

**Supplementary Table 1:** Multivariate analyses of the associations between frequency of GERD<sup>1</sup> symptoms and **incident** Barrett's esophagus

Frequency of GERD symptoms	Primary care		OR <sup>2</sup> (95% CI)	
	BE cases n (%)	controls n (%)		
Ever				
No	34 (18.4)	241 (53.9)	1.00	(Ref)
Yes	151 (81.6)	206 (46.1)	5.31	(3.48, 8.09)
At age 10-19 y				
Never symptoms	34 (18.4)	241 (53.9)	1.00	(Ref)
≥ 1 time per month	5 (2.7)	0 (0.0)	-	-
1 time per week	5 (2.7)	0 (0.0)	-	-
> 1 time per week	6 (3.2)	3 (0.7)	16.7	(3.87, 71.8)
No symptoms <sup>3</sup>	135 (73.0)	203 (45.4)	4.83	(3.15, 7.40)
At age 20-29 y				
Never symptoms	34 (18.4)	241 (53.9)	1.00	(Ref)
≥ 1 time per month	9 (4.9)	8 (1.8)	8.34	(2.94, 23.7)
1 time per week	8 (4.3)	8 (1.8)	6.36	(2.21, 18.3)
> 1 time per week	20 (10.8)	9 (2.0)	18.5	(7.62, 44.9)
No symptoms <sup>3</sup>	114 (61.6)	181 (40.5)	4.56	(2.95, 7.05)
At age 30-49 y				
Never symptoms	34 (18.4)	241 (53.9)	1.00	(Ref)
≥ 1 time per month	15 (8.1)	34 (7.6)	3.28	(1.60, 6.73)
1 time per week	15 (8.1)	26 (5.8)	4.35	(2.06, 9.19)
> 1 time per week	74 (40.0)	59 (13.2)	9.65	(5.74, 16.2)
No symptoms <sup>3</sup>	47 (25.4)	87 (19.5)	3.84	(2.30, 6.40)
At age 50-79 y				
Never symptoms	34 (18.4)	241 (53.9)	1.00	(Ref)
≥ 1 time per month	16 (8.6)	49 (11.0)	2.41	(1.23, 4.72)
1 time per week	23 (12.4)	37 (8.3)	4.52	(2.38, 8.61)
> 1 time per week	83 (44.9)	94 (21.0)	6.52	(4.06, 10.5)
No symptoms <sup>3</sup>	29 (15.7)	26 (5.8)	8.00	(4.06, 15.7)
10 years prior to diagnosis				
Never symptoms	34 (18.4)	241 (53.9)	1.00	(Ref)
≥ 1 time per month	14 (7.6)	46 (10.3)	2.20	(1.09, 4.45)
1 time per week	23 (12.4)	33 (7.4)	5.07	(2.64, 9.75)
> 1 time per week	93 (50.3)	100 (22.4)	6.86	(4.29, 10.9)
No symptoms <sup>3</sup>	21 (11.3)	27 (6.0)	5.65	(2.84, 11.3)
Frequency of GERD and age at onset				
Never symptoms	34 (18.4)	241 (53.9)	1.00	(Ref)
≥ weekly age < 30 y	31 (16.7)	18 (4.0)	13.1	(6.54, 26.3)
≥ weekly age 30-49 y	58 (31.4)	69 (15.4)	6.19	(3.67, 10.4)
≥ weekly age 50-79 y	47 (25.4)	72 (16.1)	4.70	(2.79, 7.91)
< weekly age < 30 y	5 (2.7)	6 (1.3)	6.07	(1.72, 21.5)
< weekly age 30-49 y	4 (2.2)	21 (4.7)	1.37	(0.44, 4.28)
< weekly age 50-79 y	6 (3.2)	20 (4.5)	2.22	(0.82, 6.02)

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

<sup>1</sup> Highest reported symptoms of either heartburn or acid regurgitation.

<sup>2</sup> Adjusted for age, sex, highest level of education, cumulative smoking history, body mass index, alcohol intake, and use of aspirin or non-steroidal anti-inflammatory drugs.

<sup>3</sup> Symptoms were present at other age intervals.

