

Sex and Gender Difference in Overlap Syndrome of Functional Gastrointestinal Disorder and the Effect of Genetic Polymorphism

Nayoung Kim^{1,3*} Ju Yup Lee^{1,2,}

Department of ¹Internal Medicine, Seoul National University Bundang Hospital, Seoungnam, South Korea; ²Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea;
³Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea;

Introduction

Coexistent gastrointestinal symptom profiles and prevalence or associated factors for the overlap among non-erosive reflux disease (NERD), functional dyspepsia (FD) and irritable bowel syndrome (IBS) remain unclear. As little is known about sex or gender differences among patients with over functional gastrointestinal disorders (FGIDs) therapeutic approach is rather difficult.

Objectives

To evaluate the clinicodemographic features of NERD, FD, and IBS and their overlaps in the view of sex and gender difference and to assess the risk factors including genetic polymorphisms for NERD-FD-IBS.

Patients and Methods

Data collected from 494 FGID patients and 239 controls visiting the outpatient clinic of Gastroenterology at Seoul National University Hospital in Korea. Diagnostic criteria of FGID were based on the Rome IV. Risk factors including genetic polymorphisms of neurotransmitters and cytokines were evaluated.

1. Neurotransmitters that cause FGIDs

HTR3A C178T (serotonin gene), SLC6A4 (serotonin reuptake

transporter), GNB3 C825T (G protein beta3 subunit), ADRA2C

(Adrenergic receptors, adrenoceptor), CCKAR (Cholecystokinin, CCK),

5-HTTLPR (serotonin-transporter), Rs 25531 (serotonin-transporter)

