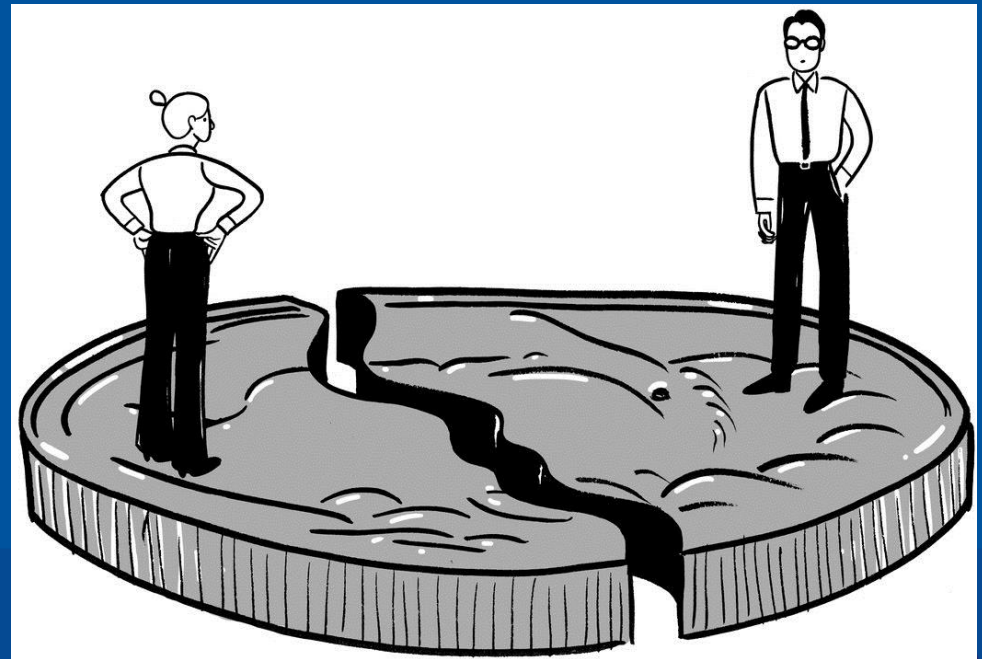




UMC Utrecht

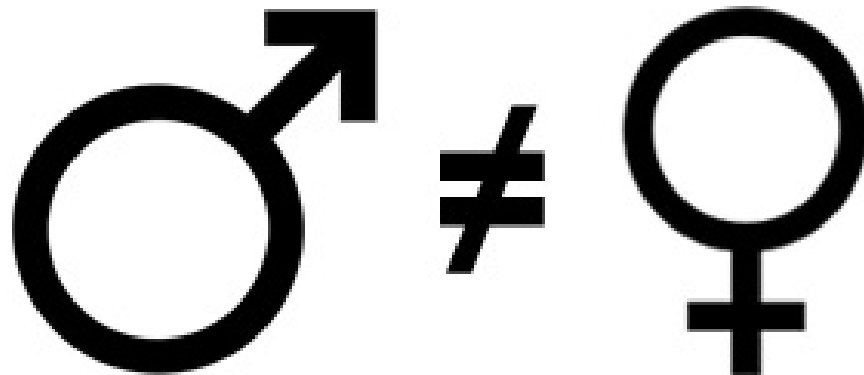
Vrouwsspecifieke behandelstrategieën: kansen voor kostenbeheersing?

Herma Fidler, MDL-arts
UMC Utrecht



Pharmacology: gender differences

- Sex-specific oral bioavailability/ absorption
- Amount and distribution of body fat, volume distribution,
- Drug-metabolising enzymes differ (CYPs, etc.)
- Urinary excretion
- Weight



Adverse drug events

- Predominantly women display dose-related adverse drug events
- 60% of patients admitted to the hospital for adverse drug events are women
- US GAO: six drugs were withdrawn from market for adverse effects and health risks to women > men
- Costs to launch new drug entity 1,78 billion

Pirmohamed M, *BMJ* 2004

Gurwitz JH, *J Womens Health* 2005

Patel H, *BMC Clin Pharmacol* 2007

Sikdar KC, *Ann Pharmacother* 2010

United States General Accounting Office *GAO-01-286R*, 2006



Hypothesis

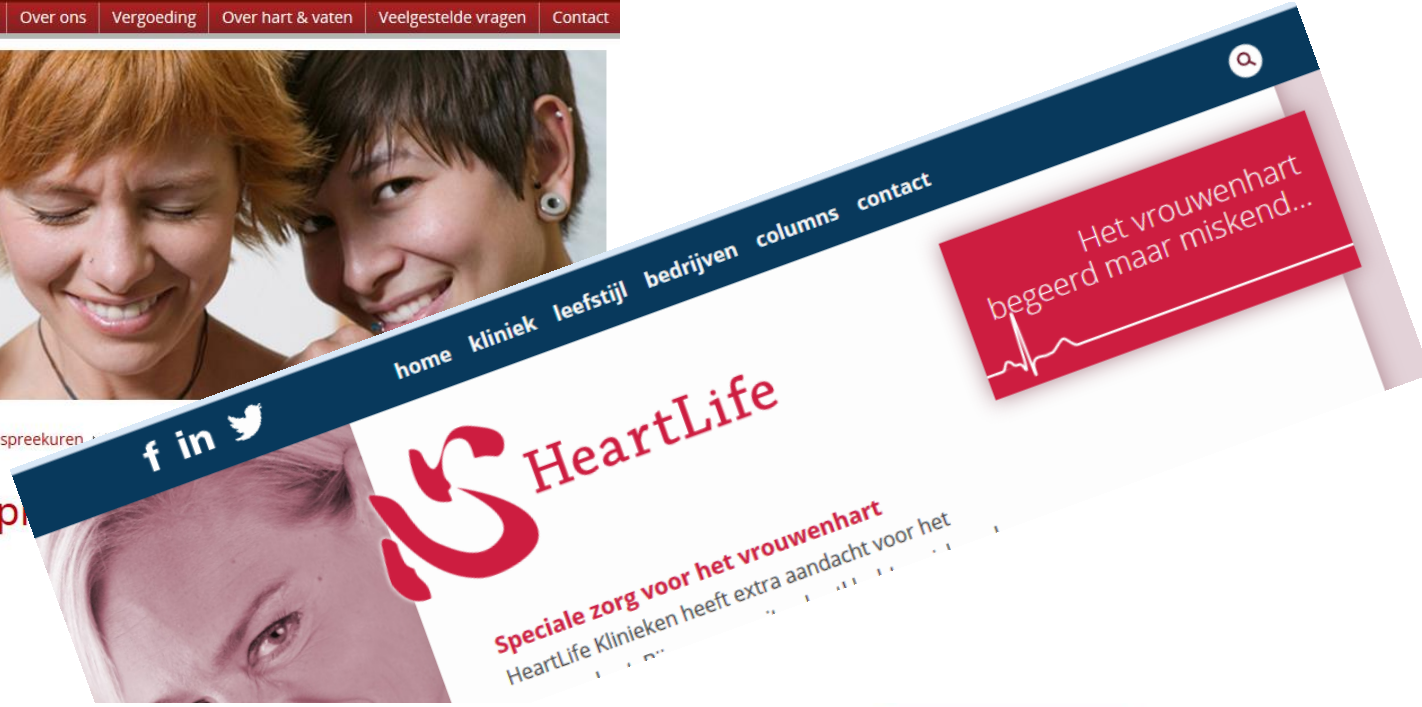
Better targeting drugs and doses for women may save billions







