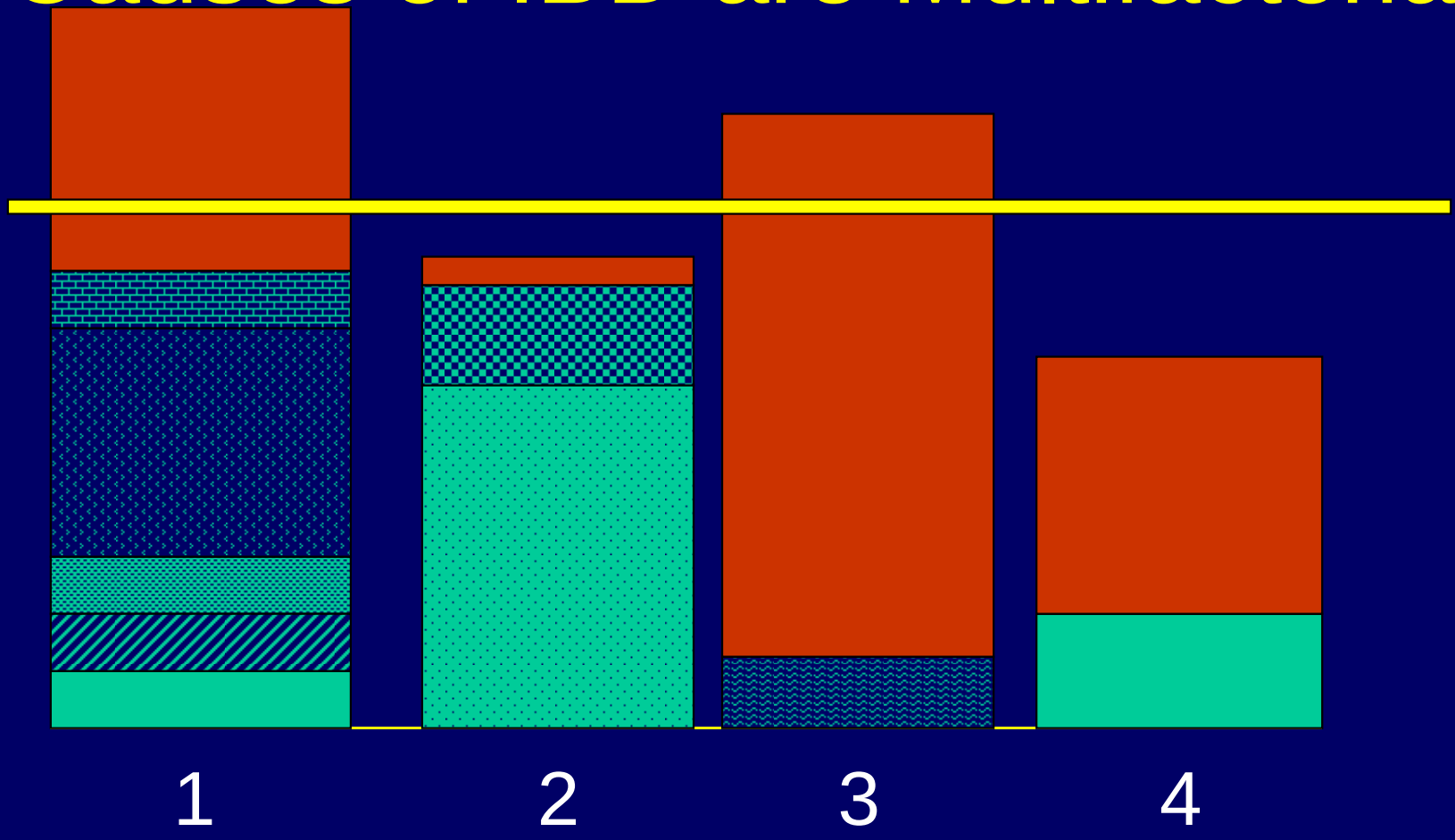
Childhood vege garden	0.6	0.4-0.9
Childhood SES	1.7	1.2-2.4

Do environmental factors play an important role in IBD?

- Environmental factors are very important
- Some environmental factors may be modifiable
- Associations give us clues as to why IBD occurs
- Many risk factors may occur in infancy / childhood

