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The Association between Incident Self-reported Fibromyalgia and Non-psychiatric Factors: 25-years Follow-up of the Adventist Health Study

Chan-Jin Choi, MD, PhD[1,2], **Raymond Knutsen, MD, MPH**[1], **Keiji Oda, MSPH**[1], **Gary E Fraser, MD, PhD**[1], and **Synnove Fonnebo Knutsen, MD, PhD**[1]

[1]Dept. of Epidemiology and Biostatistics, School of Public Health, Loma Linda University, Loma Linda, CA 92399, USA

[2]Dept. of Family Medicine, College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, 505 Banpo-dong, Seocho-gu, Seoul, Korea

Abstract

The purpose of the study was to investigate the association between incident self-reported fibromyalgia (FM) and prior somatic diseases, lifestyle factors and health behaviors among 3,136 women who participated in two cohort studies 25–26 years apart (the Adventist Health Study 1 and 2). The women completed a comprehensive lifestyle and medical history questionnaire at baseline in 1976. Information on new diagnosis of doctor-told FM was obtained at the 2[nd] survey in 2002. A total of 136 women reported a diagnosis of FM during 25 years of follow-up, giving a period incidence of 43/1,000 or 1.72/1000 per year. In multivariable logistic regression analyses, a significant, dose-response association was found with number of allergies with OR of 1.61 (95% CI:0.92–2.83) and 3.99 (95% CI:2.31–6.88), (p[trend]<0.0001, respectively, for 1 and 2 or more allergies versus none. A history of hyperemesis gravidarum was also associated with FM with OR of 1.32 (95% CI:0.75–2.32) and 1.73 (95% CI:0.99–3.03), (p[trend]<0.05), respectively, for some or all pregnancies versus none. A positive association with smoking was also found with OR of 2.37 (95% CI:1.33–4.23) for ever smokers versus never smokers. No significant association was found with number of surgeries, history of peptic ulcer or taking medications to control various symptoms.

Keywords

Fibomyalgia; allergy; hyperemesis gravidarum; smoking; Adventist Health Study

Introduction

Fibromyalgia (FM) is a chronic and debilitating syndrome with chronic, widespread musculoskeletal pain (CWP) and discrete tender points.[67] FM has been proposed as the extreme end of CWP[20] with more clinical pain, additional symptoms and more negative consequences as a result of the pain.[17]

Correspondence to: Synnove Fonnebo Knutsen.

A large number of additional symptoms are also often present, including sleep disturbance, fatigue, headache, morning stiffness, paresthesias, psychological distress and cognitive disturbances.[65] Patients with FM present high rates of functional disability and have high levels of healthcare utilization.[66] Yearly health care costs have been estimated to be three times higher among FM patients than patients without any healthcare encounters for FM.[7] The overall health status burden of subjects with FM has been found to be of greater magnitude than among persons with other pain conditions.[34]

The prevalence of FM in the general population of the United States (US) has been reported to be 3.4 percent in women and 0.5 percent in men.[65] The number of prevalent cases of primary FM in the US was estimated to more than 5.0 million adults in 2005.[39] Female preponderence and gender differences in symptoms and psychologic functioning are consistent epidemiologic findings across various populations.[39, 45, 64]

The pathophysiology of FM is unclear. Several hypotheses such as central sensitization,.[68] hypothalamic-pituitary-adrenal (HPA) axis alteration[30, 43] and neurotransmitter abnormality[50] have been proposed, but more research is needed.

In cross-sectional studies, the factors associated with FM are low socioeconomic status, higher rates of divorce, surgical interventions, acute or chronic emotional stress, some reproductive and/or gynecologic histories[49, 54, 65] and elevated incidence of psychiatric co-morbid conditions.[25] However, associations observed in cross sectional studies may not imply causation. Several short-term prospective studies support the findings of an association between psycho-social factors and CWP.[31, 42, 44]

To our knowledge, no long-term large prospective study of somatic risk factors for FM has been reported. Previous prospective studies mainly focused on psychosocial or psychiatric risk factors for FM/CWP.[31, 42, 44] The longitudinal association between physical illness and mental illness is bi-directional. Mental illness, especially major depression, predicts an increased risk of future poor physical health, independent of prior physical health and demographic factors and in addition, poor physical health independently predicts an increased risk of future mental illness.[16] Few have studied non-psychiatric disease predictors for FM. Including such factors could provide us a more integrated overview and a broader understanding of the temporal relationships between FM and other possible risk factors.