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Vrouwencardiologie sp...



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Per dag sterven in
Nederland 57 vrouwen
aan hart- en vaatziekten



Gender differences cardiovascular drugs

Table 4 Sex differences in drug effects (adapted from Regitz-Zagrosek and Seeland¹⁵⁹)

Treatment	Sex-specific drug effects	References
Digitalis	Higher risk for death among women with HF compared with placebo Reduced distribution volume, lower drug elimination in women	146 165
Antiarrhythmics	Drug-induced Torsades de pointes (TdP) observed predominantly in women	166–170
Anticoagulants and ASA	Haemorrhage incidence increased in women Haematuria, haemoptysis, and intracranial bleeding incidence increased in men Higher benefit observed in women (Vitamin K antagonists, Fondaparinux) Increased bleeding risk observed in women (Bivalirudin)	171 172 173,174 175

ASA, Acetylsalicylic Acid.



Immune Mediated Inflammatory Diseases

- Sjögren's disease
- Primaire Biliary Cirrhosis
- Systemic sclerosis
- Systemic Lupus erythematosus
- Rheumatoid arthritis

- Crohn's disease (CD)

- Ulcerative colitis (CU)
- Psoriasis, SpAs



Immune Mediated Inflammatory Diseases

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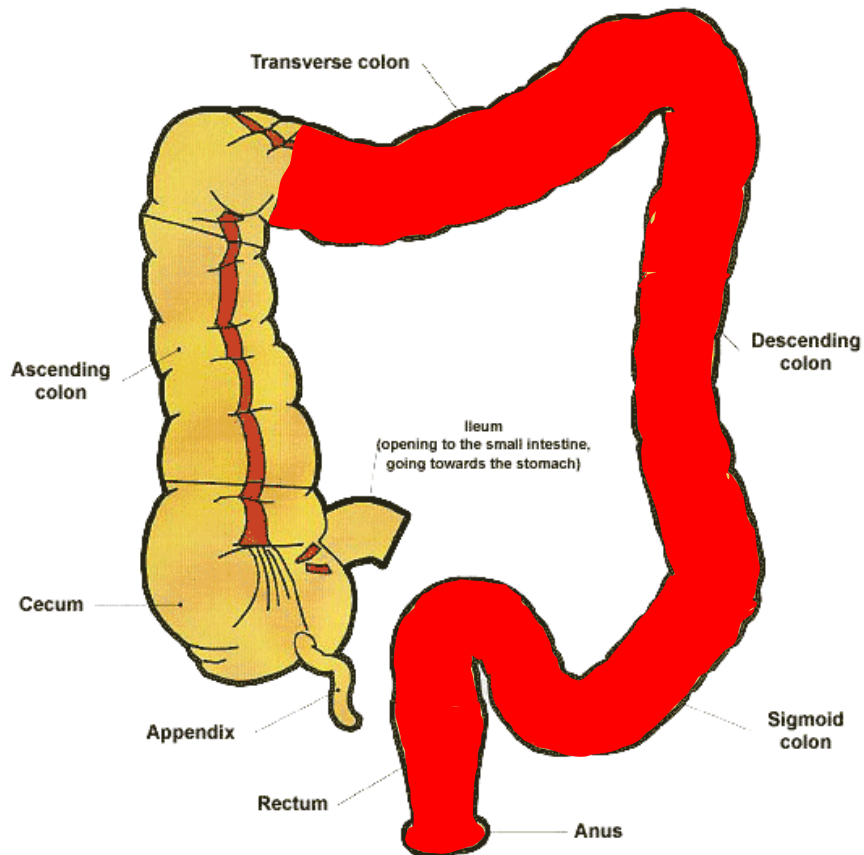
- Crohn's disease (CD)