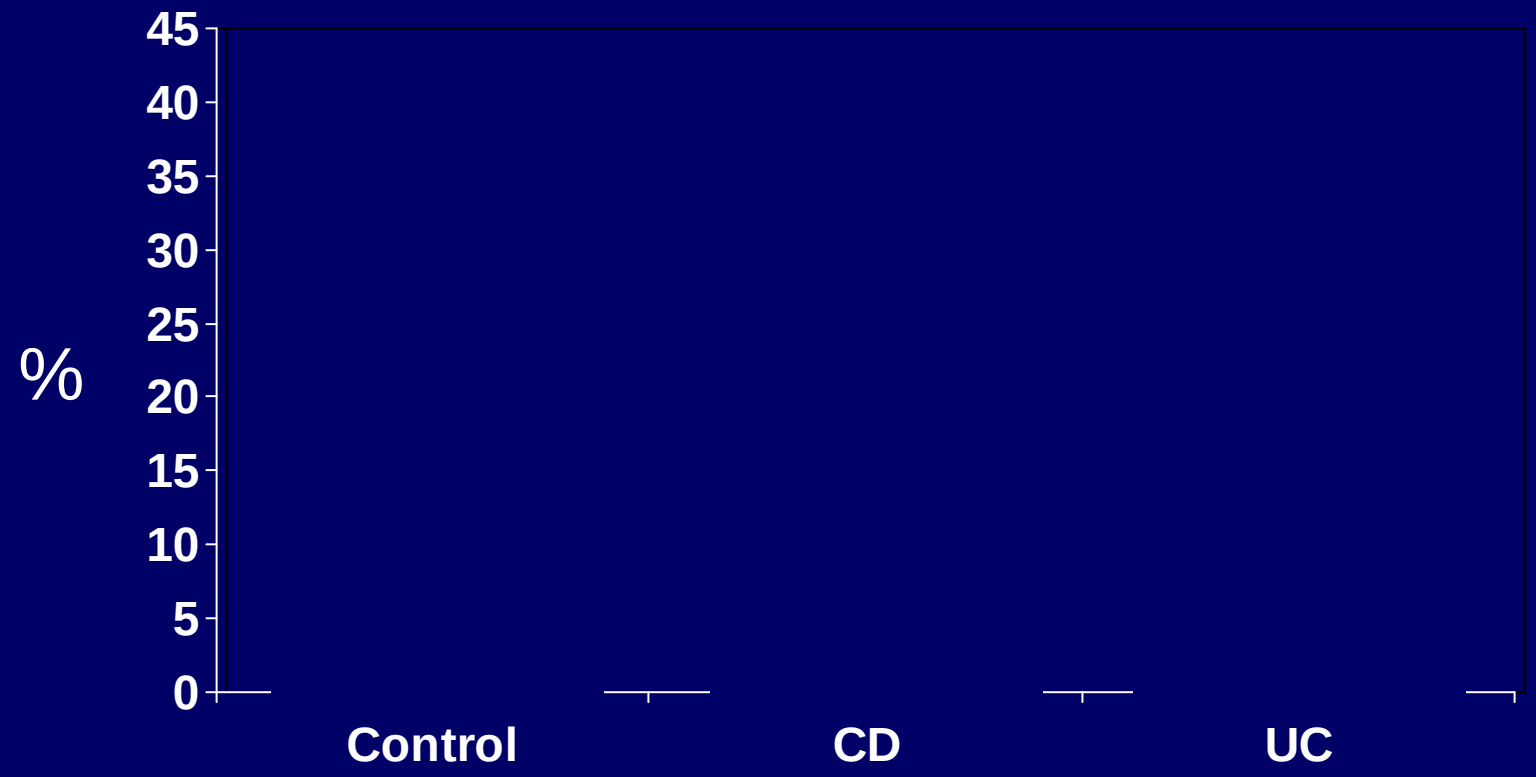
Causes of IBD are Multifactorial



The effect of IBD

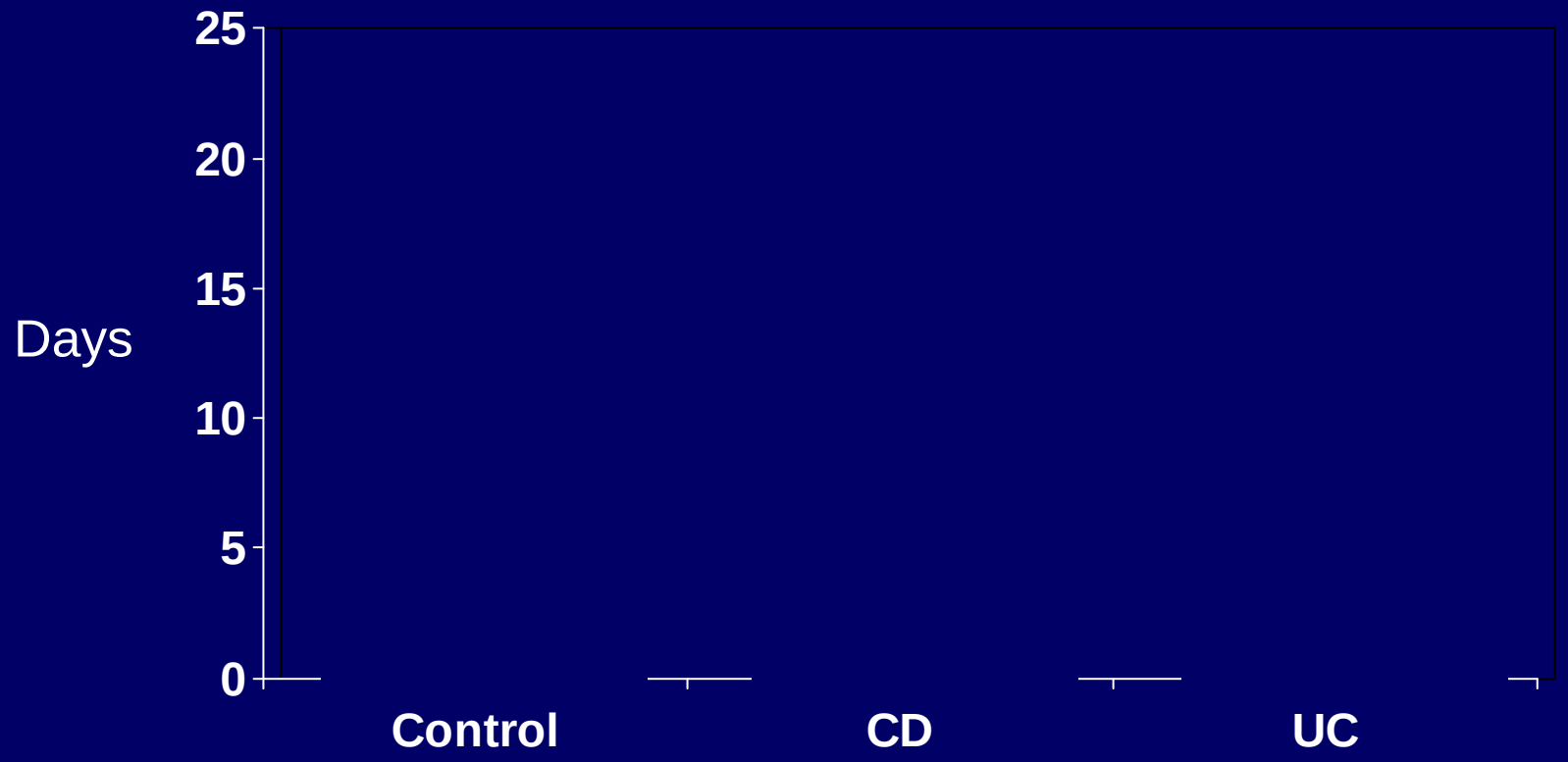
- Important to measure the effects of disease
  - Resource allocation
    - New treatments
    - Medical /nursing staff
    - Community support
  - Prognostic information for patients

The effects of IBD (1)



Does a health problem or condition you have (>6 months) cause you difficulty with or stop doing everyday activities that people you age can usually do?

Average number of days away from usual activities



The Canterbury IBD Study
Conclusions

- IBD is not rare in Canterbury; CD is very common
- IBD in Canterbury is similar to elsewhere
- Genes are important – but not the whole story
- Environment is important – but difficult to unravel
- IBD has a significant impact on the lives of many Cantabrians
- The Canterbury IBD Study provides a unique tool for ongoing population-based research

Drug Treatment of IBD

the battle to get and keep you well

canterbury medical research foundation

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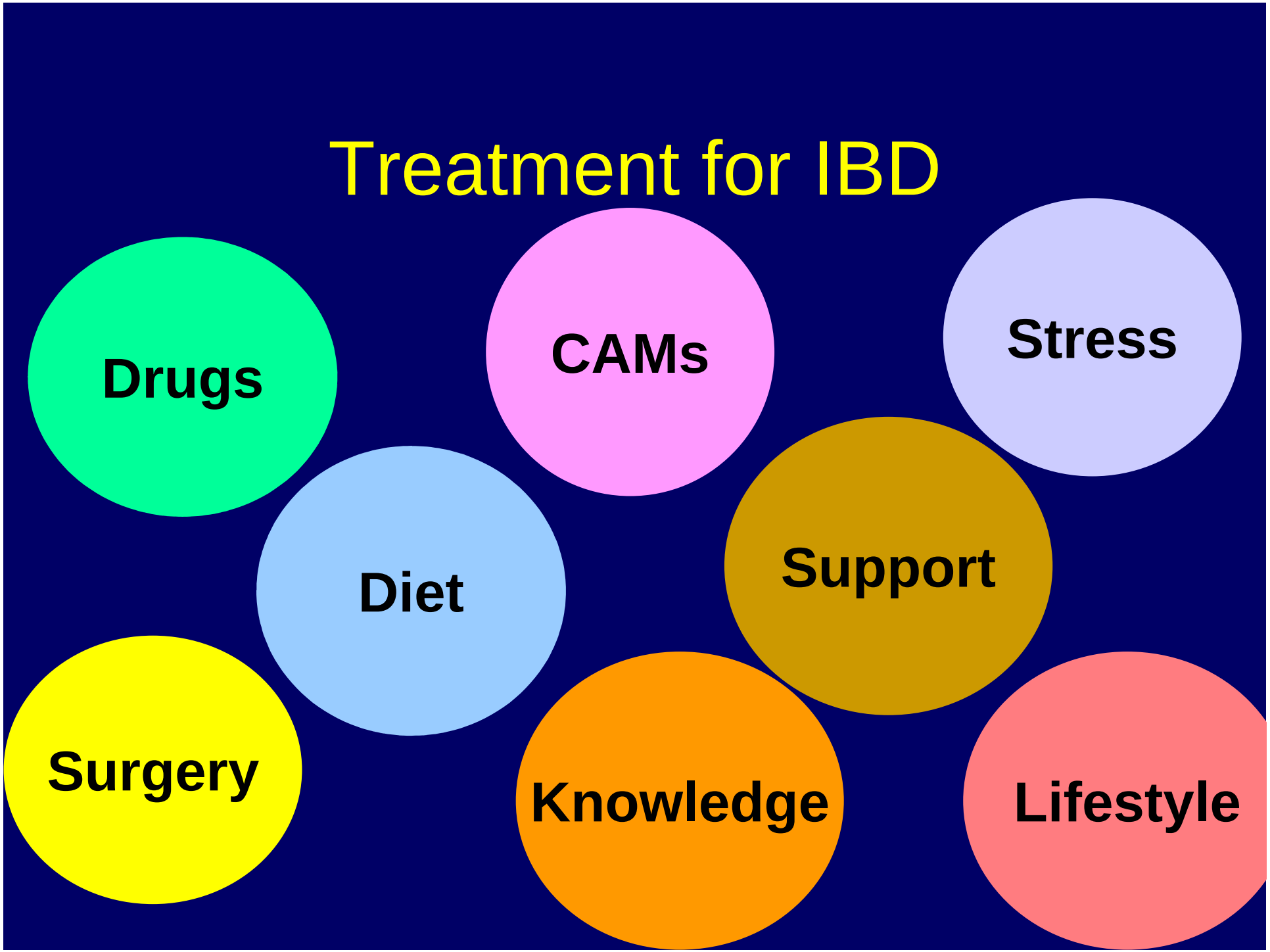
Te Whare Wānanga o Otāgo

