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CLINICAL AT

Sex-Based Differences in Incidence of Inflammatory Bowel Diseases—Pooled Analysis of Population-Based Studies From Western Countries

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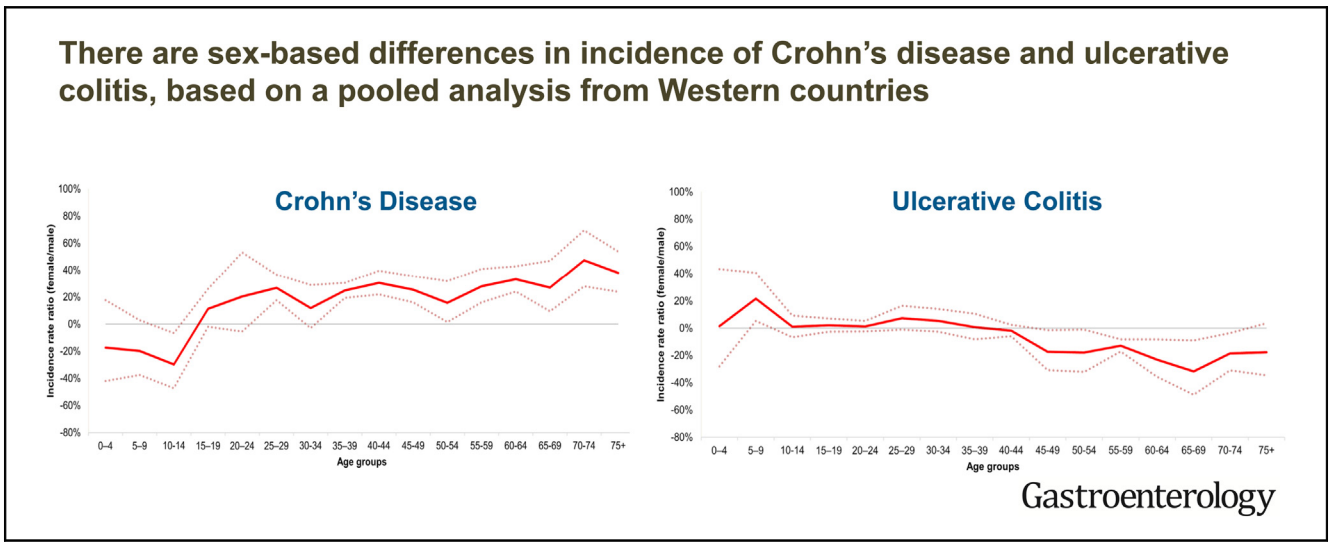
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e16. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify risk factors for Crohn's disease and ulcerative colitis (UC) and recognize sex-based differences in the natural course of inflammatory bowel disease (IBD).



See Covering the Cover synopsis on page 945.

BACKGROUND & AIMS: Although the incidence of inflammatory bowel diseases (IBDs) varies with age, few studies have examined variations between the sexes. We therefore used population data from established cohorts to analyze sex differences in IBD incidence according to age at diagnosis. **METHODS:** We identified population-based cohorts of patients with IBD for which incidence and age data were available (17 distinct cohorts from 16 regions of Europe, North America, Australia, and New Zealand). We collected data through December 2016 on 95,605 incident cases of Crohn's disease (CD) (42,831 male and 52,774 female) and 112,004 incident cases of ulcerative colitis (UC) (61,672 male and 50,332 female). We pooled incidence rate ratios of CD and UC for the combined cohort and compared differences according to sex using random effects meta-analysis. **RESULTS:** Female patients had a lower risk of CD during childhood, until the age range of 10–14 years (incidence rate ratio, 0.70; 95% CI, 0.53–0.93), but they had a higher risk of CD thereafter, which was statistically significant for the age groups of 25–29 years and older than 35 years. The incidence of UC did not differ significantly for female vs male patients (except for the age group of 5–9 years) until age 45 years; thereafter, men had a significantly higher incidence of ulcerative colitis than women. **CONCLUSIONS:** In a pooled analysis of population-based studies, we found age at IBD onset to vary with sex. Further studies are needed to investigate mechanisms of sex differences in IBD incidence.

Keywords: Epidemiology; Estrogen; Menopause; Puberty.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Few studies have examined differences in the incidence of inflammatory bowel disease (IBD) between the sexes.

NEW FINDINGS

In a pooled analysis that included over 207,600 incident cases of IBD among over 478 million people, age of IBD onset varied by sex. Sex hormones might affect pathogenesis of IBD in patients with epigenetic and genetic risk factors.

LIMITATIONS

The data were primarily derived from developed economies in Western population. The authors were not able to control for possible misclassification in patient registries.

IMPACT

These findings complement the increasing experimental evidence supporting hormonal influences in the pathogenesis of IBD. The mechanisms remain largely undefined but might lead to novel therapeutic and preventative opportunities.

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are chronic inflammatory disorders of the gastrointestinal tract with marked heterogeneity in disease presentation and natural history.[1,2] The pathogenesis of IBD is complex and dictated by genetic susceptibility, dysregulation of the innate and adaptive immune systems, and environmental factors. Sex differences in disease incidence and prevalence have been reported in other chronic immune-mediated disorders, such as rheumatoid arthritis, scleroderma, multiple sclerosis, and systemic lupus erythematosus, pointing to potential biological roles of sex hormones in disease pathogenesis.[3–7] Differences in IBD incidence have been reported according to the age of diagnosis, but few individual studies have examined variations in incidence according to sex and with inconsistent findings.

There is, however, accumulating evidence implicating sex hormones in susceptibility to IBD, disease symptom severity, and disease progression.[8,9] A recent meta-analysis concluded that oral contraceptive pill use is associated with an increased risk of IBD,[10] and a large cohort study of women with IBD reported changes in symptom severity during times of hormone fluctuation (eg, menstruation, pregnancy, postpartum, postmenopause).[11] Furthermore, among patients with inactive IBD at the time of cancer diagnosis, hormonal therapy, alone or in combination with cytotoxic chemotherapy, increased the risk of IBD reactivation.[12] We hypothesize that sex hormones may be implicated in IBD pathogenesis. The aim of the present study was to comprehensively assess sex differences in both CD and UC incidence according to age of diagnosis using robust population-based data.