- Ulcerative colitis (CU)
- Psoriasis, SpAs

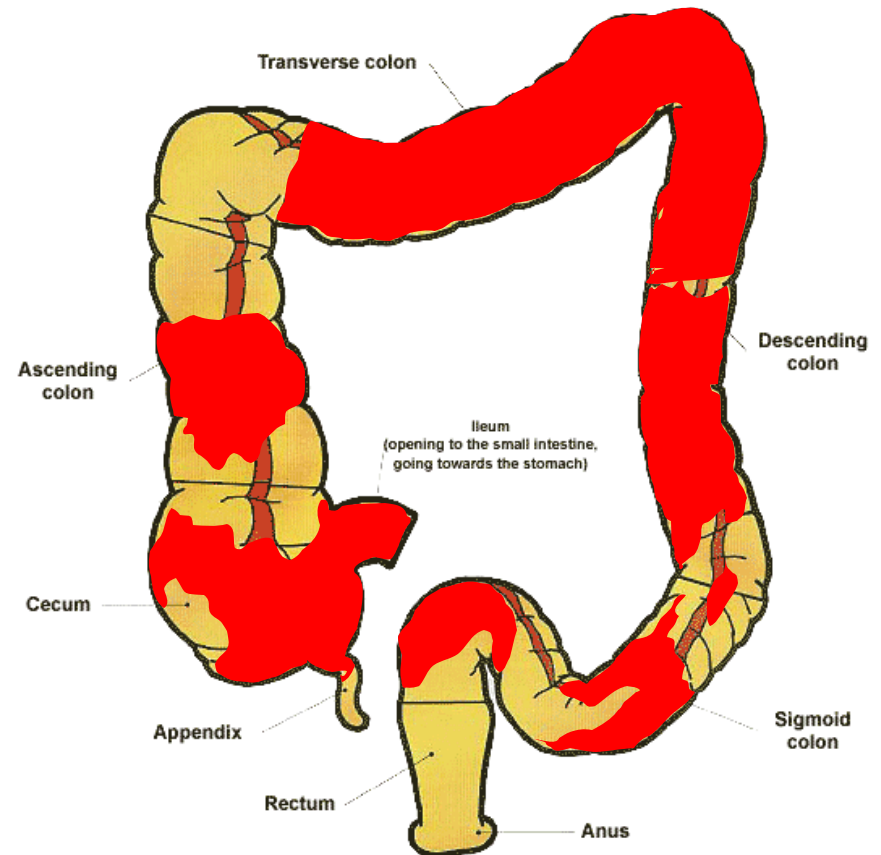


Inflammatory Bowel Disease (IBD)

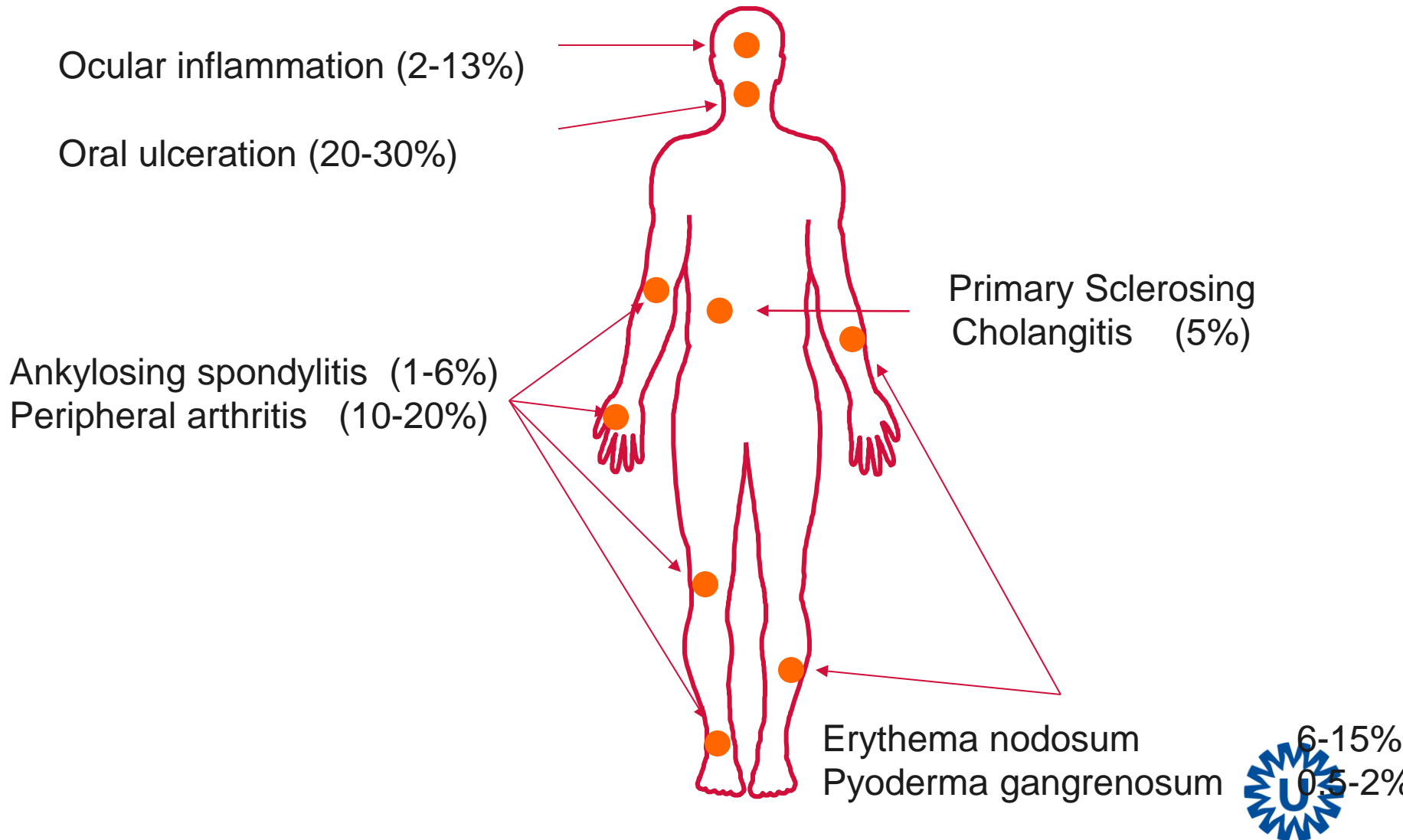
Ulcerative colitis



Crohn's disease



Extra-intestinal manifestations in IBD



Gender differences in IBD

Wagtmans M, Am J Gastroenterol 2001

- 541 CD pts., male:female= 1:1
- Extra-intestinal manifestations (arthritis, erythema nodosum and ocular manifestations) more in women
- Ileocecal resection more in women



Gender differences in IBD

Wagtmans M, Am J Gastroenterol 2001

- 541 CD pts., male:female= 1:1
- Extra-intestinal manifestations (arthritis, erythema nodosum and ocular manifestations) more in women
- Ileocecal resection more in women

Blumenstein I, JCC 2011

- 986 pts, (CD and UC)
- No differences in disease characteristics, EIMs or age of onset
- More often active disease in women



Gender differences in IBD

COIN Study



COIN	2351	
PSI	3387	
<hr/>		+
Total	5738 Pts.	