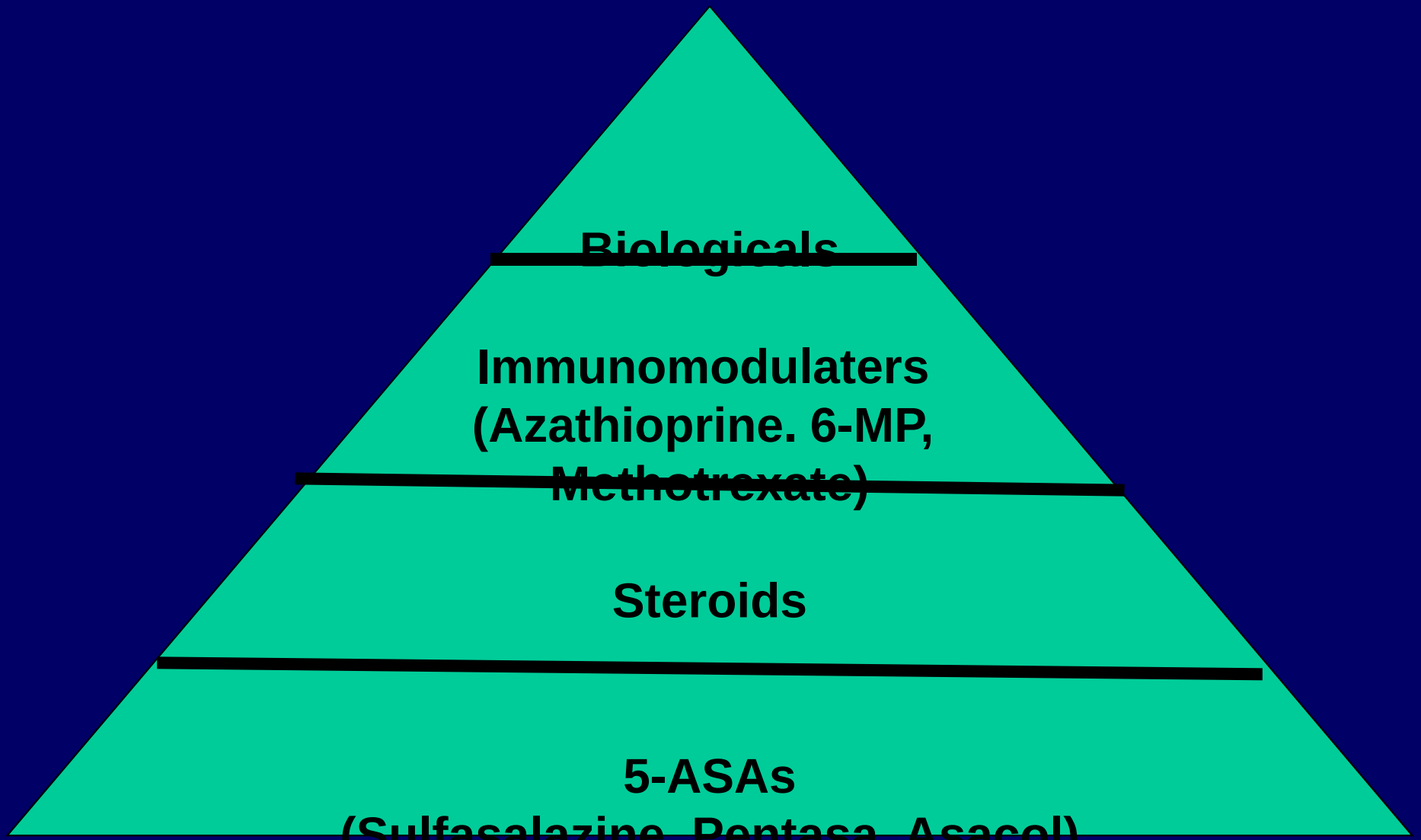
Overview

- Treatment for IBD
- Medical treatment for IBD
- Medical treatment for severe IBD
- Remicade (Infliximab)
- Humira (Adalimumab)
- Costs and implications
- Future directions
- ACCA document


Treatment for IBD
Drugs
CAMs
Stress
Diet
Support
Surgery
Knowledge
Lifestyle

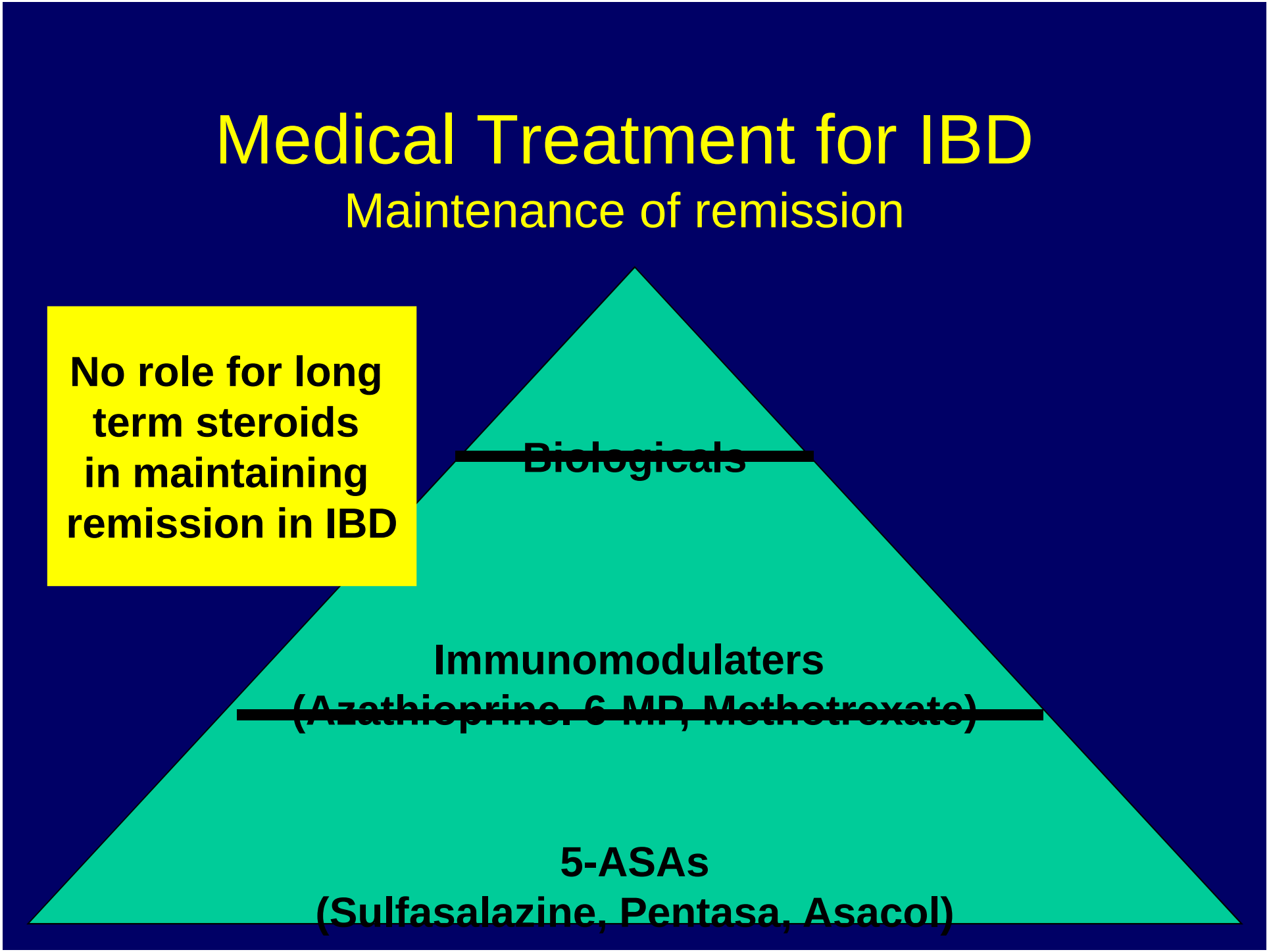
Medical Treatment for IBD

Disease flare



Medical Treatment for IBD

Maintenance of remission



Medical treatment for severe IBD
(requiring admission to hospital)

