

Letter to the Editor

Postmenopausal hormone therapy and asthma-related hospital admission*To the Editor:*

There is considerable evidence that female sex hormones are involved in the asthma pathogenesis. Asthma is most prevalent in boys during childhood but after puberty it is more common in females. Also, changes in bronchial responsiveness and asthma symptoms have been demonstrated in relation to the menstrual cycle.¹ These findings suggest that treatment with exogenous sex hormones, such as postmenopausal hormone replacement therapy (HRT), may affect the risk for asthma morbidity, and this is supported by several observational studies showing increased asthma prevalence and incidence in women using HRT.²⁻⁶ Still, HRT is not considered an established risk factor for asthma in clinical guidelines.⁷

Hospital admission for asthma, due to acute exacerbations or difficult to control disease, represents severe disease with major impact on quality of life of the individual and health care expenditures. However, the association between HRT use and risk of hospital admission for asthma has not yet been studied.

Here, we studied prospectively the association between HRT use and risk of first-ever hospital admission for asthma in postmenopausal women. The use of HRT and potential confounders, including smoking status, occupational exposure, educational level, body mass index, and hysterectomy, were assessed in the period 1993-1997 in women recruited from the Danish Diet, Cancer and Health cohort. Participants were asked during the study clinic visit about their use of HRT (never used HRT, previous user of HRT, current user of HRT), the age at which they began using HRT, the duration of HRT use, and the brand of HRT product currently used. Data on incident asthma admission were obtained prospectively from the Danish National Patient Register until 2010. Admissions included hospitalization (inpatient), emergency department visits, and outpatient admission, and the combined measure was used as the main outcome. Potential association with HRT was analyzed with Cox's regression analyses. We included analyses of hospital admissions for chronic obstructive pulmonary disease (COPD) to account for the overlap and potential misclassification of asthma and COPD in the elderly, and studied potential effect modification by comorbidities including heart disease, stroke, and diabetes (see this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org for further details).

The final cohort for analyses comprised 22,958 postmenopausal women (see [Fig E1](#) in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org). Baseline characteristics for the entire study population and stratified on groups according to the use of HRT are given in [Table E1](#) in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org. A total of 11,487 (50.0%) women ever used HRT ([Table E1](#)). We observed 476 (2.1%) incident asthma hospital admissions and 1,161 (5.1%) incident COPD admissions over 13.2 years of mean follow-up.

Ever using HRT was associated with increased risk of hospital admission for asthma, with hazard ratio (HR) and 95% CI of 1.46 (1.21-1.76) in the fully adjusted model ([Table I](#)); additional adjustment for menopausal status or oophorectomy did not substantially change our observations (data not shown). No significant risk of asthma admission was observed for triers of HRT as compared with never users, whereas the association was statistically

significant among previous and current users. The risk of asthma admission was highest with the longest duration of HRT use (≥ 10 years, 1.74 [1.34-2.25]; 3-10 years, 1.46 [1.14-1.85]; < 3 years, 1.28 [0.99-1.65]), corresponding to 19% (11% to 28%) increase in the risk of hospital admission for asthma for each 5-year use of HRT. The different types of hospital admission (inpatient hospitalization, emergency department visit, and outpatient admission) showed similar association with the use of HRT, including a trend of higher risk with the longest duration of HRT use (see [Table E2](#) in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org).

The risk was significantly increased for all types of HRT regimens. We could not confirm previous reports that the association between asthma and HRT was modified by body mass index,^{3,4} smoking status,^{3,5,6} and type of HRT⁶ (see [Table E3](#) in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org).

Ever using HRT was also associated with hospital admission for COPD, but with an HR approximately half of that for asthma (1.19 [1.06-1.34]). A stronger association was observed with longer duration of HRT use ([Table II](#)).

Prospective registration of hospital admission for asthma was obtained from the nationwide hospital discharge register, which was recently shown to have a high specificity (0.98) for asthma diagnoses.⁸ Asthma requiring hospital admission is mainly at the severe end of the disease spectrum and is traditionally confirmed by objective measures of lung function and reversible airflow obstruction in Danish hospitals. It might therefore be less subject to misclassification and bias than an asthma diagnosis based on self-reported symptoms or a primary care diagnosis.

It is a limitation of this study that we did not have data on self-reported asthma at baseline. We were therefore not able to analyze to which extent the observed association with hospital admission reflects increased asthma incidence (onset of symptoms after HRT use), progression of existing disease, or both. It is another limitation that our study did not include lung function measurements or allergy assessment.