Spekhorst L, Severs M. COIN & PSI cohort

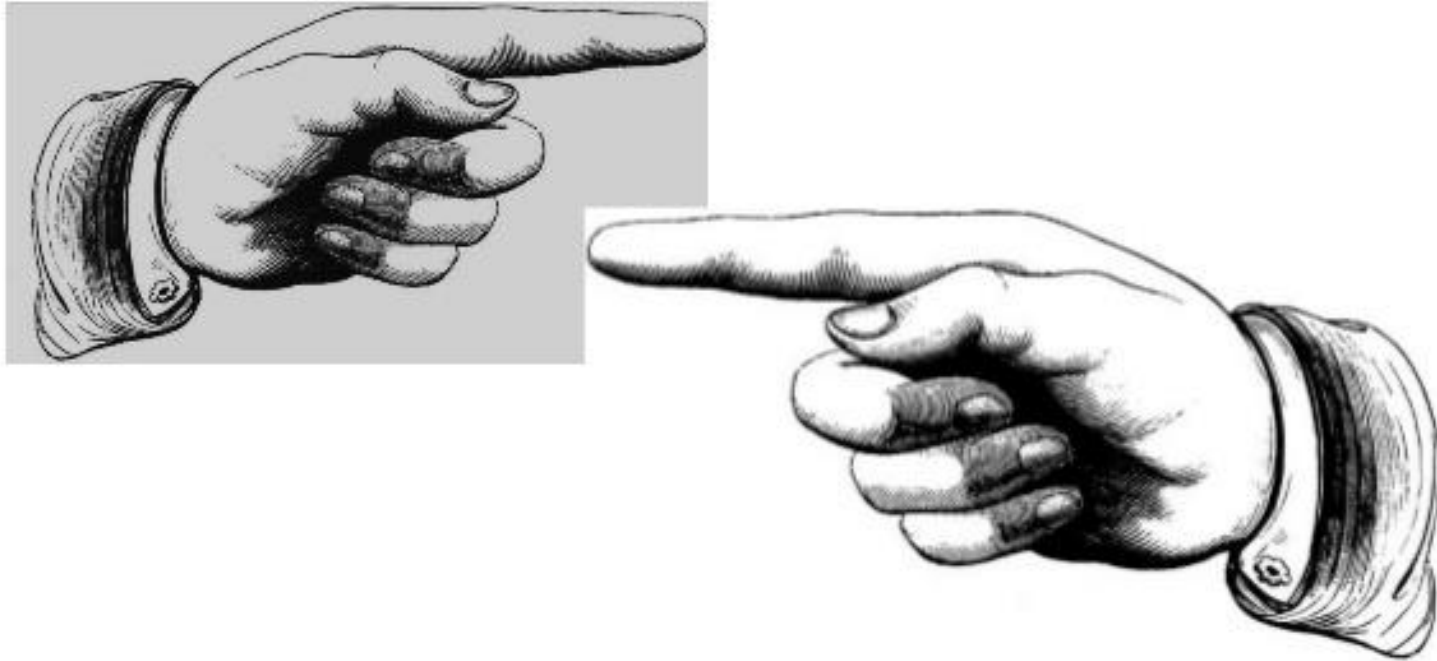


Gender differences in IBD

- Diagnosis UC at younger age in women
- Early onset Crohn's disease more often in males
- Crohn's disease more often in small bowel in men
- Extra-intestinal manifestations more frequent in women (skin and joints)



Gender differences in IBD



Gender differences in other IMIDs

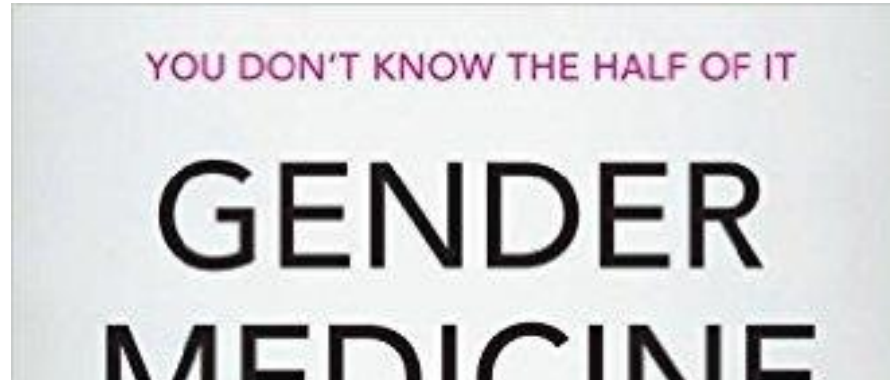
- Ankylosing spondylitis/Psoriatic Arthritis
 - Women: peripheral joint involvement, more functional disability
 - Men: axial involvement, severe radiographic damage
- Rheumatoid Arthritis
 - Women: higher disease activity scores, more pain and greater loss of function



Gender differences in IBD: HRQoL

Baseline	CD (n=1,139)			UC (n=1,213)		
	Male	Female	P-value	Male	Female	P-value
IBDQ (Disease specific HrQoL – median (IQR))						
IBDQ Total	183 (161 – 199)	172 (152 – 193)	<0.01	193 (170 – 206)	180 (155 – 198)	<0.01
IBDQ Bowel	56 (49 – 63)	54 (47 – 61)	<0.01	60 (53 – 66)	57 (47 – 63)	<0.01
IBDQ Emotional	70 (61 – 76)	67 (57 – 74)	<0.01	73 (64 – 78)	69 (58 – 75)	<0.01
IBDQ Social	32 (27 – 35)	31 (26 – 35)	0.03	34 (29 – 35)	33 (27 – 35)	<0.01
IBDQ Systemic	25 (20 – 29)	23 (19 – 27)	<0.01	27 (23 – 30)	24 (19 – 28)	<0.01
Utility scores and EQ5D-3L dimensions (Generic HrQoL)						
Utility scores (mean, SD)	0.74 (0.18)	0.72 (0.18)	0.33	0.75 (0.16)	0.74 (0.17)	0.18
Mobility*	15.7	18.6	0.14	15.8	16.4	0.79
Self-care*	3.7	2.8	0.38	2.1	2.9	0.34
Usual activities*	39.2	48.0	<0.01	30.1	38.3	<0.01
Pain/discomfort*	52.1	62.0	<0.01	39.0	57.8	<0.01
Anxiety/depression*	23.7	25.7	0.38	19.4	25.7	<0.01





SEXUAL MEDICINE REVIEWS

Is Testosterone a Food for the Brain?