Intravenous steroids (5-7 days given 6 or 8 hourly)

Biological Agents (Remicade / Humira)

Only for UC - IV Cyclosporin (rarely)

Only for CD Exclusive Enteral Nutrition (paediatrics)

Surgical Opinion

Medical therapy for IBD

Treatment	UC		CD	
	relapse	remission	relapse	remission
5-ASA/SSZ	+	+	±	±
Steroid	+	-	+	-
Aza/6MP/MTX	±	+	±	+
Biological Agents	+	+	+	+
Antibiotics	-	-	±	±

Biological Therapies
what are they?

- Designer drugs
- Aimed at specific molecules in the inflammatory cascade
- Also known as “MABs” – Monoclonal AntiBodies
- New drug - ?long term safety…
- At least as effective as anything we have now
- Fewer obvious side effects
- Very expensive …

Remicade (infliximab)

- Monoclonal antibody to TNF-α
  - Central cytokine in the inflammatory / immune response
- Given Weeks 0, 2, 8 then 8 weekly
- 97% human sequence / 3% mouse sequence
- Given as a 2-3 hour infusion
- Rapid onset of action
- Infection / ? Lymphoma / Allergy

- www.remicade.com

Remicade for Perianal Disease

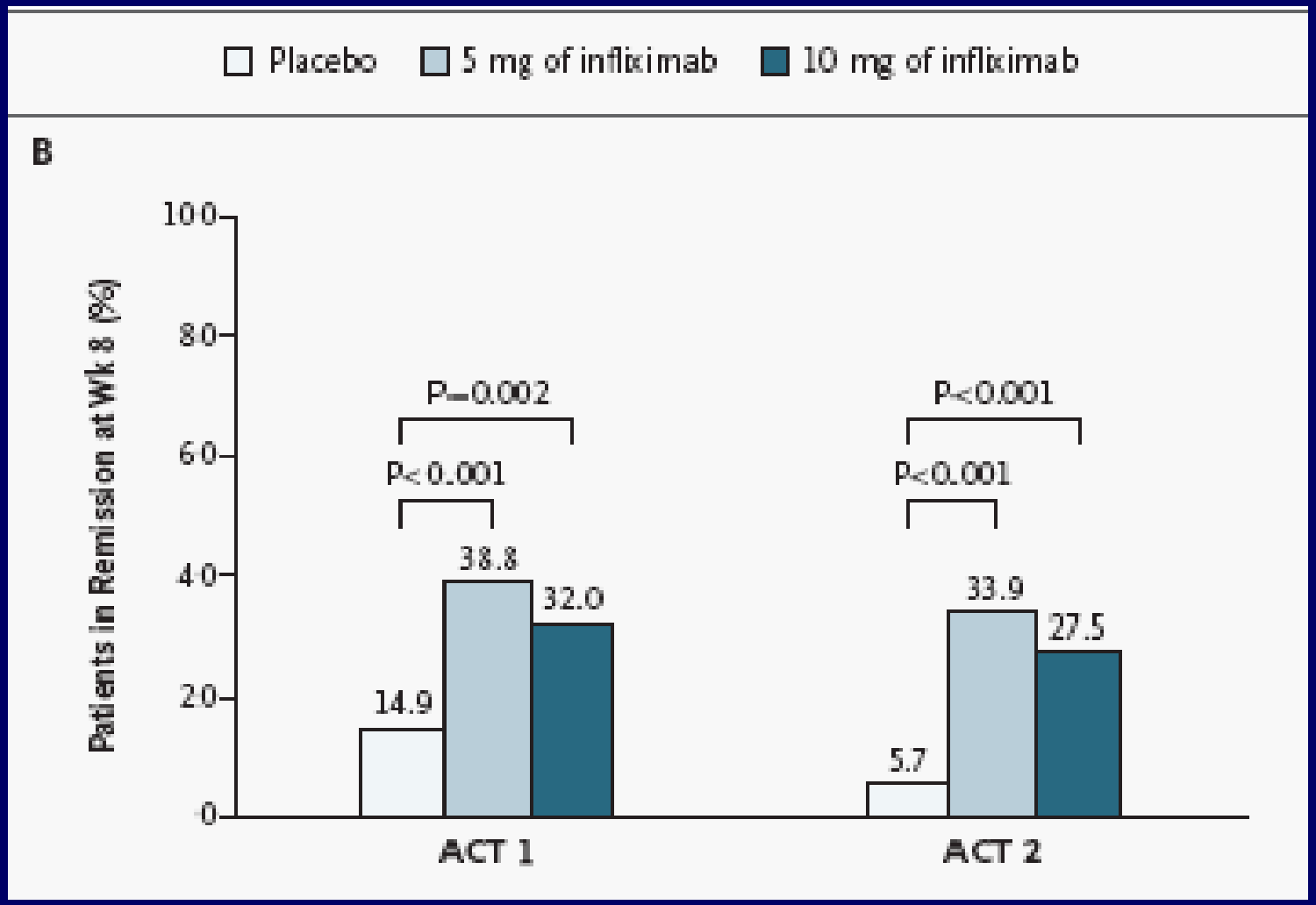
- 68% v 26% had >50% of fistulas closed
- 55% v 13% had all fistulas close
- Well-tolerated

- But if you stop taking it – they come back!!