Methods

Identification of Population-Based Studies

We reviewed a recently published comprehensive systematic review and meta-analysis describing the incidence and prevalence of IBD globally in which 260 population-based cohorts reporting incidence and prevalence rates of UC and CD were identified between 1950 and 2010.[13] An updated systematic review from 2010 to 2016 identified an additional 41 population-based studies on the incidence of UC or CD from 2010 to 2016.[14] From these 2 comprehensive studies, we identified unique population-based cohorts with incidence data reported. We additionally performed an updated search through December 2017 using this same methodology and identified 1 new population-based study that included IBD incidence data.[15] We decided a priori to include only established population-based cohorts from developed

*Authors share co-first authorship; § Authors share co-senior authorship.

Abbreviations used in this paper: **CI, confidence interval; CD, Crohn's disease; ER, estrogen receptor; F:M, female-to-male ratio; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; IRR, incidence rate ratio; OCP, oral contraceptive pill; UC, ulcerative colitis.**

Most current article

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countries/provinces in the West (ie, Europe, North America, Australia, and New Zealand). This was done to maximize diagnostic accuracy and minimize heterogeneity. Because IBD is an emerging disease in the East and some developing countries, the accuracy of IBD incidence data with respect to the total population has not been established. Also, apparent sex-based differences in disease incidence may or may not be biological in origin (eg, sex-based differences in health care use and access).[16–19] Including established population-based cohorts from developed countries/provinces in the West further minimized heterogeneity because epidemiologic data suggest that some key established risk factors for IBD in the West have a different risk profile than in Eastern cohorts.[18] Additional inclusion criteria were population-based study; clear description of geographic area encompassed; clear description of criteria for confirmation of IBD diagnosis and, where appropriate, a published validation study detailing diagnostic accuracy; and access to raw incidence data stratified by sex across the full age spectrum, starting from birth and divided into 5-year age intervals. Studies in which only prevalence data were reported, raw incidence data were not available, incidence data were limited to an age-specific population (eg, pediatric only), or data stratified by age interval and sex were not available were also excluded. There was no a priori exclusion based on language. Authors and guarantors were contacted if their incidence data were published in a format that did not strictly follow the inclusion criteria detailed—for example, congregate CD and/or UC incidence not stratified according to age interval—and were requested to provide data in a format appropriate to the present study. Background population data were also requested.

Because the sex ratio of IBD onset may have varied with time, we also analyzed sex differences among the combined cohorts stratified by year of diagnosis (before 2000 vs after 2000).

Study Design and Analysis

Incidence rate ratios (IRR) across the full age spectrum according to sex (female [F]:male [M])) were determined. We pooled IRRs of CD and UC across cohorts to examine the overall differences according to sex by random effects meta-analysis according to the method of DerSimonian and Laird.[20] For analyses of incidence rate according to sex and age, there were a modest number of zero cases across categories (<10%), which significantly increased bias and reduced the coverage of the traditional inverse variance method of meta-analysis. Therefore, all analyses were performed using mixed-effects Poisson regression to estimate the IRR of F:M and 95% confidence interval (CI). This method has previously been shown to be flexible and offer substantial improvement compared with the traditional inverse variance method.[21] Hierarchical (multilevel fixed effect) models for each age category were fit to predict the number of UC or CD cases as a function of sex (fixed effect) while incorporating random intercepts representing the contribution of time period and region (random effect). In our sensitivity analyses, we also pooled incidence rates using zero-inflated negative binomial regression and obtained similar results. Additionally, IRRs were compared temporally (based on the distribution of data and defined as incidence data reported before 2000 vs after 2000). For cohorts that spanned the calendar year 2000, authors were requested to supply incidence data for each category; for example, data from Iceland (1995–2009) were provided as January 1995–December 1999 and January 2000–December 2009. Statistical significance for 2-tailed hypothesis was set at $P \leq .05$. Because each population is considered distinct with no significant overlap—that is, each age group is independent—we did not account for multiple testing. All analyses were carried out using STATA 11.2 (StataCorp, College Station, TX).

Results

Cohort Characteristics

After application of inclusion and exclusion criteria, we identified 21 possible population-based inception cohorts.[15,22–43] Unpublished data were available from 5 of the included cohorts and were provided by the respective authors and guarantors.[26,32,35,37,43–45] After exclusion of cohorts for which the authors and guarantors did not respond (n = 1)[22] and for which raw incidence data for the full age spectrum were not available (n = 3),[23–25] 17 distinct cohorts from 16 separate countries/provinces met final inclusion criteria (Figure 1). Characteristics of these cohorts according to country/province are detailed in Table 1 and Supplementary Figure 1*A* and *B*. Cohorts originated from Northern Europe, Southern/Central Europe, Eastern Europe, Australia, New Zealand, and North America. Where relevant, we have also cited the corresponding validation studies for the diagnostic accuracy of CD and UC diagnoses in the cohorts in Table 1; each of these validation studies confirmed the diagnoses with very high sensitivity and specificity. Diagnoses of CD and UC in the remaining cohorts were according to standard diagnostic criteria via review of patient files by the investigators in the original studies.

Among more than 478 million people (236,181,614 males and 242,373,419 females), there were 95,605 incident cases of CD (42,831 males and 52,774 females) and 112,004 incident cases of UC (61,672 males and 50,332 females) (Table 1). Pooled incidence rates for each country according to sex ratio (F:M) for CD and UC are available in Supplementary Figure 1*A* and *B*, respectively. We did not observe heterogeneity in the pooled analyses of sex ratio of CD and UC incidence according to age ($P_{heterogeneity} > .28$ for all age groups).