These observations do not prove a causal relationship between HRT and asthma admission. It is possible that the observed association is related to underlying asthma susceptibility in women treated with HRT rather than the treatment itself. Supporting evidence for a causal role is the relatively large effect size, the minor change in effect estimate after adjustment for potential confounders, and the "dose-response-relationship" in terms of increasing HR with increasing duration of therapy. Furthermore, a causal role of HRT in the pathogenesis of asthma exacerbations is biologically plausible and in keeping with considerable epidemiological and experimental evidence of a role of sex hormones in asthma pathology.¹ Our results are in agreement with several previous studies on milder asthma observed in both cross-sectional³⁻⁵ and longitudinal studies.^{2,6}

We also observed an association between HRT and hospital admission for COPD but with smaller effect estimates than seen for asthma. This strongly suggests that the association between HRT and asthma was not driven by misclassification from COPD, further supported by the finding that the asthma-HRT association was strongest in never smokers. One previous longitudinal study found no association between HRT and the incidence of COPD.² In recent years, it has been increasingly recognized that asthma and COPD coexist in a substantial proportion of patients.

TABLE I. Association between HRT and incidence of asthma admission ($n = 476/IR = 1.6$) among 22,958 women in the Diet, Cancer and Health cohort, by duration and type of treatment

Health benefit, by duration and type of treatment					
HRT variable	n _{asthma}	IR	HR (95% CI)		
			Crude	Adjusted for smoking*	Fully adjusted†
HRT use					
Never	189	1.2	1.00	1.00	1.00
Ever	287	1.9	1.52 (1.26-1.82)	1.50 (1.25-1.80)	1.46 (1.21-1.76)
HRT status					
Never	189	1.2	1.00	1.00	1.00
Tried (<6 mo) HRT	34	1.4	1.11 (0.77-1.59)	1.09 (0.75-1.56)	1.03 (0.72-1.48)
Previous	47	2.2	1.81 (1.31-2.49)	1.73 (1.25-2.38)	1.66 (1.21-2.29)
Current	206	1.9	1.56 (1.28-1.90)	1.55 (1.27-1.89)	1.53 (1.25-1.87)
HRT duration					
Risk per 5 y of use			1.24 (1.15-1.32)	1.22 (1.13-1.30)	1.19 (1.11-1.28)
Never	189	1.6	1.00	1.00	1.00
<3 y	89	1.6	1.30 (1.01-1.67)	1.30 (1.01-1.68)	1.28 (0.99-1.65)
3-10 y	107	1.8	1.46 (1.15-1.85)	1.45 (1.15-1.85)	1.46 (1.14-1.85)
≥10 y	91	2.4	1.93 (1.51-2.48)	1.83 (1.43-2.36)	1.74 (1.34-2.25)
HRT type‡					
Never	189	1.6	1.00	1.00	1.00
Estrogen	74	2.4	1.75 (1.34-2.28)	1.72 (1.32-2.24)	1.88 (1.43-2.45)
Sequential	73	1.7	1.30 (1.00-1.70)	1.31 (1.00-1.71)	1.40 (1.07-1.84)
Continuous	35	2.0	1.53 (1.07-2.18)	1.48 (1.04-2.11)	1.60 (1.11-2.29)

IR, Incidence rate.

*Smoking status (current/previous/never), duration, intensity, and environmental tobacco smoke.

†Adjusted for smoking* and educational level, occupational exposure, physical activity, obesity, null parity, number of children, and hysterectomy.

‡For 18,464 cohort participants who had information about HRT type, of these 394 with asthma.

TABLE II. Association between HRT and incidence of COPD admission ($n = 1161/IR = 3.9$) among 22,958 women in the Diet, Cancer and Health cohort, by duration and type of treatment