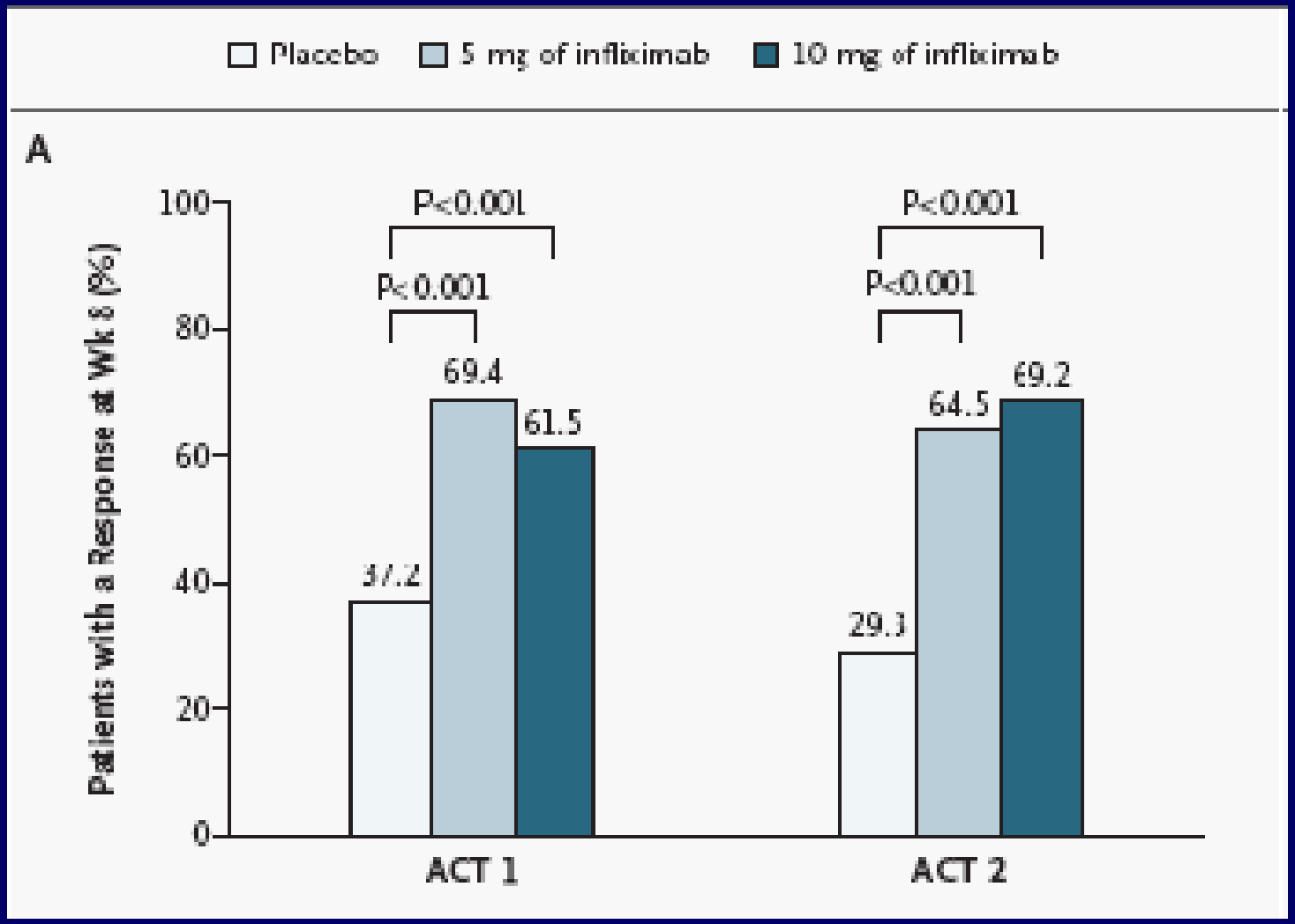
Remicade for Luminal CD

- Remission at 4 weeks
  - 33% v 4%
- Improvement at 4 weeks
  - 81% v 17%
- Maintenance of remission (1 year)
  - 39% v 21%

Remicade for UC

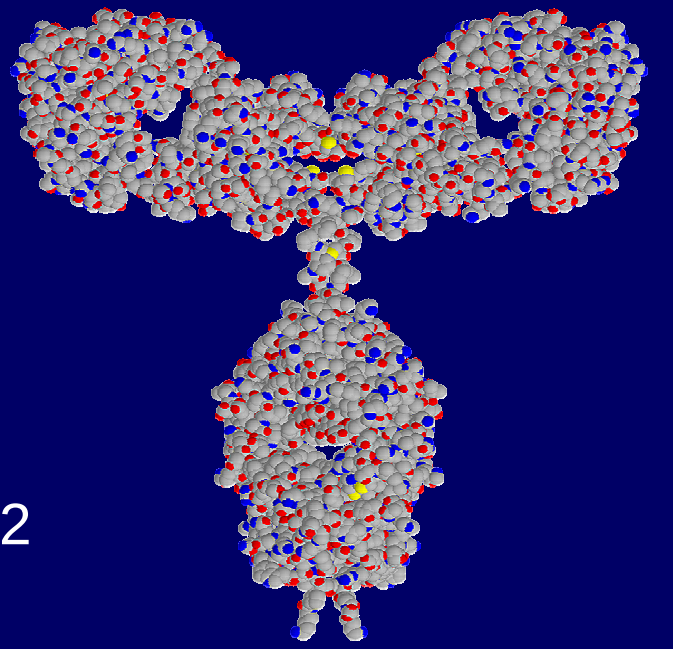


Remicade for UC



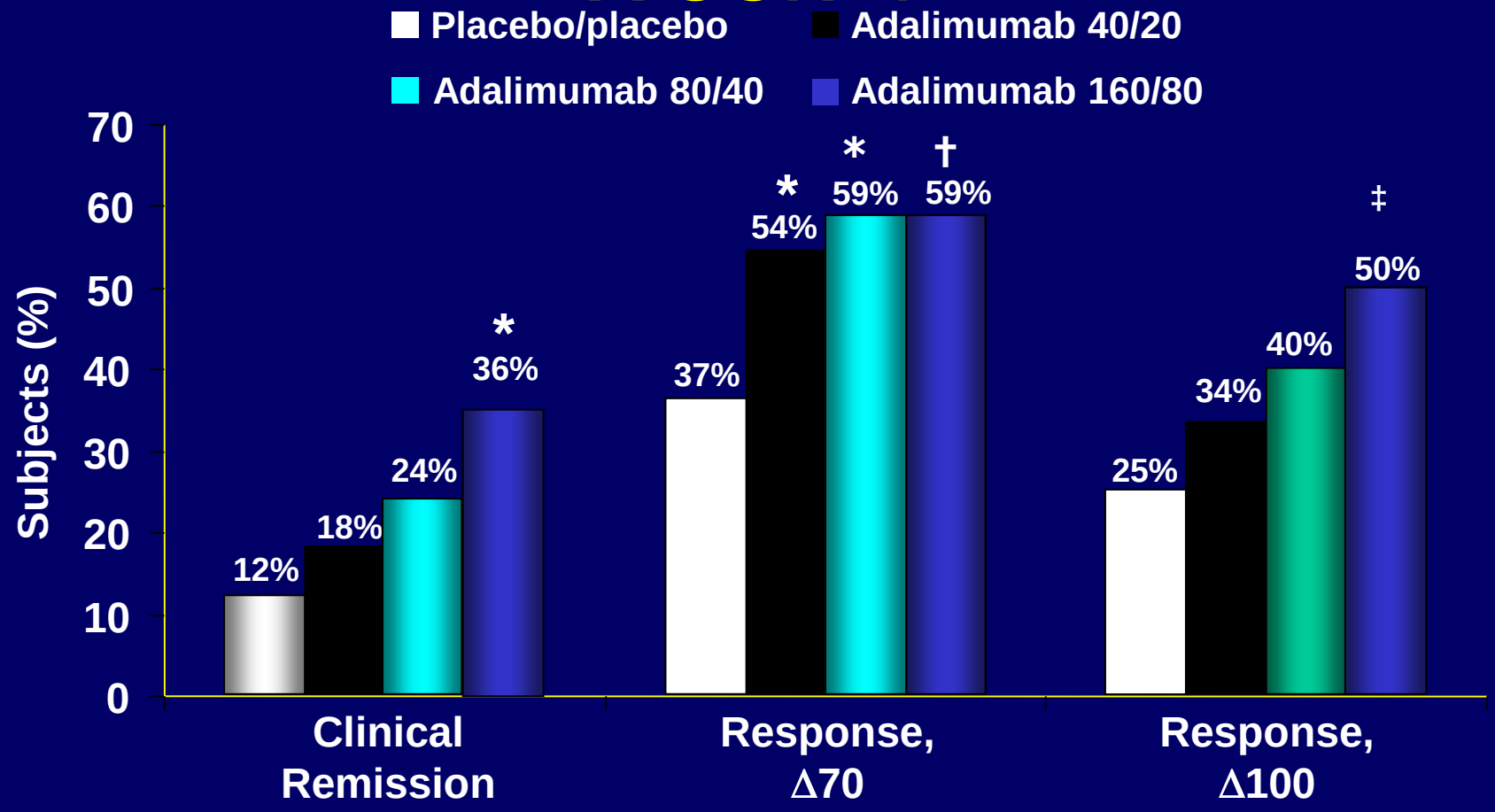
HUMIRA (Adalimumab)

- Fully human monoclonal antibody (IgG_1)
  - specifically neutralizes TNF-α
- Self-administered sub cut injection
- RA / PsA / AS dose
  - 40 mg every other week (eow)



- Crohn's Disease:
  - Induction 160mg week 0 / 80mg week 2
  - Maintenance 40 mg eow
- >180,000 patients currently being treated worldwide