**Supplementary Table 2:** Multivariate analyses of the association between severity of pain from GERD<sup>1</sup> and incident Barrett's esophagus

Severity of pain from GERD	Primary care		OR <sup>2</sup> (95% CI)
	BE cases n (%)	controls n (%)	
Ever			
Never symptoms	34 (18.5)	241 (53.9)	1.00 (Ref)
Mild	22 (11.9)	67 (15.0)	2.30 (1.25, 4.23)
Moderate	55 (29.9)	89 (19.9)	4.63 (2.80, 7.66)
Severe	73 (39.7)	50 (11.2)	11.2 (6.61, 18.9)
At age 10-19 y			
Never symptoms	34 (30.6)	241 (63.2)	1.00 (Ref)
Mild	8 (7.2)	0 (0.0)	-
Moderate	7 (6.3)	3 (0.8)	19.0 (4.57, 79.2)
Severe	2 (1.8)	0 (0.0)	-
No symptoms <sup>3</sup>	60 (54.1)	137 (36.0)	3.20 (1.98, 5.16)
At age 20-29 y			
Never symptoms	34 (27.9)	241 (61.3)	1.00 (Ref)
Mild	11 (9.0)	11 (2.8)	11.3 (4.80, 26.8)
Moderate	16 (13.1)	11 (2.8)	11.6 (4.84, 27.6)
Severe	5 (4.1)	3 (0.8)	13.0 (2.87, 58.6)
No symptoms <sup>3</sup>	56 (45.9)	127 (32.3)	3.19 (1.97, 5.18)
At age 30-49 y			
Never symptoms	34 (20.3)	241 (56.6)	1.00 (Ref)
Mild	23 (13.8)	51 (12.0)	3.30 (1.78, 6.13)
Moderate	43 (25.7)	44 (10.3)	7.68 (4.29, 13.8)
Severe	37 (22.2)	23 (5.4)	11.8 (6.10, 22.7)
No symptoms <sup>3</sup>	30 (18.0)	67 (15.7)	3.10 (1.76, 5.47)
At age 50-79 y			
Never symptoms	34 (19.2)	241 (54.8)	1.00 (Ref)
Mild	21 (11.9)	61 (13.9)	2.38 (1.27, 4.43)
Moderate	47 (26.6)	84 (19.1)	4.18 (2.49, 7.02)
Severe	53 (29.9)	33 (7.5)	12.1 (6.79, 21.7)
No symptoms <sup>3</sup>	22 (12.4)	21 (4.8)	8.05 (3.79, 17.1)
Severity of pain from GERD and age at onset			
Never symptoms	34 (18.5)	241 (53.9)	1.00 (Ref)
Severe GERD < 30y	5 (2.7)	3 (0.7)	12.3 (2.73, 55.6)
Severe GERD 30-49y	34 (18.5)	21 (4.7)	12.0 (6.09, 23.7)
Severe GERD 50-79y	34 (18.5)	26 (5.8)	10.4 (5.45, 19.9)
Less severe GERD < 30y	20 (10.9)	20 (4.5)	7.64 (3.67, 15.9)
Less Severe GERD 30-49y	34 (18.5)	65 (14.5)	3.98 (2.26, 7.01)
Less Severe GERD 50-79y	23 (12.5)	71 (15.9)	2.24 (1.23, 4.09)

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

<sup>1</sup> Highest severity of pain from either heartburn or acid regurgitation.

<sup>2</sup> Adjusted for age, sex, highest level of education, cumulative smoking history, body mass index, alcohol intake, and use of aspirin or non-steroidal anti-inflammatory drugs.

<sup>3</sup> Symptoms were present at other age intervals.

**Supplementary Table 3:** Multivariate analyses of the association between cumulative GERD<sup>1</sup> symptom duration (years) and **incident** Barrett's esophagus, overall and within strata of age at onset

Age at onset of frequent GERD symptoms	Never symptoms		≤ 20 years		> 20 years		P-trend
	Cases / Controls	OR <sup>2</sup> (95% CI)	Cases / Controls	OR <sup>2</sup> (95% CI)	Cases / Controls	OR <sup>2</sup> (95% CI)	
All	34/241	1.00 (Ref)	69/123	4.01 (2.51, 6.40)	82/83	7.49 (4.61, 12.2)	0.01
≥ weekly symptoms <sup>3</sup>							
Age at onset < 30y	34/241	1.00 (Ref)	8/10	4.02 (1.34, 12.1)	18/8	24.8 (9.79, 12.1)	0.01
Age at onset 30-49y	34/241	1.00 (Ref)	26/32	6.33 (3.20, 12.5)	32/37	6.05 (3.22, 11.4)	0.96
Age at onset 50-79y	34/241	1.00 (Ref)	22/34	4.27 (2.17, 8.40)	25/38	5.30 (2.75, 10.2)	0.66

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

<sup>1</sup> Number of years with at least weekly heartburn or acid regurgitation symptoms.