			HR (95% CI)		
HRT variable	n _{COPD}	IR	Crude	Adjusted for smoking*	Fully adjusted†
HRT use					
Never	512	3.4	1.00	1.00	1.00
Ever	649	4.3	1.27 (1.13-1.43)	1.20 (1.07-1.35)	1.19 (1.06-1.34)
HRT status					
Never	512	3.4	1.00	1.00	1.00
Tried HRT	102	4.2	1.23 (0.99-1.52)	1.10 (0.89-1.36)	1.09 (0.88-1.34)
Previous	118	5.8	1.69 (1.39-2.07)	1.38 (1.13-1.69)	1.36 (1.11-1.67)
Current	429	4.1	1.20 (1.05-1.36)	1.18 (1.04-1.34)	1.18 (1.03-1.34)
HRT duration					
Risk per 5 y of use			1.19 (1.14-1.25)	1.09 (1.04-1.14)	1.09 (1.04-1.14)
Never	512	3.4	1.00	1.00	1.00
<3 y	199	3.6	1.07 (0.91-1.26)	1.10 (0.93-1.30)	1.11 (0.93-1.29)
3-10 y	217	3.7	1.09 (0.93-1.28)	1.13 (0.97-1.33)	1.14 (0.97-1.33)
≥10 y	233	6.3	1.85 (1.59-2.16)	1.38 (1.18-1.61)	1.37 (1.17-1.61)
HRT type					
Never‡	512	3.4	1.00	1.00	1.00
Estrogen	122	3.9	1.15 (0.95-1.41)	1.13 (0.93-1.38)	1.06 (0.84-1.34)
Sequential	162	3.9	1.14 (0.95-1.36)	1.16 (0.97-1.39)	1.16 (0.97-1.39)
Continuous	81	4.8	1.42 (1.12-1.79)	1.28 (1.01-1.62)	1.29 (1.02-1.63)

IR, Incidence rate per 1000.

*Smoking status (current/previous/never), duration, intensity, and environmental tobacco smoke.

†Adjusted for smoking* and educational level, occupational exposure, physical activity, obesity, null parity, number of children, and hysterectomy.

‡For 18,464 cohort participants who had information about HRT type, of these 925 with COPD.

Furthermore, patients who have both asthma and COPD have been shown to have more frequent respiratory exacerbations and a higher hospital admission rate⁹ and it plausible that the observed association between HRT and COPD is driven by this the so-called asthma-COPD-overlap syndrome.

Our results emphasize the need for further understanding of the role of sex hormones and the associated pathways in asthma

pathology. Our study also stresses the clinical relevance of a potential causal relationship between HRT and asthma by showing that HRT use is associated with severe disease requiring hospital admission. We need randomized trials to clarify the causal relationship between HRT and asthma. However, in light of the present results, it may be relevant to stress this potentially causal relationship to the clinician.

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METHODS

Cohort

Between 1993 and 1997, a total of 160,725 persons (72,729 women), aged 50 to 64 years, born in Denmark, living in Copenhagen or Aarhus (the 2 largest cities in Denmark), and with no record of cancer in the Danish Cancer registry, were invited to participate in the Danish prospective Diet, Cancer and Health study. In total, 57,053 people, of whom 29,875 were women (37% of invited women and 7% of the entire Danish female population in this age group), accepted the invitation and participated in the study and answered a detailed questionnaire on diet, health, education, occupation, lifestyle, and reproductive characteristics. A detailed description of the Danish prospective Diet, Cancer and Health cohort has been published previously.^{E1} Information on the disease end point was obtained by linkage with Danish registries via the unique identification number assigned to all Danish citizens.^{E2} We identified participants who were registered with a discharge diagnosis of asthma (*International Statistical Classification of Diseases, Tenth Revision* [ICD-10], codes DJ45-46) and COPD (ICD-10 codes DJ40-44) in the Danish National Patient Register, which includes all discharge diagnoses from all Danish hospitals since 1977 and from outpatient clinics since 1995.^{E3} Information on vital status, including date of death or immigration, was obtained from the Danish Civil Registration System. We defined the main outcome as the first-ever hospital admission for asthma (inpatient hospitalization, emergency department visit, or outpatient admission) and secondary first-ever hospitalization for COPD between cohort baseline (1993-1997) and December 31, 2009. We excluded women with a hospital admission for asthma or COPD before baseline.

Exposure assessment

Participants were asked during the study clinic visit about their use of HRT at baseline (never used HRT, previous user of HRT, current user of HRT), the age at which they began using HRT, the duration (years) of HRT use, and the brand of HRT product currently used. *Triers* were defined as former HRT users with less than 6 months of use. Based on the self-reported brand of HRT product used, the HRT regimen was coded as either *unopposed estrogen* or *estrogen + progesterone combination*, which was further classified as either continuously or sequentially administered regimens.