CLASSIC I Trial: Results at Week 4



•p<0.05; † p=0.003; ‡ p=0.002

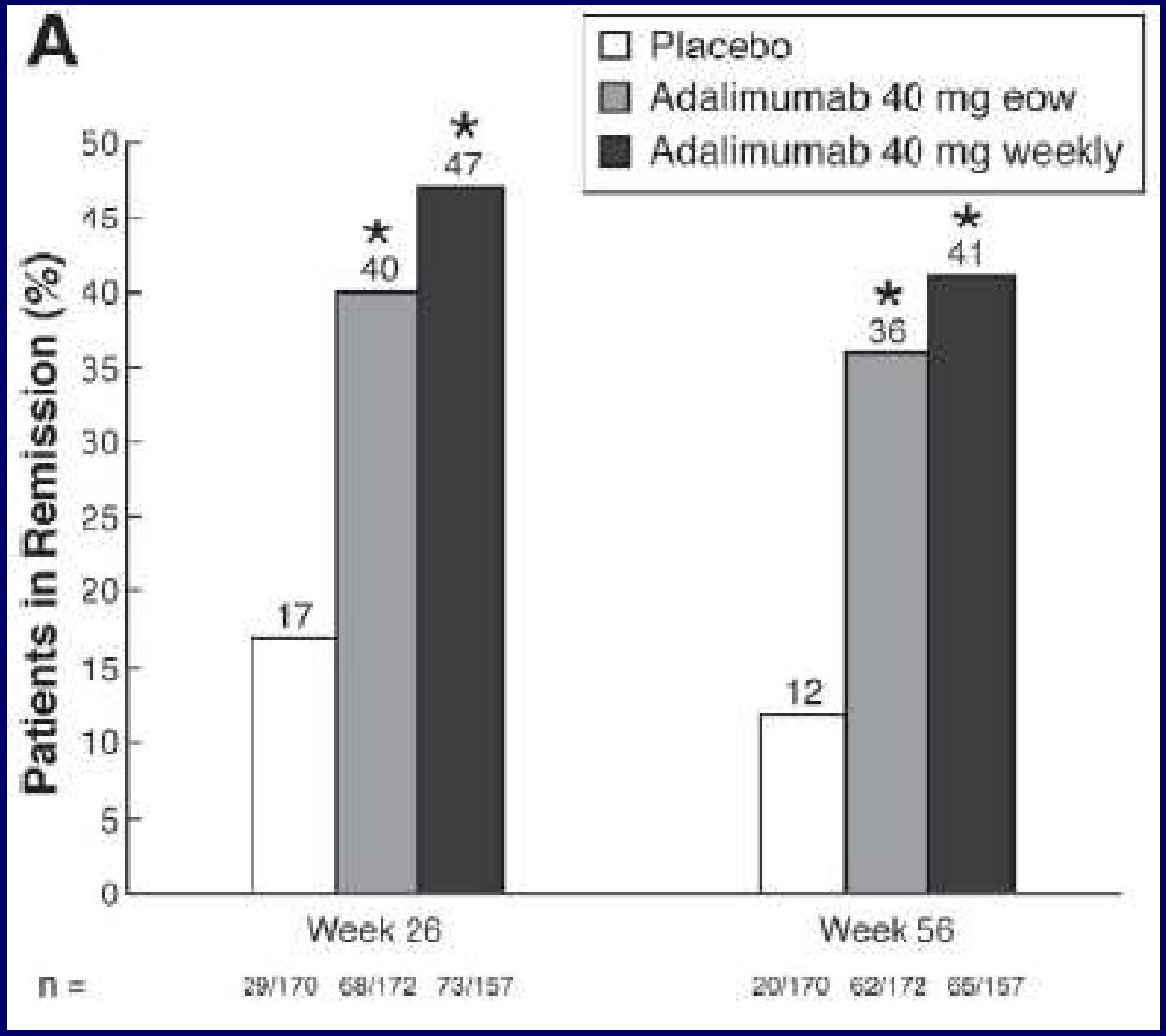
Clinical remission=CDAI<150

Clinical response Δ70 or Δ100=CDAI decrease from baseline ≥70 or ≥100

CLASSIC I: Treatment-Emergent Serious Adverse Events Summary

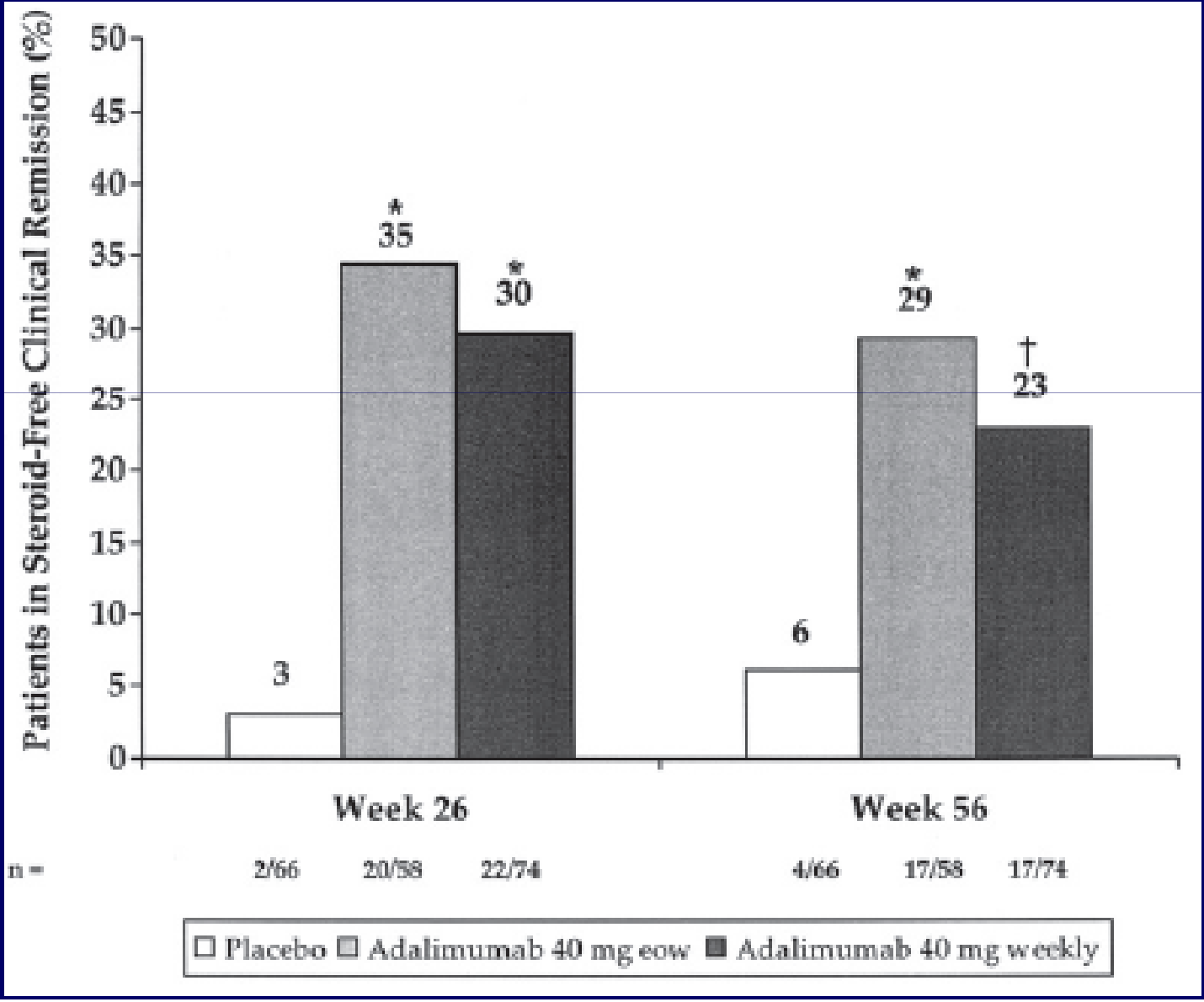
	Placebo n=74	40/20 mg EOW n=74	80/40 mg EOW n=75	160/80 mg EOW n=76
SAE*, n (%)	3 (4)	0 (0)	1 (1)	3 (4)
Serious infections	0 (0)	0 (0)	0 (0)	2 (3)
Perianal abscess	0 (0)	0 (0)	0 (0)	1 (1)
Pneumonia	0 (0)	0 (0)	0 (0)	1 (1)