Incidence Rates of CD According to Age and Sex

Beginning in early childhood in the age group 5–9 years, there was a trend toward lower incidence of CD in females compared with males (IRR, 0.80; 95% CI, 0.63–1.03; $P = .08$), which was statistically significant in adolescence (age group 10–14 years), with females having a 30% lower risk of CD compared with males (IRR, 0.70; 95% CI, 0.53–0.93). As seen in Figure 2, the rate of incident cases of CD then increased in females compared with males between ages 15 and 24 years. Except in the age group 30–34 years, there was a reversal in the sex ratio after age 25 years such that females remained at significantly higher risk of CD compared with males, with between 16% and 47% higher risk (Figure 2 and Table 2).

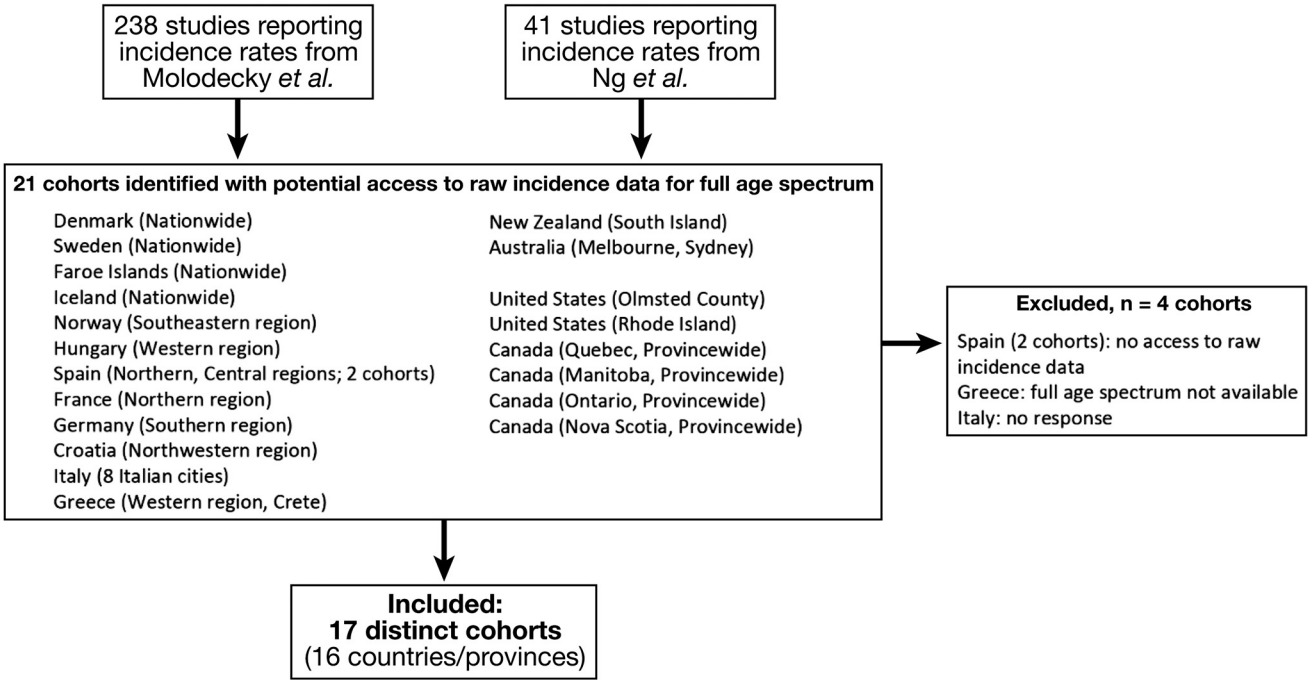

Figure 1. Flow diagram of study inclusion.

Incidence Rates of UC According to Age and Sex

In contrast to CD, the incidence rates of UC were similar for females and males until middle age (age group 40–44 years) with the exception of early childhood (age group 5–9 years), when females had a 22% higher risk of being diagnosed with UC vs males (IRR, 1.22; 95% CI, 1.05–1.41). As seen in Figure 3, after age 45 years, females had anywhere from 13% to 32% lower likelihood of being diagnosed with UC compared with males, a pattern that persisted until age 70–74 years (Figure 3 and Table 3).

Table 1. Cohort Characteristics

Country/Province	Area Included	Years Included	Validation Study Reference (if applicable[a])
Northern Europe			
Denmark[32]	Nationwide	1980–2013	46
Faroe Islands[26]	Nationwide	1960–2014	n/a
Iceland[27]	Nationwide	1995–2009	n/a
Norway[40–42]	Southeastern Norway	1990–1993	n/a
Sweden[43,44,47]	Nationwide	2003–2014	48
Southern/Central Europe			
Germany[28]	Southern region	2004–2008	n/a
France[29]	Northern region	1988–2013	n/a
Croatia[30]	Northern, Western regions	2000–2004	n/a
Eastern Europe			
Hungary[31]	Veszprem province	2011	n/a
Australia[49]	Geelong region	2010 and 2012	n/a
New Zealand[34]	South Island	2014	n/a
North America			n/a
United States[39]	Minnesota (Olmsted County)	1970–2011	n/a
United States[15]	Rhode Island	2008–2010	n/a
Canada[35]	Manitoba	1988–2014	35
Canada[36]	Ontario	1999–2008	50
Canada[37]	Nova Scotia	1996–2009	51
Canada[38]	Quebec	2001–2008	51

NOTE. n/a, not applicable.
[a]If not applicable, diagnoses of CD and UC were confirmed via manual review of patient files according to standard diagnostic criteria by the original investigators.