Confounders and comorbidity

The lifestyle questionnaire provided information about tobacco smoking (never, previous, current smoker), smoking duration (years), smoking intensity (g/d), *environmental tobacco smoke*, defined as indicator of exposure to second-hand smoke at home or work for minimum 4 h/d, occupational exposures to dust/fumes, education (≤ 7 years, 8-10 years, > 10 years), parity, age at

first birth, history of hysterectomy or oophorectomy, body mass index, and fruit consumption (g/d). Smoking intensity was calculated by equating a cigarette to 1 g, a cheroot or a pipe to 3 g, and a cigar to 5 g of tobacco. Occupational exposures related to asthma indicate minimum 1-year employment in 1 of the following industries: mining, electroplating, textile, shoe/leather manufacturing, metal production, paper manufacturing, china/pottery manufacture, painter, or hairdresser. Similarly, occupational exposures related to COPD indicate minimum 1-year employment in electroplating, rubber, textile, and shoe/leather manufacturing, wood, metal production and painting, printing and paper manufacture, electrical industry, and glass and porcelain/pottery manufacture or as bus or taxi driver, butcher, waiter, or cook. Comorbidity, including ischemic heart disease (ICD-10 codes DI20-25), other heart disease (ICD-10 codes DI42-50), and stroke (ICD-10 codes DI60-63), was defined by a record of hospitalization in the Danish National Patient Register before baseline. Comorbidity with diabetes was defined by a self-report or record in the Danish Diabetes Register.^{E4}

Statistical methods

We applied the Cox proportional hazards model to study the association of incident hospital admissions for asthma or COPD with HRT use with age as the underlying time, and event on date of first-ever asthma or COPD admission or right censoring at date of death, emigration, or December 31, 2009, whichever came first. We adjusted for *a priori* defined confounders in 3 steps: (1) age; (2) also including smoking status, duration, and intensity, and environmental tobacco smoke; and (3) also including educational level, occupational exposure to dust/fumes related to asthma or COPD, obesity, null parity, number of children, age at first birth, and hysterectomy. The potential effect modification of an association between HRT (ever/never) and asthma/COPD admission by smoking status, obesity, hysterectomy, and comorbid conditions was evaluated by introducing interaction terms into the model and tested by using the Wald test. The results are presented as HRs with 95% CIs, estimated with *stcox* procedure in Stata 12.0.

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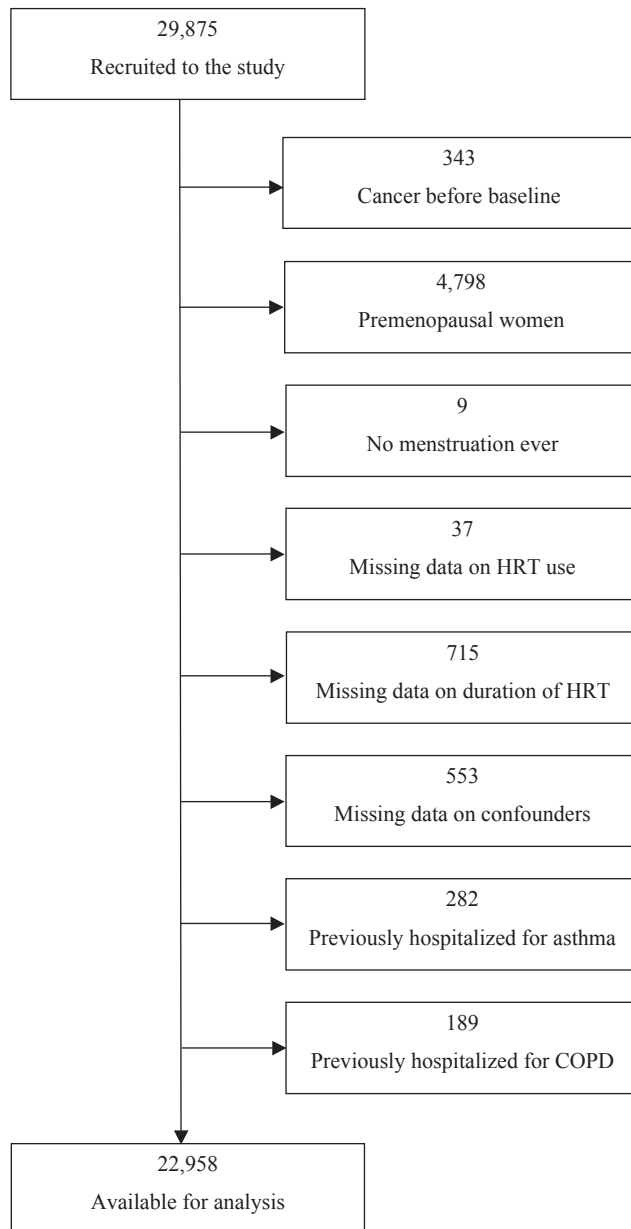
**FIG E1.** Study flow chart.