CHARM Co-Primary End points



Primary Responders

CHARM Secondary End points – steroid weaning



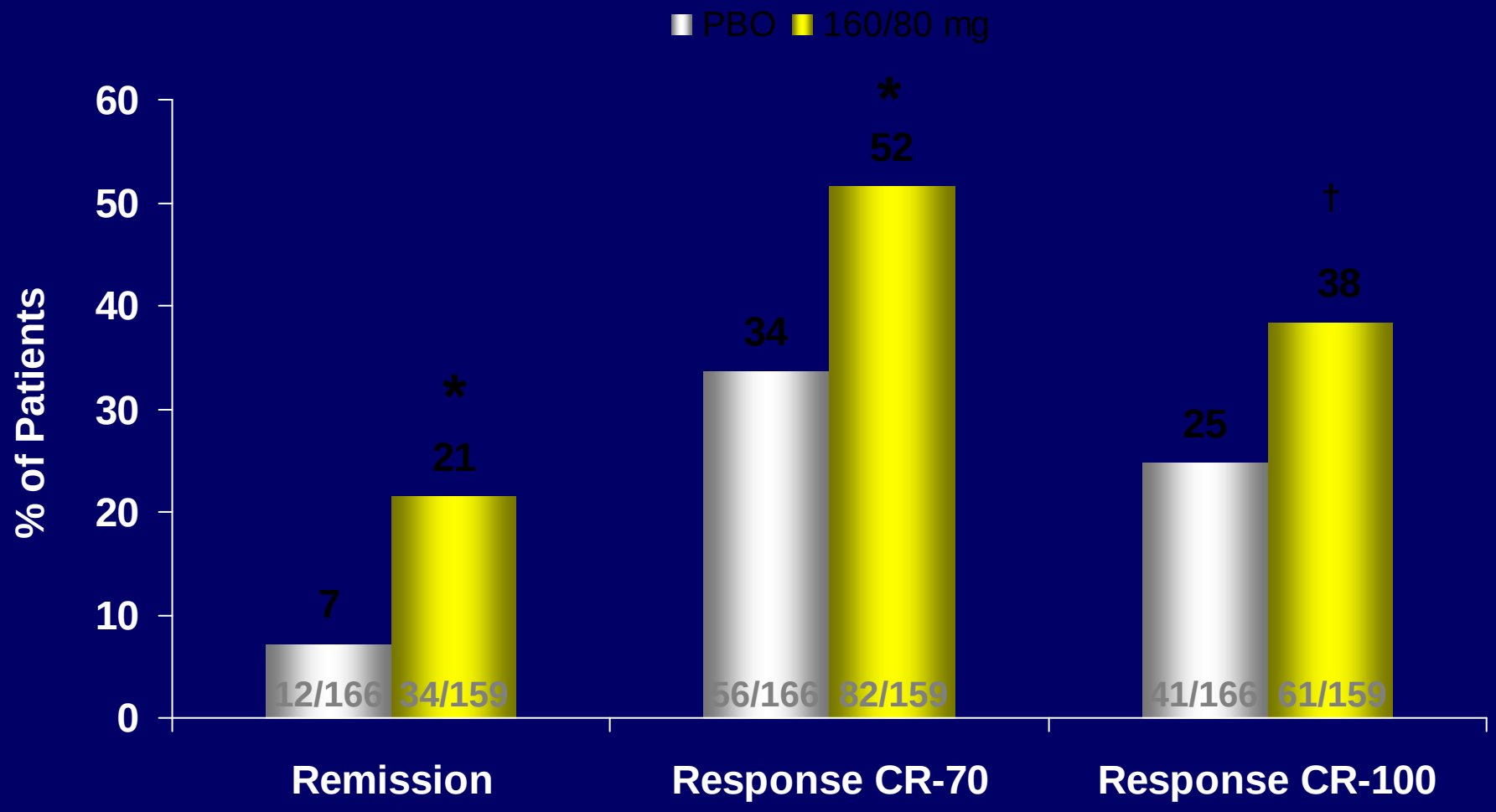
CHARM: SAEs of Interest

All Adalimumab-treated Patients

n (%)	4-week OL n=854	Post randomization (weeks 4–56) Placebo n=261	40 mg EOW n=535	40 mg weekly n=410
Infections and infestations*	10 (1.2)	9 (3.4)	16 (3.0)	11 (2.7)
Infectious SAEs of Interest				
Abscess	7 (0.8)	5 (1.9)	5 (0.9)	6 (1.5)
TB	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Other opportunistic infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound infection, sepsis, post-operative infection	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Cancer	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Multiple Sclerosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Serum Sickness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Colombel JF, et al. T686d, DDW 2006; data on file.

GAIN: Efficacy Outcomes at Week 4



*P<0.001, †P<0.01, both vs. placebo.

Sandborn WJ, et al. *Ann Intern Med*. 2007;146(12).

Outside the square

- Children
  - Remicade
    - Used effectively
    - Safety data
    - Clinical trial data
- Pregnancy
  - Remicade
    - Contraindicated
    - Pregnancy may occur on the drug
- Breastfeeding
  - Remicade
    - Not advised

Costs and Implications

- These drugs only work if you keep taking them
  - Need to have a viable alternative option in the future (eg azathioprine or methotrexate)
  - No other alternative available (including surgery)
- Long term safety data are lacking

Costs and Implications

- Remicade cost $1175/ 100mg vial
  - 5mg/kg is the standard dose
  - 5 X 60kg = 300mg ($3525/dose)
  - 3 X induction doses then 8 weekly = $31725 per year
  - 3 X induction doses only = $10575
- Humira cost $900/ 40mg injection
  - 160mg / 80mg / 40mg eow
  - 3 X induction doses then 40mg fortnightly = $27000 per year
  - 3 X induction doses only = $6300

Costs and Implications

- Current use at Christchurch Hospital
- Remicade
  - July-Sept 2005 $70500
  - July-Sept 2006 $185395
  - July-Sept 2007 …
- No Humira data as yet

Implications

Canterbury IBD incidence (2004)