Giacomo Ciocca, PhD, PsyD,^{1*} Erika Limoncin, PhD, PsyD,^{1*} Eleonora Carosa, PhD, MD,¹
Stefania Di Sante, PhD, MD,² Giovanni L. Gravina, PhD, MD,¹ Daniele Mollaioli, PsyD,¹ Daniele Gianfrilli, MD,²
Andrea Lenzi, MD,² and Emmanuele A. Jannini, MD³

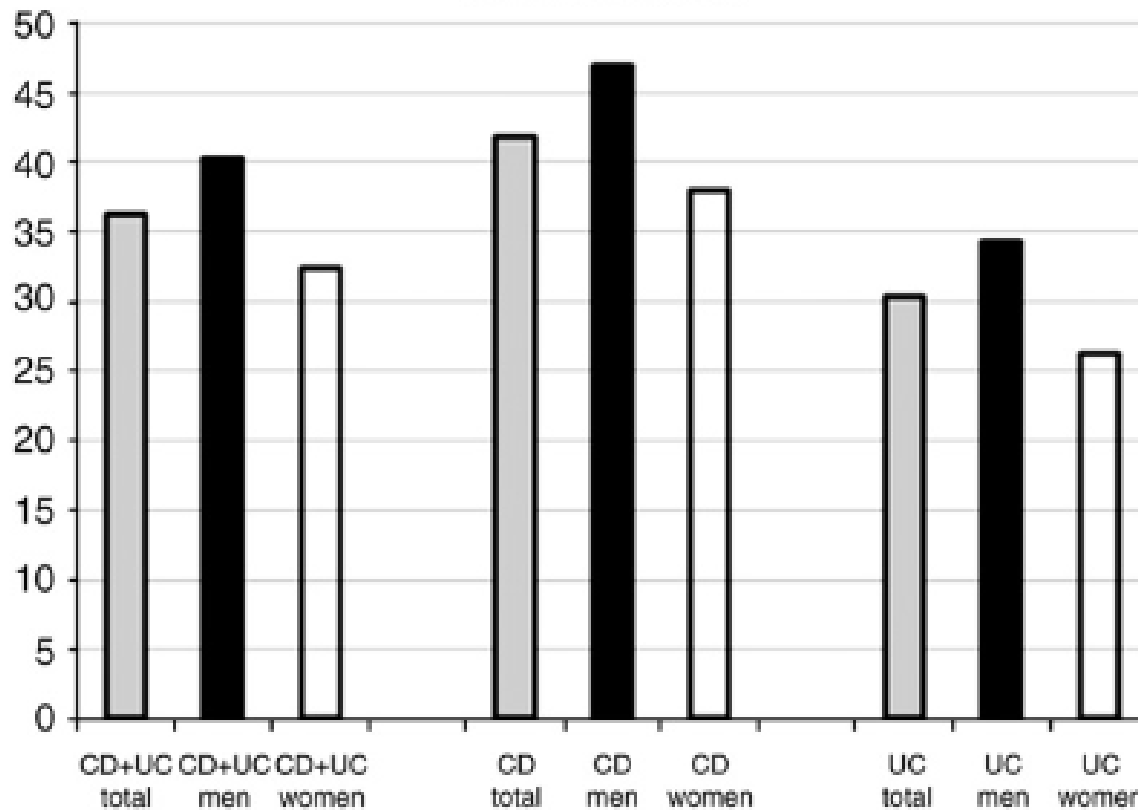


Gender differences: medication in IMiDs



Gender differences medication-IBD

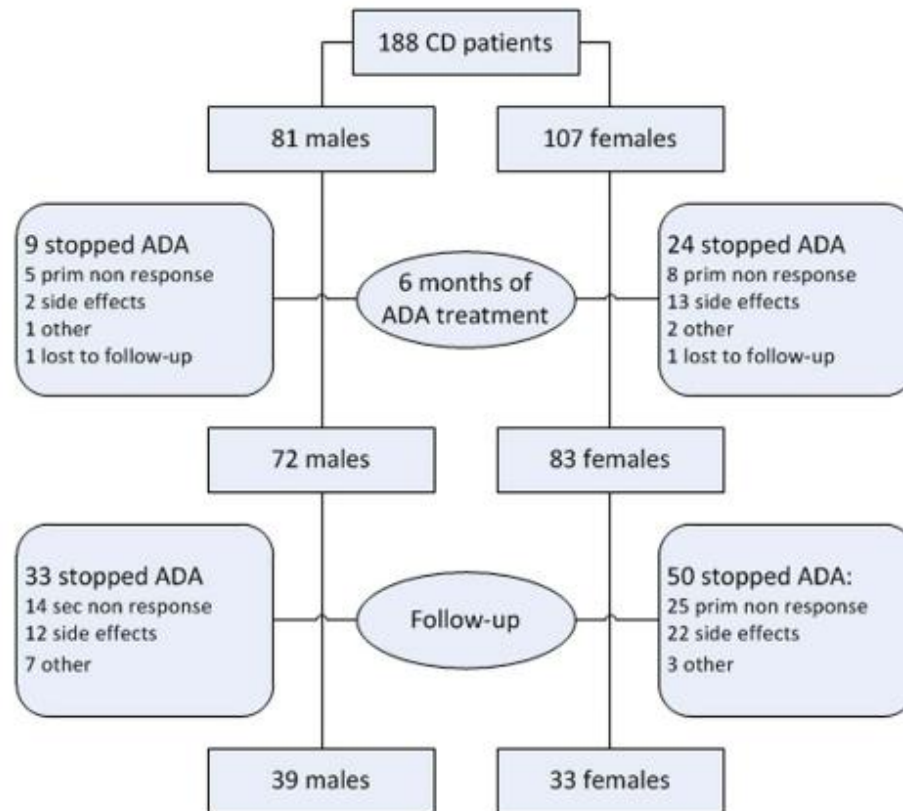
% of patients with immunosuppressive medication