<sup>2</sup> Adjusted for age, sex, highest level of education, cumulative smoking history, body mass index, alcohol intake, and use of aspirin or non-steroidal anti-inflammatory drugs.

<sup>3</sup> Numbers do not add to total as the group of participants with infrequent (< weekly) GERD symptoms throughout life were excluded from this analysis.

**Supplementary Table 4:** Odds ratios for Barrett's esophagus associated with frequency of symptoms of GERD<sup>1</sup> combined with BMI category or smoking or NSAID use or PPI use

Frequency of GERD symptoms	Frequency of GERD combined with BMI					
	BMI < 25		BMI 25-29.9		BMI ≥ 30	
	Controls/cases	OR <sup>2</sup> (95% CI)	Controls/cases	OR <sup>2</sup> (95% CI)	Controls/cases	OR <sup>2</sup> (95% CI)
Never	44/7	1.00 (Ref)	86/10	0.74 (0.26, 2.11)	111/24	1.39 (0.55, 3.52)
< weekly	6/3	3.09 (0.60, 15.8)	14/4	1.86 (0.47, 7.39)	26/12	2.92 (1.00, 8.49)
≥ 1 time per week	15/23	9.88 (3.46, 28.2)	46/61	8.90 (3.63, 21.9)	72/68	6.12 (2.54, 14.7)
Synergy index (95% CI)						0.55 (0.24, 1.26)

  

Frequency of GERD symptoms	Frequency of GERD combined with smoking status			
	Never smoker		Ever smoker	
	Controls/cases	OR <sup>3</sup> (95% CI)	Controls/cases	OR <sup>3</sup> (95% CI)
Never	65/9	1.00 (Ref)	176/31	1.27 (0.57, 2.86)
< weekly	10/7	5.10 (1.53, 16.9)	34/11	2.34 (0.87, 6.28)
≥ 1 time per week	33/31	7.16 (3.01, 17.0)	98/121	9.26 (4.32, 19.8)
Synergy index (95% CI)				1.29 (0.67, 2.48)

  

Frequency of GERD symptoms	Frequency of GERD combined with NSAIDs use			
	Did not use NSAIDs		Used NSAIDs	
	Controls/cases	OR <sup>4</sup> (95% CI)	Controls/cases	OR <sup>4</sup> (95% CI)
Never	91/12	1.00 (Ref)	150/29	1.50 (0.72, 3.10)
< weekly	16/4	1.98 (0.56, 6.97)	30/15	3.81 (1.59, 9.15)
≥ 1 time per week	50/63	9.98 (4.87, 20.4)	83/89	8.48 (4.28, 16.8)
Synergy index (95% CI)				0.79 (0.46, 1.36)

  

Frequency of GERD symptoms	Frequency of GERD combined with <i>H. pylori</i>			
	Negative		Positive	
	Controls/cases	OR <sup>5</sup> (95% CI)	Controls/cases	OR <sup>5</sup> (95% CI)
Never	148/27	1.00 (Ref)	87/16	0.82 (0.40, 1.69)
< weekly	23/13	3.19 (1.43, 7.11)	21/6	1.52 (0.56, 4.17)
≥ 1 time per week	94/132	8.24 (5.00, 13.6)	34/16	2.60 (1.26, 5.40)
Synergy index (95% CI)				0.23 (0.08, 0.64)

  

Frequency of GERD symptoms	Frequency of GERD combined with PPIs			
	Never used PPIs		Ever used PPIs	
	Controls/cases	OR <sup>5</sup> (95% CI)	Controls/cases	OR <sup>5</sup> (95% CI)
Never	228/28	1.00 (Ref)	13/13	7.68 (3.21, 18.4)
< weekly	39/7	1.46 (0.59, 3.60)	7/12	13.9 (5.02, 38.7)
≥ 1 time per week	65/21	2.64 (1.40, 4.99)	68/131	16.3 (9.91, 26.9)
Synergy index (95% CI)				1.84 (0.82, 4.14)

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

<sup>1</sup> Heartburn or acid regurgitation symptoms in the 10 years prior to diagnosis.

<sup>2</sup> Adjusted for age, sex, education, cumulative smoking history, average alcohol consumption, and use of aspirin or other NSAIDs.

<sup>3</sup> Adjusted for age, sex, education, body mass index, average alcohol consumption, and use of aspirin or other NSAIDs.

<sup>4</sup> Adjusted for age, education, cumulative smoking history, body mass index, and average alcohol consumption.