Inflammatory bowel disease

25.2 / 100 000

Crohn's disease

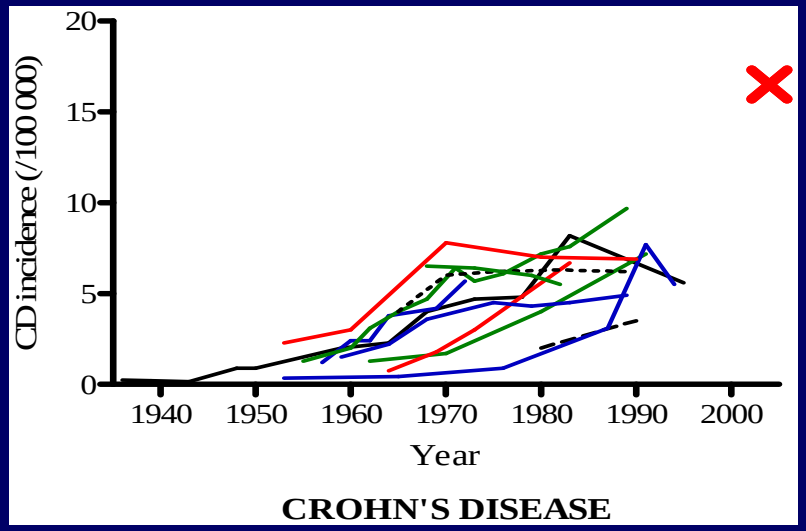
16.5 / 100 000

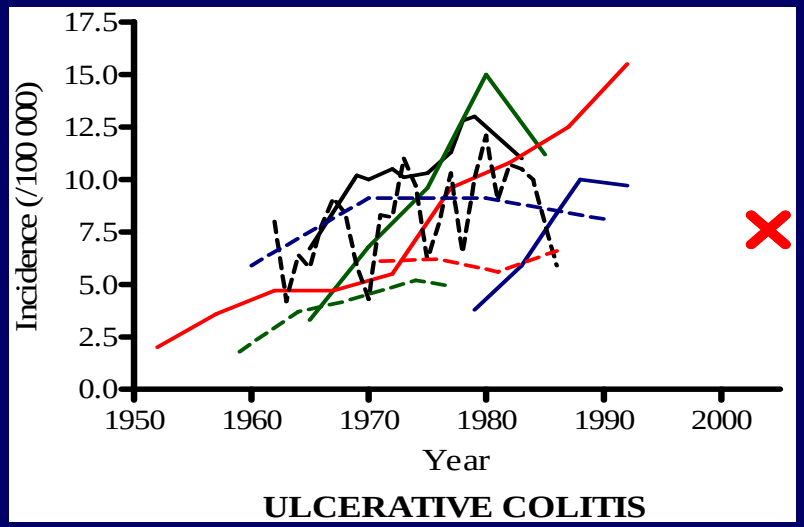
Ulcerative colitis

7.6 / 100 000

Indeterminate colitis

1.1 / 100 000

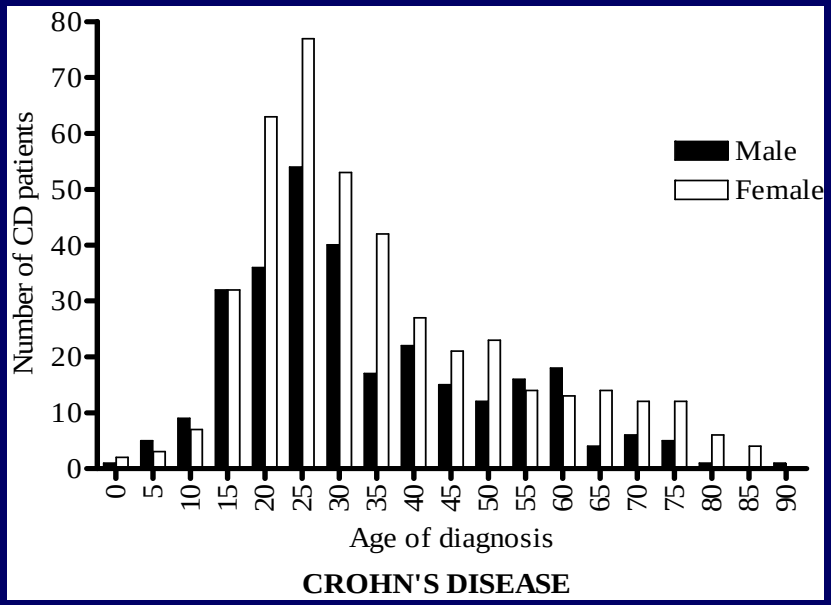


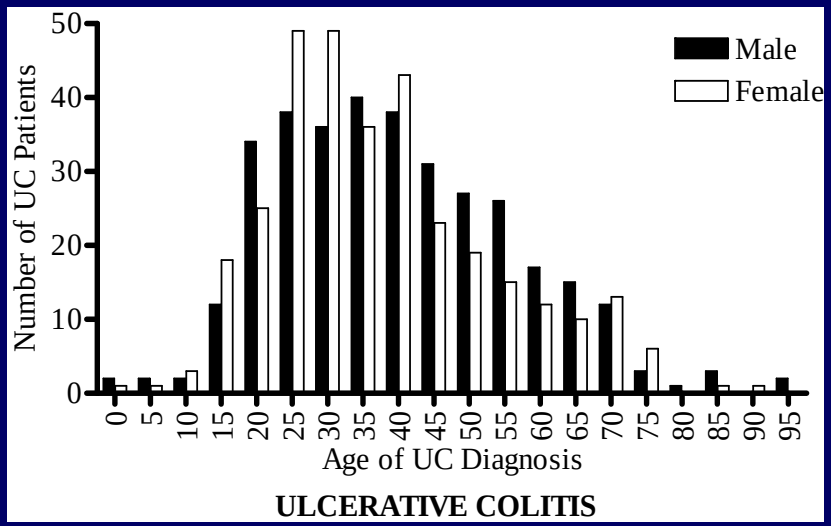


Gearry et al, *Inflammatory Bowel Diseases*, 2006

Implications

Sex and age of onset





Crohn's Disease

Female > Male (p=0.042)

Peak age onset ~25 years

Second peak ~55 years

Median age onset 29.5 years

Ulcerative colitis

Male > Female (ns)

Peak age onset ~30 years

Median age onset ~36.5 years

Future directions

- New Mabs mean competition
- Competition lowers price

- Lobbying Pharmac / Politicians
- NZSG / Gastroenterologists / Patients

- Signalling high cost to hospital managers

Key Messages

- Mabs are not magic bullets
- Long term safety data is lacking
- Effective alternative in specific situations
- Costs are high
- National disparity in access
- Pressure on Pharmac and Politicians
- Joint approach is advocated

ACCA IBD Document

- Economic cost of IBD = **$2.7 billion** (includes a financial cost of **$500 million** + net cost of lost wellbeing **$2.2 billion)**
- Lost productivity accounts for > half cost ($266.7 million)
- Estimated cost of absenteeism for IBD patients = $52.3 million
- Costs to the health system = $79 million
- 939,000 hours of informal care provided to IBD patients ($23.5 million)
- Estimated out of pocket expenses for IBD patients = $35.8 million

www.acca.net.au (media page)

IBD Drug Treatment Summary

- UC – 5ASA is the best option
- CD – less evidence for 5-ASA
- CD – immunomodulators key for maintenance
- Steroids – no long term role
- Biologicals – the missing link

Canterbury IBD Study
research team

Gastroenterology

- Murray Barclay
- Bruce Chapman
- Michael Burt
- Judith Collett
- James Yeo

Gene Structure & Function Lab

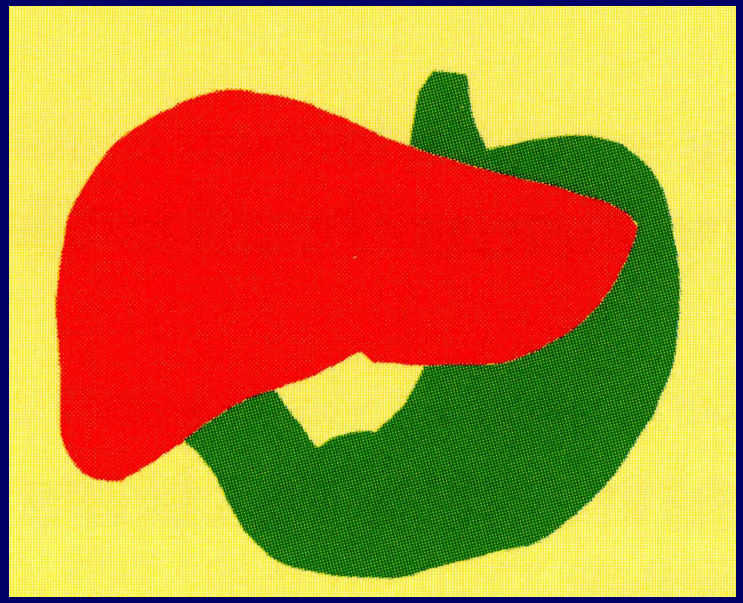
- Martin Kennedy
- Rebecca Roberts
- Nick Bockett
- Melanie Allington
- Aliison Miller

Epidemiology / Statistics

- Ann Richardson
- Chris Frampton

Research Assistants

- Judy Hoar
- Rhondda Brown
- Pip Shirley
- Ramez Ailabouni
- Andrew Dodgshun
- Megan Reilly
- Charlotte Duncan
- David Tan



canterbury medical research foundation

Canterbury DHB

District Health Board

Te Poari Hauora ō Waitaha

UNIVERSITY of OTAGO

SAPERE AUDE

Te Whare Wānanga o Otāgo

Health Sciences