Drug survival side effects of adalimumab in IBD

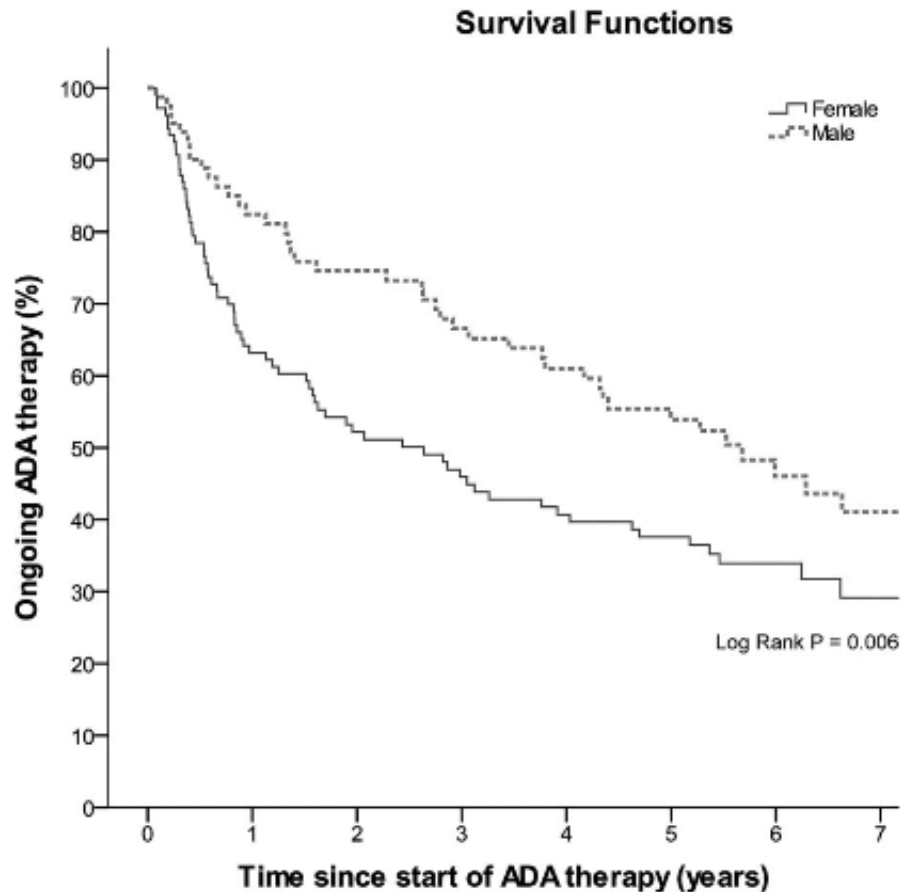
Cohort study in 188 pts.

- CDAI females higher
- Side effects: females (81.3%) > males (64.2%); $p=0.008$



Drug survival side effects of adalimumab in IBD

Cohort study in 188 pts.