2. Cytokines

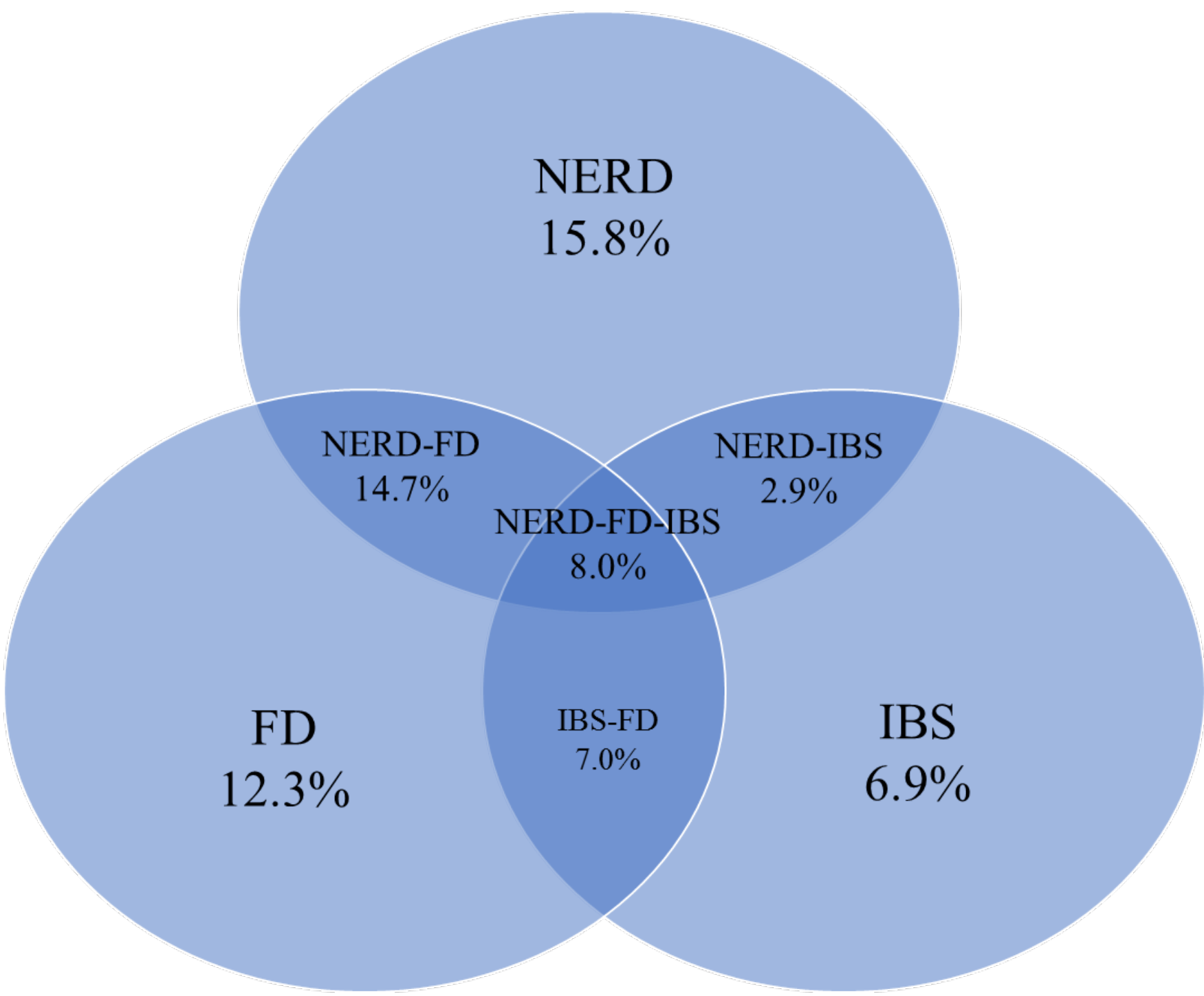
TNFα 308G>A, IL10 592C>A, IL10 1082G>A

PCR	5-HTTLPR	Real Time PCR (SNP)	Rs25531
PCR (RFLP)	ADRA2A C1291G		GNB3 C825T
	CCKAR Intron779		TRPV1 945C>G
	TRPV1 271C>T		

Results

Distribution of FGIDs

FGID: Functional Gastrointestinal Disorder (N=494), NERD: Non-erosive Reflux Disease (n=304)
FD: Functional Dyspepsia (n=308), IBS: Irritable Bowel Syndrome (n=180)
Non-overlap FGIDs (n=255), Overlap FGIDs (n=239)