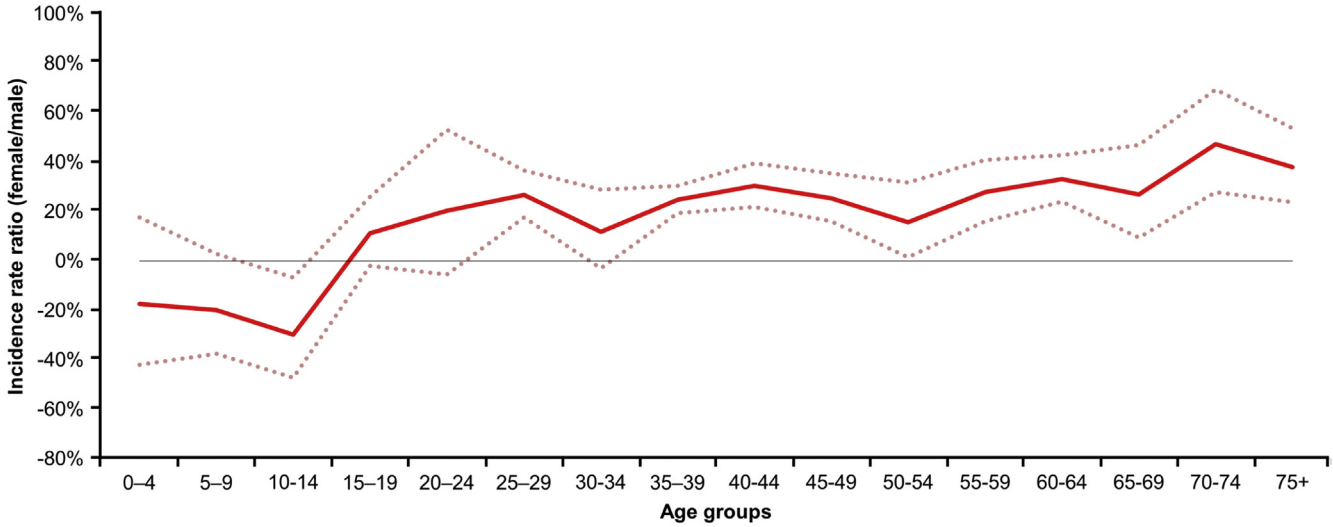

Figure 2. Trend of CD incidence according to sex ratio (F:M) for the full age spectrum.

Temporal Stratification of Incident Rates of CD and UC According to Age and Sex: Before 2000 vs After 2000

Nine cohorts included data from before the year 2000 and 15 cohorts, after 2000 (Table 1). We did not observe a distinct temporal pattern in CD before vs after 2000. Among cohorts with CD incidence data reported before 2000, the incidence of CD was comparable between females and males until age 25 years. After 25 years of age, the ratio of F:M incidence fluctuated between a strong female predominance—which ranged from 31% to 40% higher risk of CD vs males in age groups 25–29, 35–39, 40–49, 55–59, and 65–69 years—and no difference in disease incidence according to sex (age groups 30–34, 40–54, 60–64, and 70+ years) (Table 4 and Supplementary Figure 2). Among cohorts with CD incidence data reported after 2000, the sex ratio showed male predominance at the age interval 10–14 years (IRR, 0.72; 95% CI, 0.52–0.99), followed by female predominance in disease incidence between ages 20 and 29 years and after 40 years, ranging anywhere from 19% to 62% higher incidence compared with males (Table 4 and Supplementary Figure 2).

Table 2. Pooled IRRs According to Sex Ratio (F:M) for Crohn's Disease

		95% CI		
Age, *y*	IRR	Lower Bound	Upper Bound	*P* Value
0–4	0.83	0.58	1.18	.29
5–9	0.80	0.63	1.03	.08
10–14	0.70	0.53	0.93	.02
15–19	1.11	0.98	1.26	.10
20–24	1.20	0.95	1.53	.13
25–29	1.27	1.18	1.36	<.0001
30–34	1.12	0.97	1.29	.12
35–39	1.25	1.19	1.30	<.0001
40–44	1.30	1.22	1.40	<.0001
45–49	1.25	1.16	1.35	<.0001
50–54	1.16	1.02	1.32	.03
55–59	1.28	1.16	1.41	<.0001
60–64	1.33	1.24	1.43	<.0001
65–69	1.27	1.10	1.47	.002
70–74	1.47	1.28	1.69	<.0001
75+	1.38	1.24	1.54	<.0001

Among cohorts with UC incidence data reported before 2000, the incidence of UC in females vs males was similar from ages 0–64 years, with the exception of age interval 25–29 years (IRR, 1.17; 95% CI, 1.03–1.34). Starting at age 65 years, there was a marked male predominance, with UC incidence 33%–37% higher compared with females during this time (Supplementary Figure 3). Among cohorts with UC incidence data reported after 2000, a statistically significant female predominance in disease incidence was observed in ages 5–9 years (IRR 1.19; 95% CI, 1.01–1.39) and 25–29 years (IRR, 1.08; 95% CI, 1.03–1.12); otherwise, disease incidence was comparable between females and males until the ages of 45–70 years, during which there was a statistically significant male predominance in disease incidence ranging from 11% to 21% higher risk, except for age 50–54 years, when there was only a trend toward male predominance (IRR, 0.83; 95% CI, 0.69–1.01, $P = .06$). After 70 years of age, the sex ratio of UC incidence was similar. Compared to the pre-2000 trend, the shift to male predominance in UC incidence after 2000 occurred at an earlier age interval and was slightly attenuated in magnitude compared with the pre-2000 pattern (Supplementary Figure 3 and Supplementary Table 1).

Discussion

This is the first comprehensive analysis of established population-based cohorts that describes IBD incidence according to sex across the full age spectrum and with confirmed diagnostic accuracy. In this internationally collaborative study of more than 207,000 incident cases of IBD in more than 478 million people spanning more than