Patients at risk

Male	81	63	56	49	44	36	20	11
Female	107	66	50	44	39	36	17	7



Reasons for discontinuation of IFX in IBD

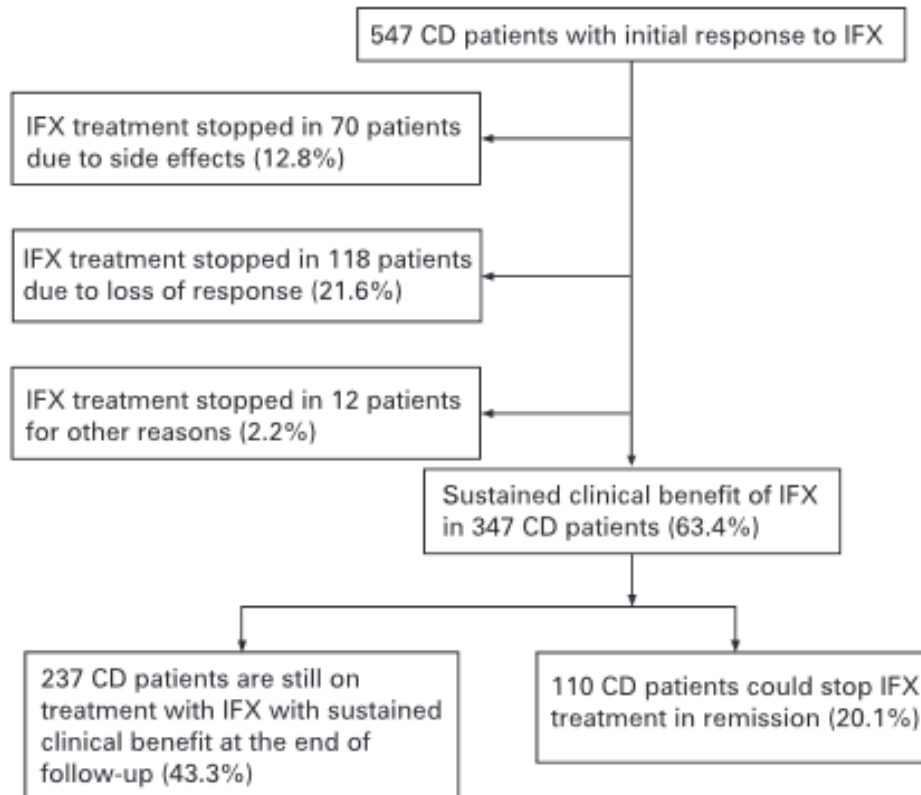


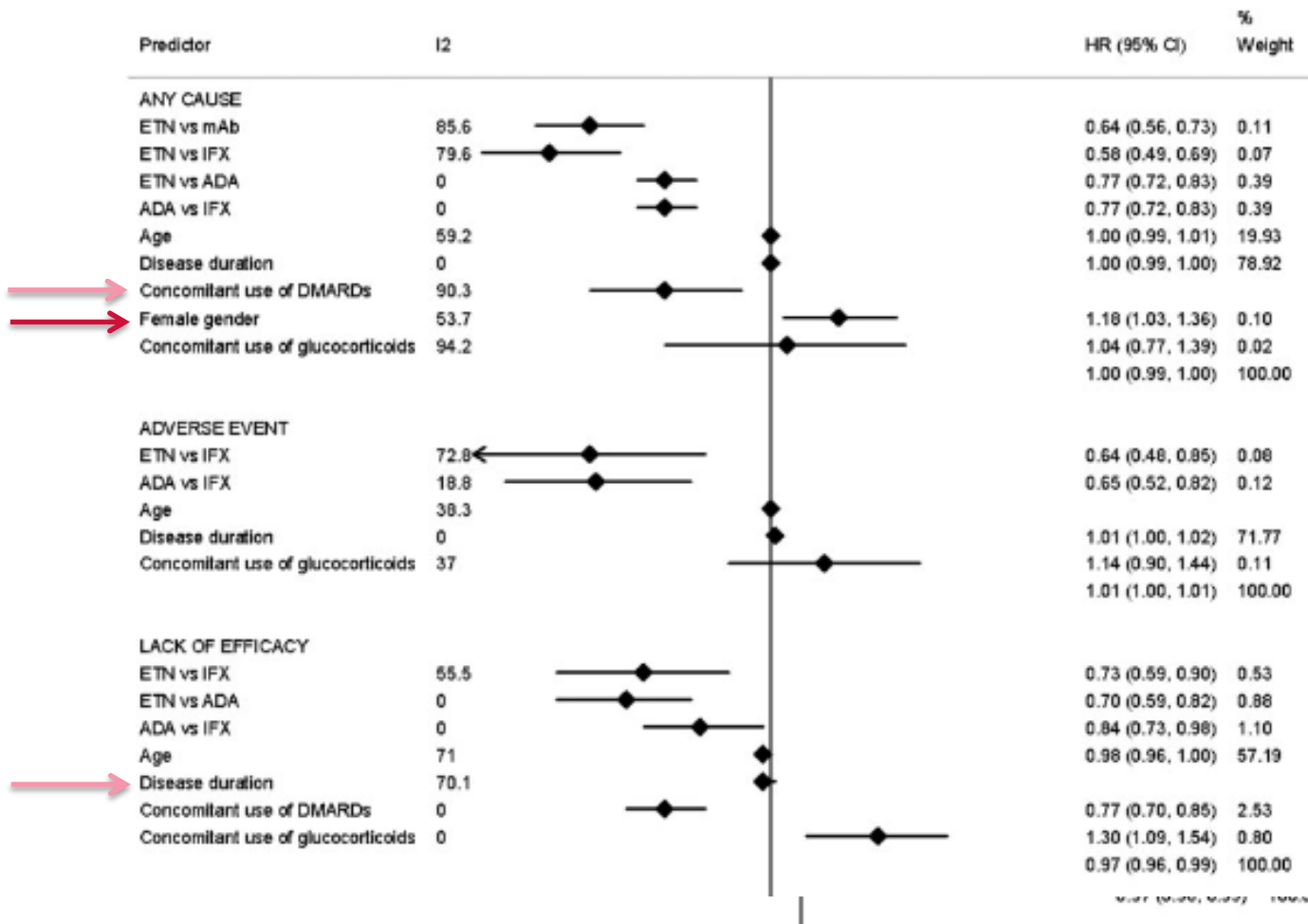
Figure 2 Outcome of treatment of patients with Crohn's disease (CD) with infliximab (IFX) and reasons for its discontinuation.



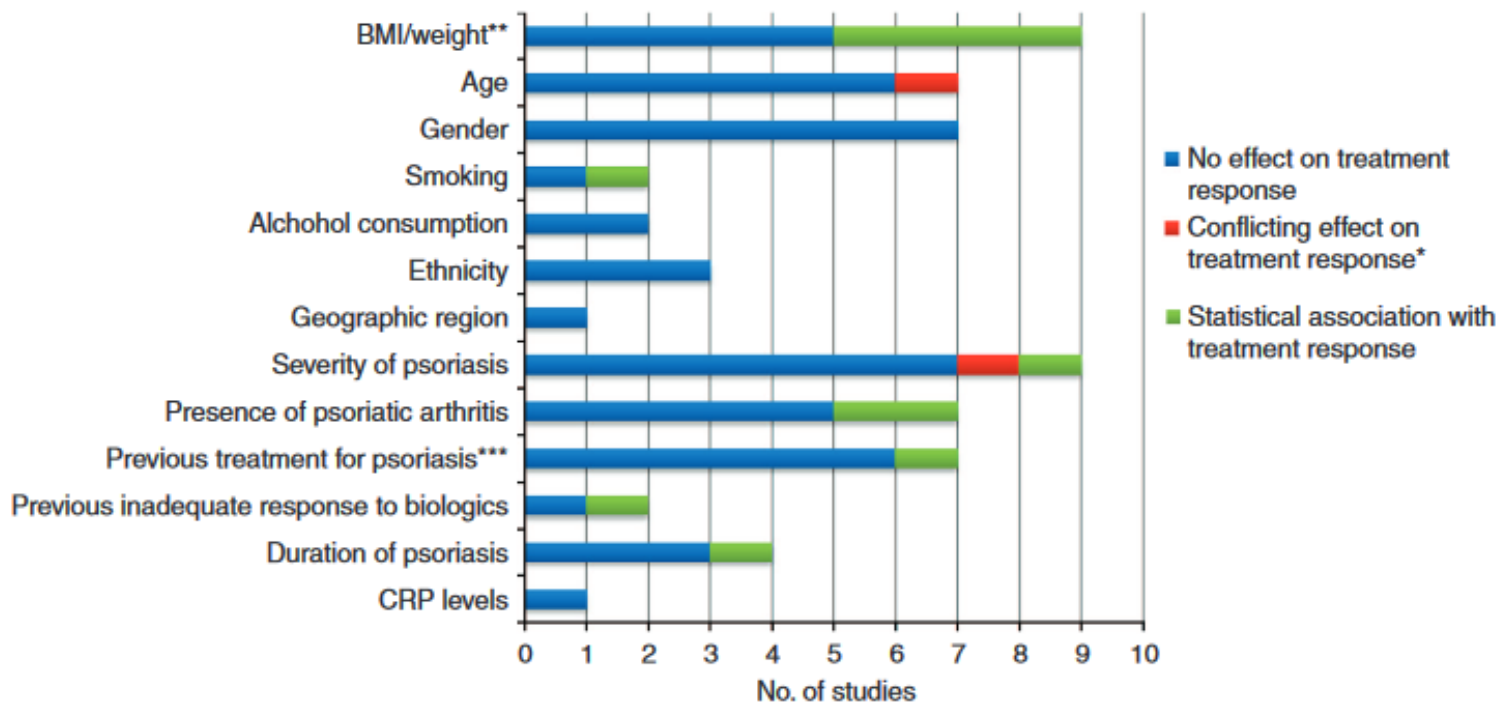
Drug survival in rheumatoid arthritis

Meta-analysis in >200.000 pts.