<sup>5</sup> Adjusted for age, education, cumulative smoking history, body mass index, average alcohol consumption, and use of aspirin or other NSAIDs.

**Supplementary Table 5:** Odds ratios for Barrett’s esophagus associated with duration of symptoms of GERD<sup>1</sup> combined with BMI category or smoking or NSAID use or PPI use

Duration of GERD symptoms	Duration of GERD combined with BMI					
	BMI < 25		BMI 25-29.9		BMI ≥ 30	
	Controls/cases	OR <sup>2</sup> (95% CI)	Controls/cases	OR <sup>2</sup> (95% CI)	Controls/cases	OR <sup>2</sup> (95% CI)
Never	19/3	1.00 (Ref)	58/7	0.77 (0.18, 3.30)	161/28	1.15 (0.32, 4.21)
< 20 years	4/8	12.1 (2.17, 67.2)	36/26	4.85 (1.28, 18.4)	82/51	4.08 (1.13, 14.7)
≥ 20 years	1/5	34.0 (2.72, 425)	25/32	8.85 (2.32, 33.8)	57/64	7.75 (2.14, 28.0)
Synergy index (95% CI)						0.20 (0.02, 2.04)
Duration of GERD symptoms	Duration of GERD combined with smoking status					
	Never smoker		Ever smoker			
	Controls/cases	OR <sup>3</sup> (95% CI)	Controls/cases	OR <sup>3</sup> (95% CI)		
Never	65/9	1.00 (ref)	176/31	1.27 (0.56, 2.84)		
< 20 years	31/26	5.97 (2.48, 14.3)	89/61	5.05 (2.30, 11.1)		
≥ 20 years	15/19	10.4 (3.83, 28.3)	66/88	10.2 (4.69, 22.4)		
Synergy index (95% CI)						0.96 (0.41, 2.22)
Duration of GERD symptoms	Duration of GERD combined with NSAIDs use					
	Did not use NSAIDs		Used NSAIDs			
	Controls/cases	OR <sup>4</sup> (95% CI)	Controls/cases	OR <sup>4</sup> (95% CI)		
Never	91/12	1.00 (Ref)	150/29	1.50 (0.72, 3.10)		
< 20 years	41/39	7.38 (3.48, 15.7)	82/49	4.65 (2.29, 9.42)		
≥ 20 years	35/40	9.54 (4.43, 20.5)	48/67	11.5 (5.60, 23.7)		
Synergy index (95% CI)						1.17 (0.61, 2.24)
Duration of GERD symptoms	Duration of GERD combined with <i>H. pylori</i>					
	Negative		Positive			
	Controls/cases	OR <sup>5</sup> (95% CI)	Controls/cases	OR <sup>5</sup> (95% CI)		
Never	148/27	1.00 (Ref)	87/13	0.80 (0.39, 1.64)		
< 20 years	81/70	4.83 (2.86, 8.16)	38/18	2.61 (1.29, 5.28)		
≥ 20 years	54/92	10.6 (6.11, 18.4)	26/10	2.11 (0.90, 4.92)		
Synergy index (95% CI)						0.12 (0.03, 0.53)
Duration of GERD symptoms	Duration of GERD combined with PPIs					
	Never used PPIs		Ever used PPIs			
	Controls/cases	OR <sup>5</sup> (95% CI)	Controls/cases	OR <sup>5</sup> (95% CI)		
Never	228/28	1.00 (Ref)	13/13	8.07 (3.37, 19.4)		
< 20 years	80/19	1.98 (1.04, 3.75)	43/69	13.0 (7.46, 22.5)		
≥ 20 years	40/18	3.64 (1.81, 7.31)	43/89	19.2 (11.0, 33.4)		
Synergy index (95% CI)						1.87 (0.84, 4.17)

BE, Barrett’s esophagus; GERD, gastroesophageal reflux disease.

<sup>1</sup> Heartburn or acid regurgitation symptoms in the 10 years prior to diagnosis.

<sup>2</sup> Adjusted for age, sex, education, cumulative smoking history, average alcohol consumption, and use of aspirin or other NSAIDs.

<sup>3</sup> Adjusted for age, sex, education, body mass index, average alcohol consumption, and use of aspirin or other NSAIDs.

<sup>4</sup> Adjusted for age, education, cumulative smoking history, body mass index, and average alcohol consumption.

<sup>5</sup> Adjusted for age, education, cumulative smoking history, body mass index, average alcohol consumption, and use of aspirin or other NSAIDs.