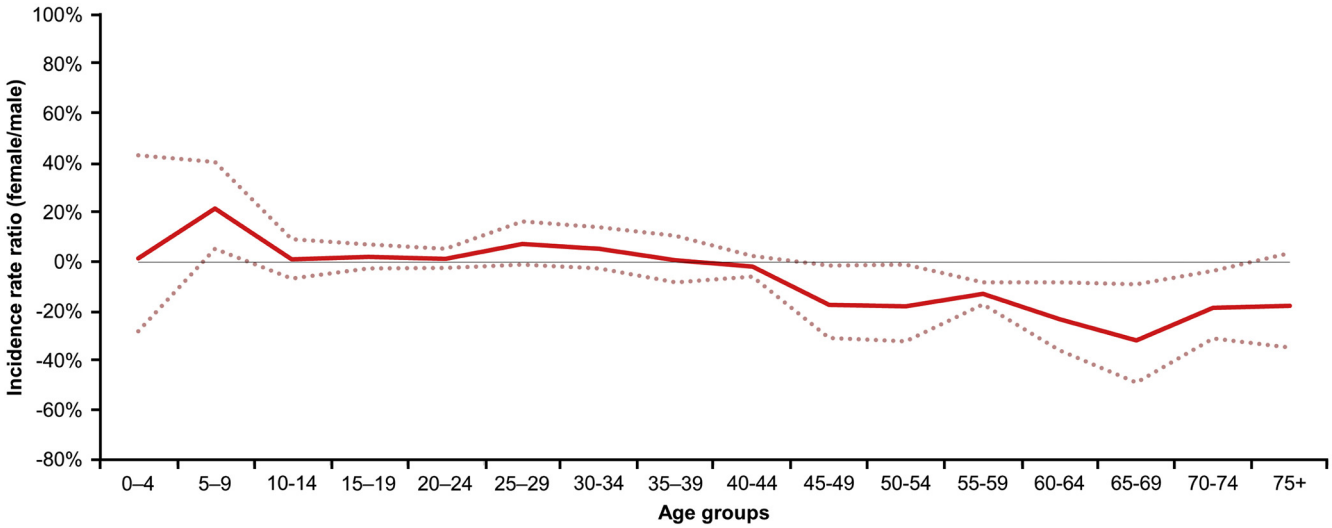

Figure 3. Trend of UC incidence according to sex ratio (F:M) for the full age spectrum.

5 decades, we found several notable trends, particularly when comparing CD and UC. Specifically, we found that the sex ratio of CD incidence shifted from male predominance in mid–late childhood and early adolescence (ages 5–14 years) to a rising incidence in females thereafter, with full reversal of the sex ratio to female predominance after age 25 until 75+ years; this trend was with the exception of age 30–34 years (when F:M incidence was comparable), which might relate to the latter part of the childbearing period in females. In contrast, UC incidence was comparable between sexes until middle age, except for age 5 to 9 years, when a female predominance was observed. After age 45 years, there was a male predominance in disease incidence. That the shift in sex ratio toward male predominance occurred at an earlier age interval for UC when data were stratified by before and after 2000 suggests temporal variation as well; there was no clear temporal pattern identified for CD. The present study galvanizes robust population-based data and extends the current literature of IBD epidemiology by showing sex differences in disease onset according to age. Collectively, these findings suggest that sex hormones may be implicated in the pathogenesis of IBD.

Table 3. Pooled IRRs According to Sex Ratio (F:M) for UC

		95% CI		
Age, *y*	IRR	Lower Bound	Upper Bound	*P* Value
0–4	1.02	0.72	1.43	.93
5–9	1.22	1.05	1.41	.008
10–14	1.01	0.93	1.09	.80
15–19	1.02	0.97	1.07	.37
20–24	1.01	0.98	1.05	.48
25–29	1.07	0.99	1.16	.09
30–34	1.05	0.98	1.14	.18
35–39	1.008	0.92	1.11	.87
40–44	0.98	0.94	1.02	.41
45–49	0.83	0.69	0.99	.03
50–54	0.82	0.68	0.99	.04
55–59	0.87	0.83	0.92	<.0001
60–64	0.77	0.64	0.92	.004
65–69	0.68	0.51	0.91	.01
70–74	0.82	0.69	0.96	.02
75+	0.82	0.66	1.04	.10

The complex interactions of 4 common denominators underlie both CD and UC pathogenesis: environmental exposures, an underlying genetic predisposition, immune dysregulation and likely intestinal dysbiosis. Our findings suggest a potential leading role of intrinsic (and perhaps extrinsic) sex hormones in disease pathogenesis for both CD and UC; although there is certainly crossover between the exact underlying pathogenic mechanisms, there are likely also idiosyncrasies given the different F:M patterns we observed between CD and UC across the age spectrum. In contrast to CD, where the most striking shifts in F:M incidence occurred around the age of puberty (with subtle changes around peak childbearing age and perhaps menopause in females), we observed changes in UC incidence only around the age corresponding to menopause in females. Although we acknowledge these patterns may be due to variations in distributions of other known and unknown environmental and genetic factors, the effect of sex hormones after puberty, during childbearing years, and in the postmenopausal years may partly account for these observations; these are biologically defined periods with dynamic shifts in sex hormones, for example, estrogen, estrogen-to-progesterone ratio, and luteinizing hormone.[9,52,53] The data describing the use of oral contraceptive pills (OCPs)—which raise serum estrogen levels and alter the estrogen-to-progesterone ratio—and the risk of IBD in genetically susceptible individuals provide some evidence for the link between sex hormones and IBD pathogenesis. In a meta-analysis of more than 75,000 women from 14 studies, there was a 46% higher adjusted risk of CD ($P < .001$) and 28% higher adjusted risk for UC ($P = .01$).[52] In a comprehensive analysis of more than 115,000 women enrolled in

Table 4. Temporal Variation in Pooled IRRs According to Sex Ratio (F:M) for Crohn's Disease: Before 2000 and After 2000