FIG. 3 Results of meta-analysis of predictors of discontinuation of TNF



Psoriasis: factors associated with response to biologic agents



Sex Differences in Psoriatic Arthritis

Meta-analysis

Table 2. Treatments investigated and arthritis co-medications

Study	MTX n (%)	Treatment	Major observations
Fabbroni et al. [15]	44 (16.4)	IFX, ADA, ETN	Women have a shorter treatment duration, and a higher risk of treatment discontinuation
Fagerli et al. [16]	270 (61.3)	IFX, ADA, ETN	Women have a higher risk of treatment termination after 3 years, not statistically significant
Glintborg et al. [17]	410 (54)	IFX, ADA, ETN	Women have lower drug retention rates at 1 and 2 years; MTX does not affect drug survival
Glintborg et al. [18]	765 (53.8)	IFX, ADA, ETN	Women have lower drug survival after switching to the 2nd biologic agent
Gomez-Reino et al. [19]	–	IFX, ADA, ETN	Female sex is not associated with discontinuation
Heiberg et al. [20]	117 (68)	IFX, ADA, ETN	Women have a higher risk of discontinuation
Kristensen et al. [21]	161 (61.6)	IFX, ADA, ETN	No differences
Lie et al. [22]	430 (100)	MTX	No differences
Mok et al. [23]	–	IFX, ADA, ETN	Women have higher discontinuation rates

IFX = infliximab, ADA = adalimumab, ETN = etanercept, MTX = methotrexate



Adherence and gender

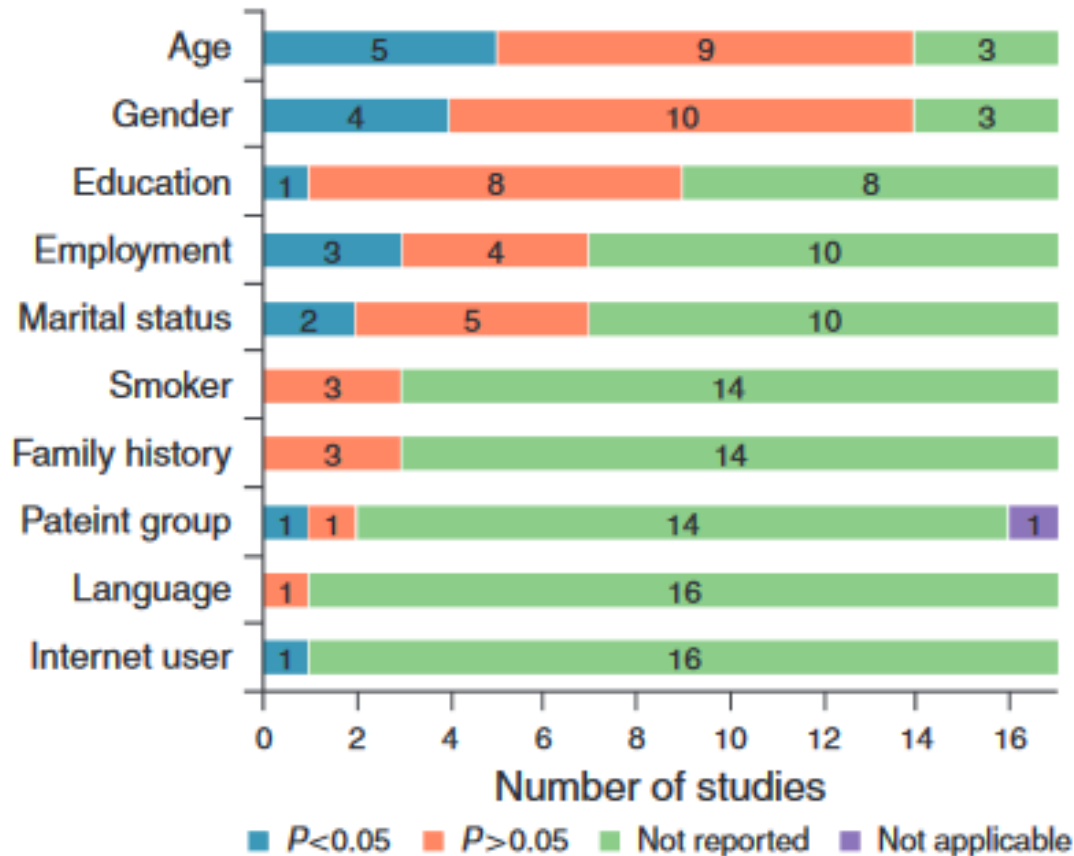


Figure 2. Demographic variables and non-adherence: frequency of findings.



Gender differences in IBD: costs

Mean € (95% CI)	Male	Female	P-value
M. CROHN (369 males and 572 females)			
Total healthcare costs	1,768 (1,502 – 2,075)	1,520 (1,298 – 1,746)	0.19
Medication costs	1,205(1,006– 1,411)	1,118 (953 – 1,286)	0.52
Hospitalization costs	370 (224 – 540)	198 (107 – 300)	0.08
Surgery costs	3 (0 – 11)	14 (3 – 29)	0.27
Diagnostics costs	48 (35 – 62)	46 (34 – 58)	0.89
Outpatient clinic costs	125 (100 – 153)	127 (100 – 165)	0.94
ULCERATIVE COLITIS (544 males and 480 females)			
Total healthcare costs	538 (429 – 646)	608 (480 – 739)	0.45
Medication costs	299 (234 – 365)	353 (269 – 447)	0.37
Hospitalization costs	113 (50 – 183)	122 (50 – 195)	0.87
Surgery costs	5 (0 – 12)	12 (0 – 24)	0.37
Diagnostics costs	32 (24 – 42)	36 (25 – 47)	0.61
Outpatient clinic costs	82 (71 – 95)	75 (62 – 88)	0.39



Conclusions

- Biologic use seems not to differ between men and women
- Women with IMIDs discontinue more often biologicals. An important reason is side effects
- Understanding mechanisms may prevent:
 - Drug failure
 - Surgery and hospitalization
 - Switch to (even) more expensive medication