TABLE E1. Characteristics of 22,958 women in the Diet, Cancer and Health cohort total and by HRT use status

Characteristic	Total (N = 22,958)	HRT use	
		Never used HRT (n = 11,471)	Current or past HRT user (n = 11,487)
Incident asthma admissions	476 (2.1)	189 (1.6)	287 (2.5)
Incident COPD	1,161 (5.1)	512 (4.5)	649 (5.6)
Age at entry (y), mean $\pm$ SD	57.5 $\pm$ 4.2	57.7 $\pm$ 4.2	57.4 $\pm$ 4.2
Never smoker	9,772 (42.5)	5,149 (44.9)	4,623 (40.3)
Previous smoker	5,338 (23.3)	2,545 (22.2)	2,793 (24.3)
Current smoker	7,848 (34.2)	3,777 (32.9)	4,071 (35.4)
Smoking duration* (y), mean $\pm$ SD	28.9 $\pm$ 12.5	28.9 $\pm$ 12.6	28.8 $\pm$ 12.4
Smoking intensity* (g/d), mean $\pm$ SD	8.5 $\pm$ 9.0	8.4 $\pm$ 8.9	8.5 $\pm$ 9.2
Environmental tobacco smoke†	14,999 (65.3)	7,353 (64.1)	7,646 (66.5)
Short education ($\leq$ 7 y)	7,608 (33.1)	4,047 (35.3)	3,561 (31.0)
Medium education (8-10 y)	11,379 (49.5)	5,544 (48.3)	5,835 (50.8)
Long education ($>$ 10 y)	3,971 (17.3)	1,880 (16.4)	2,091 (18.2)
Occupational exposure related to asthma	2,852 (12.4)	1,383 (12.1)	1,469 (12.8)
Occupational exposures related to COPD	4,199 (18.3)	2,111 (18.4)	2,088 (18.2)
BMI, mean $\pm$ SD	25.6 $\pm$ 4.4	25.9 $\pm$ 4.7	25.3 $\pm$ 4.1
Obese (BMI $\geq$ 30)	3,255 (14.2)	1,914 (16.7)	1,341 (11.7)
Null parity	2,098 (9.1)	1,087 (9.5)	1,011 (8.8)
Number of children,‡ mean $\pm$ SD	2.9 $\pm$ 1.3	2.9 $\pm$ 1.3	2.9 $\pm$ 1.4
Age at first birth,‡ mean $\pm$ SD	23.3 $\pm$ 4.3	23.5 $\pm$ 4.3	23.1 $\pm$ 4.3
Hysterectomy	4,021 (17.5)	1,474 (12.8)	2,547 (22.2)
Has ischemic heart disease	1,886 (8.2)	900 (7.8)	986 (8.6)
Has other heart disease	1,145 (5.0)	568 (4.9)	577 (5.0)
Had stroke	1,090 (4.7)	557 (4.9)	533 (4.6)
Has diabetes	1,930 (8.4)	1,038 (9.0)	892 (7.8)
Never used HRT	11,471 (50.0)	11,471 (100)	
Tried ($<$ 6-mo use) HRT	1,869 (8.1)		1,869 (16.3)
Previously used HRT	1,588 (6.9)		1,588 (13.8)
Currently using HRT	8,030 (35.0)		8,030 (69.9)
Used HRT for $<$ 3 y	—	—	4,158 (36.2)
Used HRT for 3-10 y			4,434 (38.6)
Used HRT for $\geq$ 10 y			2,895 (25.2)
Duration of HRT use (y), mean $\pm$ SD	—	—	6.0 $\pm$ 5.9
Currently using estrogen	—	—	2,384 (34.8)
Currently using sequentially administered estrogen/ progesterone	—	—	3,168 (46.2)
Currently using continuously administered estrogen/ progesterone	—	—	1,301 (19.0)
Time since HRT cessation (y), mean $\pm$ SD	—	—	2.7 $\pm$ 4.6

Values are n (%) unless indicated otherwise.