Age, y	Before 2000				After 2000			
		95% CI		P		95% CI		P
	IRR	Lower	Upper	Value	IRR	Lower	Upper	Value
0–4	0.83	0.38	1.82	.63	0.83	0.56	1.23	.34
5–9	1.00	0.66	1.52	.99	0.79	0.62	1.03	.08
10–14	0.90	0.61	1.32	.58	0.72	0.52	0.99	.045
15–19	1.23	0.95	1.59	.12	1.11	0.99	1.24	.06
20–24	1.12	0.75	1.68	.59	1.26	1.21	1.31	<.001
25–29	1.35	1.16	1.57	<.001	1.25	1.20	1.31	<.001
30–34	1.05	0.71	1.54	.82	1.04	1.00	1.09	.06
35–39	1.33	1.18	1.50	<.001	1.15	0.85	1.55	.38
40–44	1.30	1.07	1.57	.008	1.29	1.22	1.36	<.001
45–49	1.21	1.03	1.43	.03	1.25	1.12	1.40	<.001
50–54	1.22	0.86	1.72	.27	1.19	1.12	1.26	<.001
55–59	1.40	1.17	1.67	<.001	1.25	1.13	1.40	<.001
60–64	1.47	0.86	2.53	.16	1.32	1.23	1.42	<.001
65–69	1.31	1.07	1.59	.008	1.27	1.07	1.50	.006
70–74	1.14	0.93	1.40	.21	1.62	1.47	1.80	<.001
75+	1.06	0.82	1.36	.66	1.49	1.32	1.68	<.001

the Nurses' Health Study II Cohorts since 1989, there was a more than 2-fold higher risk of CD in OCP users compared with nonusers after adjusting for age at menarche, body mass index, smoking, parity, and endometriosis (a common indication for OCPs); by contrast, the increased risk of UC in OCP users was only among smokers or prior smokers, but there was no increased risk of UC among OCP users who never smoked.[9] Another analysis from the Nurses' Health Study reported that menopausal hormone replacement therapy was associated with an increased risk of UC but not CD in older women and further supports the possible differential effect of sex hormones on CD and UC incidence.[9,54] Underlying genetic predisposition may also have sex biases. Several genetic susceptibility loci for both CD and UC have been identified on chromosome X, particularly haplotypes of toll-like receptor 8, and support the prevailing hypothesis that the gene–environment interaction is key in forming the platform and baseline proclivity for IBD development according to sex and age. Notably, toll-like receptor 8 on chromosome X has also been implicated in other immune-mediated disorders that show sex variation, such as systemic lupus erythematosus.[55,56] Indeed, distinct hormone-induced epigenetic modifications that affect immune regulation and vary according to age may further underlie the sex differences in disease incidence between CD and UC observed in our study across the age spectrum.[57,58] Although the nature of the current literature implicates female sex hormones more so than male sex hormones, the potential biological role of perturbation in male sex hormones in IBD pathogenesis and natural course of disease should not be discounted; unfortunately, supporting literature is sparse. Although the present study was not designed to define etiologies and the pathobiology for the observed trends in sex ratio across the age spectrum, understanding these epidemiologic patterns may generate novel mechanistic insights with clinical application.

As human data supporting the influence of sex hormones on the natural course of IBD accumulate, investigations in animal models continue to be fundamental in elucidating the underlying molecular mechanisms. Substantial experimental data implicate estrogen in IBD pathogenesis. Posited mechanisms include increased intestinal permeability via dysregulation of the estrogen-receptor subtype β (ER-β), the loss of estrogen-mediated immunoprotection, and hormone-mediated gut microbial dysbiosis.[59–64] ER-β plays a critical role in colonic mucosal immune homeostasis by maintaining the integrity of tight junctions and barrier function in the colon.[62,65] Although there is ample expression of ER-β in healthy colonic tissue, expression is markedly decreased in active UC and CD.[66] Furthermore, very recent data suggest sex-specific differences in ER-β–mediated protection according to experimental IBD phenotype—UC or CD—in males and females,[63,67,68] which is particularly relevant to our findings. Specifically, ER-β signaling protects against experimental UC in female but not male mice, whereas ER-β signaling protects against experimental CD in male but not female mice.[63,67,68] There are also clear hormonal effects on the intestinal microbiota itself, with intestinal dysbiosis an established factor in IBD pathogenesis and other immune-mediated and autoimmune disorders.[69–71] That the gut microbiota itself also influences sex hormones as well as innate and adaptive immunity further complicates our understanding.[69,71–74]

Although we did not observe a distinct temporal pattern in CD before vs after 2000, the changes in the incidence of UC according to sex and age observed over time deserve future attention. Among plausible explanations for this observation includes the increase in maternal age witnessed over the past 20 years, which, in turn, is associated with age-related changes in immune function and altered maternal microbiome with age. Also contributory may be the changes in the rate of menopausal HRT use before and after 2000 because of the landmark findings of the Women's Health Initiative around 2002 that menopausal HRT is associated with significantly increased risk of cardiovascular and thrombotic events, such as stroke.[75–77]

We acknowledge a few limitations. First, our data may not fully represent worldwide trends because the observations reported here represent analyses from established, population-based cohorts from developed economies in Western populations. Indeed, most population-based and nationwide IBD cohorts come from North American or European countries, and the number of high-quality, long-term epidemiologic cohorts from Asia, the Middle East, South America, and Africa is still limited. Our study nevertheless represents the largest and most comprehensive analysis to date that attempts to understand sex variations in disease incidence according to age, and given the large power of our study, we were able to detect even small differences. That said, generalizing our overall findings to the whole IBD population, especially in countries where IBD is an emerging disease, should be done with caution,

particularly because some established risk factors for IBD in Western countries have not shown the same risk profile in Eastern countries. For example, smoking and OCP use, both risk factors for CD when investigated in Western populations, were not associated with increased risk of CD in Eastern populations.[18] A second limitation is that we were not able to control for possible misclassification in patient registries, nor for possible cultural and geographic differences in health use across countries; although we would expect that such influences would bias our estimates toward the null (nondifferential misclassification). Nevertheless, although we acknowledge the potential for some intrinsic systematic errors, by including only nationwide or population-based inception cohorts with access to the full age spectrum, we ensured that the included studies were at least representative of their respective study area and time period and thus represent the most valid data currently available. Moreover, we maximized diagnostic accuracy by including only validated population-based cohorts or those in which the diagnoses of CD or UC were confirmed by the investigators of the original studies according to diagnostic criteria. Because there are many local ethical restrictions that limited our ability to obtain individual-level data for purposes of a pooled analysis, we were unable to explore sex-based differences for different phenotypic manifestations. Along these lines, we could not account for differences in environmental exposures (eg, smoking) across countries and provinces or between sex and age groups. Delineating the impact of certain environmental exposures is further complicated in that the risk of such exposures is often differential according to duration of exposure, amount or intensity of the exposure, and timing of the exposure (eg, antibiotic exposure in the first years of life), among other factors, and is particularly problematic when one is specifically interested in disease incidence. It is also difficult if not impossible to isolate the distinct contribution of an individual exposure, because people are confronted with a mixture of exposures over their lifetime. Some environmental exposures have been shown to both influence IBD risk[78] and also differ according to country of origin and age group. Smoking[79] and antibiotic exposure[80] are 2 examples. Further complicating this, smoking also affects some endogenous sex hormones, although the exact mechanisms and patterns are not fully defined.[81,82] Indeed, the effect of smoking on IBD incidence according to sex is likely complex. We look forward not only to future studies validating our findings in other geographic cohorts (particularly those where IBD is an emerging disease), but also to focused investigations specifically designed to rigorously address the impact of environmental exposures on IBD risk stratified by sex across different age groups.