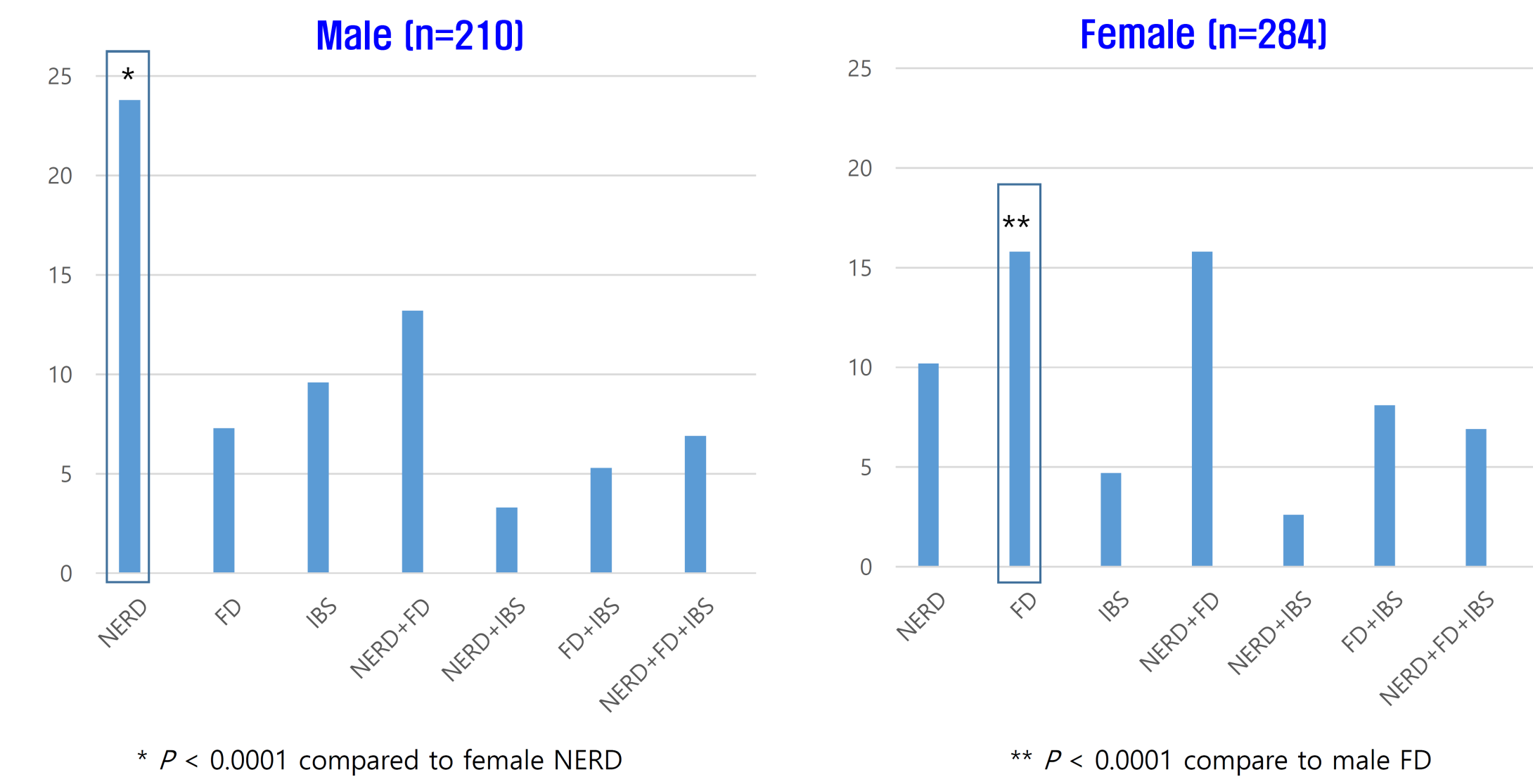


Baseline characteristics and Distribution of FGIDs

Variables	Healthy control (n = 239)	NERD only (n = 116)	FD only (n = 90)	IBS only (n = 180)	NERD-FD (n = 108)	NERD-IBS (n = 21)	FD-IBS (n = 51)	NERD-FD-IBS (n = 59)
Age (years)	55.1 ± 11.7	57.0 ± 12.2	52.5 ± 12.7	46.8 ± 15.2*	51.3 ± 13.1	50.5 ± 10.7	50.9 ± 13.6	44.0 ± 13.2*
Females (%)	146 (61.1)	44 (37.9)*	68 (75.6)*	20 (40.8)	68 (63.0)	11 (52.4)	35 (68.8)	38 (64.4)
BMI (Kg/m ³)	23.4 ± 3.4	24.1 ± 3.1	22.2 ± 3.3	22.7 ± 2.9	22.7 ± 3.1	23.3 ± 2.8	22.6 ± 3.6	23.0 ± 3.4
Single/divorced /widowed (%)	32 (13.7)	15 (12.9)	8 (8.9)	6 (14.0)	18 (16.7)	2 (9.5)	13 (25.5)*	21 (35.6)*
Anxiety HADS score	5.1 ± 3.5	4.6 ± 2.7	7.9 ± 5.6	6.0 ± 3.3	6.1 ± 3.6	6.7 ± 3.1	8.0 ± 3.6	9.0 ± 3.7**
Depression HADS score	5.3 ± 3.5	5.3 ± 3.2	6.9 ± 2.9	6.0 ± 3.3	7.3 ± 3.4	9.7 ± 1.2	10.0 ± 3.6	10.2 ± 3.6**

* *P*<0.05 compare to control

** *P*<0.05 compare to NERD only group and control



* *P* < 0.0001 compared to female NERD

** *P* < 0.0001 compare to male FD

Clinical characteristics of non-overlap and overlap FGIDs

Variables	Healthy control (a) (n = 239)	Non-overlap FGID (b) (n = 255)	Overlap FGID (C) (n = 239)	P value	Post-hoc
Upper GI Symptoms (frequency)					
Early satiation (%)	26 (11.2)	51 (20.6)	136 (57.1)	< 0.0001	a<b<c
Postprandial fullness (%)	30 (12.9)	83 (33.6)	185 (77.4)	< 0.0001	a<b<c
Epigastric pain/burning (%)	40 (17.3)	88 (35.5)	169 (71.3)	< 0.0001	a<b<c
Bloating (%)	31 (13.7)	65 (26.9)	146 (63.2)	< 0.0001	a<b<c
Nausea (%)	19 (8.3)	31 (13.1)	101 (43.2)	< 0.0001	a<b<c
Vomiting (%)	7 (3.1)	10 (4.2)	37 (15.7)	< 0.0001	a<b<c
Upper GI Symptoms (Severity) (mean ± SE)					
Early satiation severity	0.0 ± 0.1	0.5 ± 0.1	1.8 ± 0.1	< 0.0001	a<b<c
Postprandial fullness severity	0.0 ± 0.1	0.8 ± 0.1	2.5 ± 0.1	< 0.0001	a<b<c
Epigastric pain severity	0.3 ± 0.1	1.0 ± 0.1	2.2 ± 0.1	< 0.0001	a<b<c
Bloating pain severity	0.3 ± 0.1	0.7 ± 0.1	2.0 ± 0.1	< 0.0001	a<b<c

Variables	Healthy control (a) (n = 239)	Non-overlap FGID (b) (n = 255)	Overlap FGID (C) (n = 239)	P value	Post-hoc
Lower GI Symptoms (frequency)					
Less than three bowel movements/week	18 (8.0)	21 (8.8)	23 (9.8)	0.803	
Hard or lumpy stools	70 (30.0)	93 (37.5)	146 (61.1)	< 0.0001	a<b<c
Loose or watery stools	54 (23.6)	92 (37.2)	137 (57.6)	< 0.0001	a<b<c
Defecation straining	53 (23.3)	91 (37.4)	144 (60.3)	< 0.0001	a<b<c
A feeling of incomplete bowel movement	51 (43.2)	99 (84.6)	158 (94.6)	< 0.0001	a<b<c
Urgency	8 (3.5)	23 (9.6)	26 (11.1)	0.007	a<b<c

Genetic polymorphisms

NERD: IL10 1082G>A, no sex differences

IBS: GNB3 825C>T, no sex differences / IL10 592C>A, difference in men

NERD-FD: ADRA2A 1291C>G, difference in men and women

NERD-IBS: IL10 592C>A, difference in men

NERD-FD-IBS: SLC6A4 5-HTTLPR, SLC6A4 3609A>G, GNB3 825C>T

difference in men (GNB3 is different for both men and women)

Conclusion

Patients with overlap FGIDs should be a focus of attention due to their association with anxiety/depression and more severe symptoms, especially in women. Genetic polymorphisms seem to be pathophysiological factors of overlap FGIDs. (UN SDGs: Advancing human well-being 1)