**Supplementary Table 6:** Odds ratios for Barrett’s esophagus associated with age at onset of symptoms of GERD<sup>1</sup> combined with BMI category or smoking or NSAID use or PPI use

Age at onset of GERD combined with BMI						
Age at onset of GERD symptoms	BMI < 25		BMI 25-29.9		BMI ≥ 30	
	Controls/cases	OR <sup>2</sup> (95% CI)	Controls/cases	OR <sup>2</sup> (95% CI)	Controls/cases	OR <sup>2</sup> (95% CI)
Never	44/7	1.00 (Ref)	86/10	0.77 (0.27, 2.19)	111/24	1.43 (0.56, 3.62)
≥ GERD age <30 years	16/23	9.63 (3.35, 27.7)	52/48	6.27 (2.54, 15.4)	73/61	5.58 (2.31, 13.5)
≥ GERD age ≥ 30 years	4/4	6.29 (1.26, 31.5)	5/20	26.9 (7.43, 97.6)	9/21	15.3 (4.94, 47.6)
Synergy index (95% CI)	2.51 (0.43, 14.7)					

  

Age at onset of GERD combined with smoking status				
Age at onset of GERD symptoms	Never smoker		Ever smoker	
	Controls/cases	OR <sup>3</sup> (95% CI)	Controls/cases	OR <sup>3</sup> (95% CI)
Never	65/9	1.00 (Ref)	176/31	1.27 (0.57, 2.86)
≥ GERD age <30 years	31/27	6.41 (2.67, 15.4)	107/105	7.43 (3.46, 16.0)
≥ GERD age ≥ 30 years	5/12	18.8 (5.26, 67.4)	13/33	18.3 (7.03, 47.7)
Synergy index (95% CI)	0.96 (0.26, 3.54)			

  

Age at onset of GERD combined with NSAIDs use				
Age at onset of GERD symptoms	Did not use NSAIDs		Used NSAIDs	
	Controls/cases	OR <sup>4</sup> (95% CI)	Controls/cases	OR <sup>4</sup> (95% CI)
Never	91/12	1.00 (Ref)	150/29	1.52 (0.74, 3.15)
≥ GERD age <30 years	0/0	-	141/132	7.50 (3.90, 14.2)
≥ GERD age ≥ 30 years	5/16	26.7 (8.09, 88.0)	13/29	17.3 (7.01, 42.6)
Synergy index (95% CI)	0.62 (0.18, 2.21)			

  

Age at onset of GERD combined with <i>H. pylori</i>				
Age at onset of GERD symptoms	Negative		Positive	
	Controls/cases	OR <sup>5</sup> (95% CI)	Controls/cases	OR <sup>5</sup> (95% CI)
Never	148/27	1.00 (Ref)	87/13	0.79 (0.39, 1.63)
≥ GERD age 30-79 years	96/112	6.74 (4.08, 11.1)	41/16	2.15 (1.05, 4.42)
≥ GERD age <30 years	12/38	18.7 (8.57, 40.8)	5/6	6.01 (1.69, 21.4)
Synergy index (95% CI)	0.29 (0.06, 1.43)			

  

Age at onset of GERD combined with PPIs				
Age at onset of GERD symptoms	Never used PPIs		Ever used PPIs	
	Controls/cases	OR <sup>5</sup> (95% CI)	Controls/cases	OR <sup>5</sup> (95% CI)
Never	228/28	1.00 (Ref)	13/13	7.90 (3.30, 18.9)
≥ GERD age 30-79 years	72/22	2.47 (1.32, 4.61)	69/110	13.6 (8.23, 22.6)
≥ GERD age <30 years	8/8	8.12 (2.76, 24.0)	10/37	31.1 (13.9, 69.7)
Synergy index (95% CI)	2.15 (0.77, 6.02)			

BE, Barrett’s esophagus; GERD, gastroesophageal reflux disease.

<sup>1</sup> Heartburn or acid regurgitation symptoms in the 10 years prior to diagnosis.

<sup>2</sup> Adjusted for age, sex, education, cumulative smoking history, average alcohol consumption, and use of aspirin or other NSAIDs.

<sup>3</sup> Adjusted for age, sex, education, body mass index, average alcohol consumption, and use of aspirin or other NSAIDs.

<sup>4</sup> Adjusted for age, education, cumulative smoking history, body mass index, and average alcohol consumption.

<sup>5</sup> Adjusted for age, education, cumulative smoking history, body mass index, average alcohol consumption, and use of aspirin or other NSAIDs.