In conclusion, we have shown for the first time significant variations in sex according to age of IBD onset that are particularly distinct for CD compared with UC and support the hypothesis that sex hormones may be involved in IBD pathogenesis. Although our study is not designed nor is it intended to define underlying etiologies for these differences, we have provided supporting mechanisms that are biologically plausible. We hope our findings will inspire future research efforts investigating the role of sex hormones in IBD pathogenesis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.06.043.

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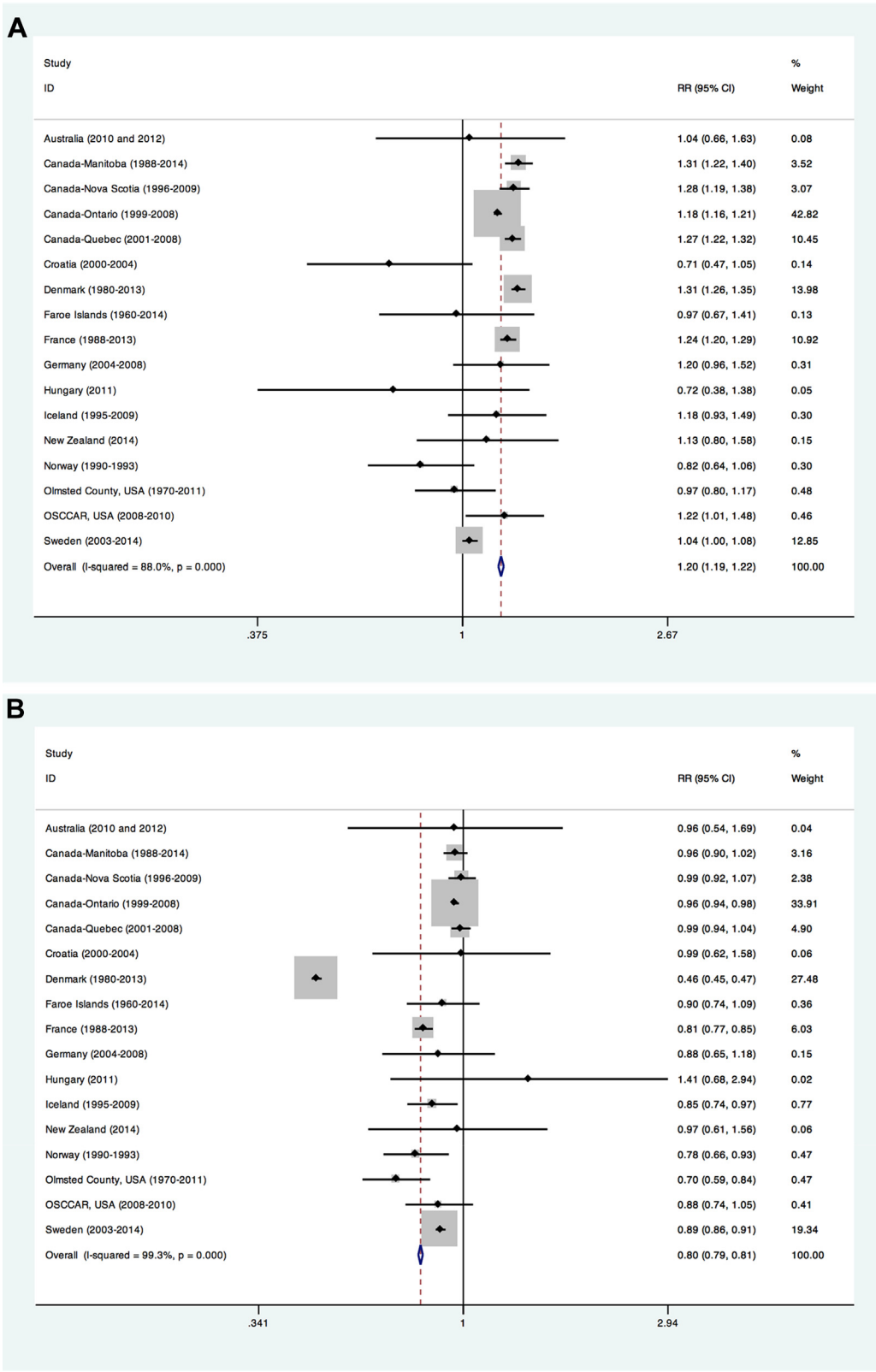
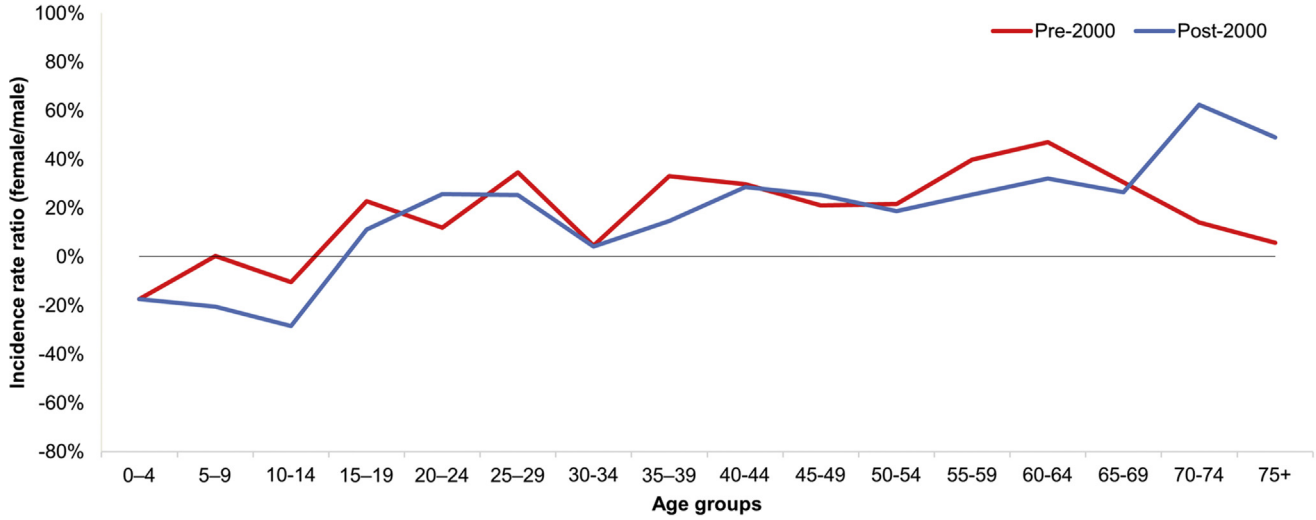
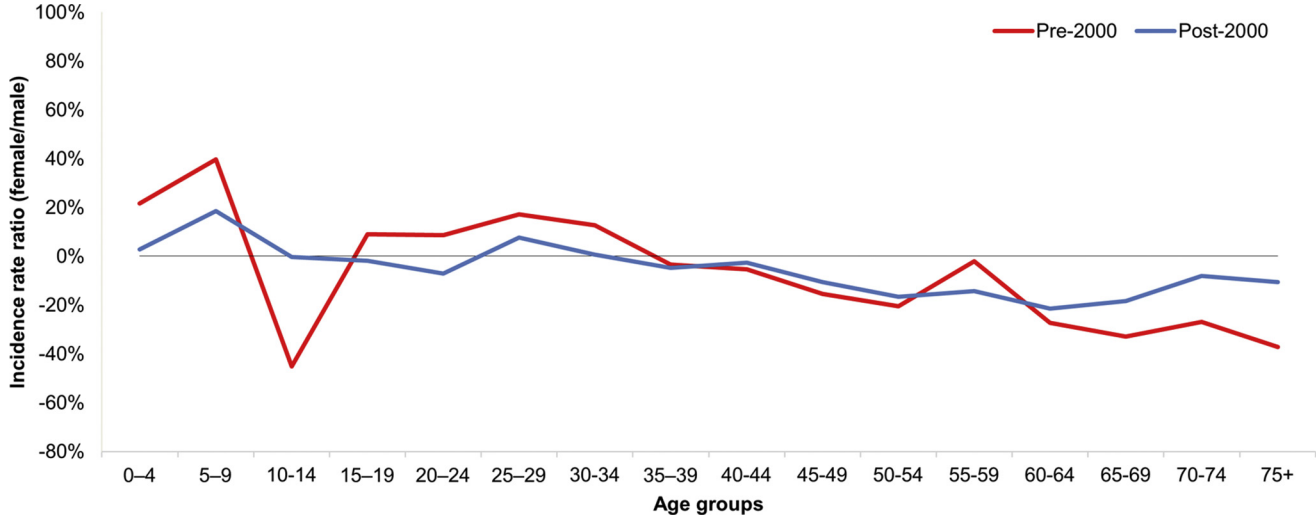
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. (*A*) Pooled IRRs of CD according to sex for each cohort (F:M). (*B*) Pooled IRRs of UC according to sex for each cohort (F:M). ID, identification; OSCCAR, Ocean State Crohn's and Colitis Area Registry; RR, relative risk.