BMI, Body mass index.

*Among 13,186 current and previous smokers.

†More than 4 h/d exposure to passive smoke at home or work.

‡Among 20,860 parous women.

TABLE E2. Association* between HRT and incidence of different subtypes of asthma admissions among 22,958 women in the Diet, Cancer and Health cohort

HRT	All types combined		Hospitalization		Emergency department visit		Outpatient admission	
	N _{asthma}	HR (95% CI)	N _{asthma}	HR (95% CI)	N _{asthma}	HR (95% CI)	N _{asthma}	HR (95% CI)
Total	476		89		96		291	
HRT use								
Never	189	1.00	33	1.00	38	1.00	118	1.00
Ever	287	1.46 (1.21-1.76)	56	1.61 (1.04-2.49)	58	1.35 (0.89-2.06)	173	1.46 (1.15-1.85)
Duration								
Never	189	1.00	33	1.00	38	1.00	118	1.00
<3 y	89	1.28 (0.99-1.65)	18	1.49 (0.84-2.66)	14	1.01 (0.54-1.87)	57	1.32 (0.96-1.82)
3-10 y	107	1.46 (1.14-1.85)	15	1.19 (0.64-2.20)	23	1.55 (0.92-2.62)	69	1.51 (1.12-2.04)
≥10 y	91	1.74 (1.34-2.25)	23	2.37 (1.36-4.11)	21	1.51 (0.87-2.63)	47	1.58 (1.11-2.23)

*Adjusted for smoking status (current/previous/never), duration, intensity, environmental tobacco smoke, educational level, occupational exposure, physical activity, obesity, null parity, number of children, and hysterectomy.

TABLE E3. Modification of association* between HRT (ever vs never users) and asthma/COPD admission by lifestyle factors and comorbid conditions

Effect modifier	N _{asthma}	IR	Asthma (n = 476, IR = 1.6), HR (95% CI)	N _{COPD}	IR	COPD (n = 1161 IR = 3.9), HR (95% CI)
Lifestyle						
Never smoked	176	1.3	1.68 (1.24-2.28)	106	0.8	1.21 (0.82-1.77)
Previously smoked	128	1.8	1.45 (1.01-2.08)	175	2.5	1.24 (0.92-1.67)
Currently smoke	172	1.7	1.27 (0.94-1.72)	880	9.0	1.16 (1.03-1.35)
P value for interaction			.44			.96
Not obese (BMI < 30)	394	1.5	1.49 (1.21-1.83)	995	3.9	1.20 (1.06-1.37)
Obese (BMI ≥ 30)	82	1.9	1.36 (0.88-2.11)	166	3.9	1.16 (0.85-1.58)
P value for interaction			.72			.82
Had hysterectomy	113		1.79 (1.16-2.75)	214	4.1	1.09 (0.81-1.45)
No hysterectomy	363		1.39 (1.13-1.71)	947	3.8	1.21 (1.07-1.38)
P value for interaction			.31			.49
Comorbidities						
No IHD	415	1.5	1.49 (1.22-1.82)	972	3.5	1.22 (1.07-1.38)
Has IHD	61	2.5	1.26 (0.76-2.10)	189	7.9	1.08 (0.81-1.44)
P value for interaction			.55			.45
No other heart disease	430	1.5	1.41 (1.16-1.71)	1033	3.6	1.19 (1.05-1.35)
Has other heart disease	46	3.1	2.10 (1.12-3.94)	128	8.9	1.18 (0.83-1.68)
P value for interaction			.23			.97
Never had stroke	455	1.6	1.42 (1.17-1.71)	1074	3.8	1.21 (1.08-1.36)
Had stroke	21	1.5	3.12 (1.14-8.53)	87	6.6	0.98 (0.64-1.49)
P value for interaction			.13			.34
No diabetes	435	1.6	1.44 (1.19-1.75)	1020	3.7	1.21 (1.07-1.37)
Had diabetes	41	1.6	1.64 (0.88-3.06)	141	5.7	1.13 (0.81-1.57)
P value for interaction			.70			.70

BMI, Body mass index; IHD, ischemic heart disease; IR, incidence rate per 1000.

*Adjusted for smoking status (current/previous/never), duration, intensity, environmental tobacco smoke, educational level, occupational exposure, physical activity, obesity, null parity, number of children, and hysterectomy.