Supplementary Figure 2. Temporal trends in incidence of CD according to sex ratio (F:M) for the full age spectrum: before and after 2000.



Supplementary Figure 3. Temporal trends in incidence of UC according to sex ratio (F:M) for the full age spectrum: pre- and post-2000.

Supplementary Table 1. Temporal Variation in Pooled IRRs According to Sex Ratio (F:M) for UC: Before 2000 and After 2000

	Before 2000				After 2000			
		95% CI				95% CI		
Age, *y*	IRR	Lower	Upper	*P* Value	IRR	Lower	Upper	*P* Value
0–4	1.22	0.66	2.25	.53	1.03	0.68	1.56	.89
5–9	1.40	0.97	2.01	.07	1.19	1.01	1.39	.04
10–14	0.55	0.25	1.21	.14	1.00	0.92	1.09	.95
15–19	1.09	0.87	1.37	.45	0.98	0.93	1.04	.50
20–24	1.09	0.87	1.36	.47	0.93	0.81	1.07	.32
25–29	1.17	1.03	1.34	.02	1.08	1.03	1.12	<.001
30–34	1.13	0.98	1.29	.09	1.01	0.97	1.04	.76
35–39	0.97	0.78	1.20	.75	0.95	0.83	1.09	.48
40–44	0.95	0.86	1.04	.25	0.97	0.87	1.09	.64
45–49	0.85	0.63	1.14	.28	0.89	0.85	0.94	<.001
50–54	0.80	0.56	1.13	.21	0.83	0.69	1.01	.06
55–59	0.98	0.65	1.47	.92	0.86	0.81	0.91	<.001
60–64	0.73	0.50	1.05	.09	0.79	0.74	0.83	<.001
65–69	0.67	0.47	0.97	.03	0.82	0.76	0.87	<.001
70–74	0.73	0.64	0.83	<.001	0.92	0.81	1.05	.20
75+	0.63	0.43	0.92	.02	0.90	0.73	1.09	.28