The objective of this study was to prospectively examine the association between health behaviors as well as somatic disease and development of new cases of FM in women.

Methods

Study population and study design

The study population consists of women who participated in two large cohort studies about 25 years apart, the Adventist Health Study in 1976 and again in 2001/2002. Both studies were approved by the Institutional Review Board (IRB) of Loma Linda University.

Adventist Health Study 1 (1976–1988)—The Adventist Health Study 1 (AHS-1) was a prospective cohort investigation of 34,198 California, non-Hispanic white subjects who were 25 years or older at baseline. The primary objective of the study was to investigate the role of lifestyle on mortality and incidence of cancer and coronary heart disease. A census questionnaire was mailed to participants in 1974 and subsequently a comprehensive lifestyle questionnaire in 1976. The details of the study have been described elsewhere.[6]

Adventist Health Study 2 (2002 to date)—The purpose of the second Adventist Health Study (AHS-2) was to extend the investigation of the effects of lifestyle choices on health, especially cancer, in black as well as a larger number of white members of the Adventist church throughout the US and Canada. Members who turned in an enrolment card and were 30 years or older received the comprehensive lifestyle questionnaire. The 5-year (2002–2006) recruitment campaign resulted in a total enrollment of 96,000 subjects, of which 25,000 were African-American. The study has been described in detail elsewhere.[13]

Record linkage—To be able to identify respondents who participated in both the first and second Adventist Health studies, the AHS-2 baseline questionnaire asked if the respondent recalled participating in the 1976 survey. A request for a maiden name and the last name that was used in 1982 (the last annual follow-up of AHS-1) was also made of female respondents. A matching process involving several steps was developed to link the appropriate records from the AHS-1 and AHS-2 studies, since the AHS-1 survey did not have a common numerical identifier such as a social security number. Ultimately 14 variables were used to determine a match of records: first, middle and last name; month, day and year of birth; state or country of birth; recalled age at baptism into the church; recalled participation in AHS-1; marital status; maiden name; last name used in 1982; birth year of first child; and last name of contact person. A number of computerized algorithms using the first 10 of these variables were developed and employed to identify potential matches of women participating in the two studies. The final number of matching records on females who responded to both the AHS-1 and AHS-2 questionnaires was 3,156.

Outcome variables

FM was defined by the response to the following question in the AHS-2 baseline questionnaire: “Has a doctor ever told you that you had fibromyalgia?” and “If you ever have been diagnosed with fibromaylgia by a physician, how long since it was first diagnosed?” and “Have you been treated for this in the last 12 months ?” The five closed-ended responses for how long ago the FM diagnosis was made were: less than 5 years ago, 5–9 years ago, 10–14 years ago, 15–19 years ago and 20 or more years ago. A total of 156 female subjects reported having been diagnosed with FM in this cohort and of these 20 were diagnosed more than 20 years ago and were therefore considered prevalent FM cases at baseline, and excluded from analysis. Thus, we have 136 incident cases of FM during follow-up.

Explanatory variables

The baseline questionnaire in 1976 included questions on educational attainment, occupation, marital status, height, weight, menopausal status, physician-diagnosed medical conditions, self-reported hyperemesis gravidarum, physical activity, medication use, history of surgery, alcohol use and some psycho-social variables. A priory candidate exposure variables were selected based on literature review. Hyperemesis gravidarum was included as a candidate exposure variable because it has been associated with psycho-social variables[24, 59]and also because it has been associated with allergies in this population (unpublished data). These variables were treated as exposures or confounders in the analysis reported below.

Physical characteristic—Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2). Participants were classified into two body mass index groups: < 25 as normal, ≥ 25 as overweight.

Smoking status—Information on respondents' smoking history and current smoking status was obtained. Adventists are encouraged to not smoke and virtually all stop smoking at the time they join the church. Thus, only 0.5% of the study population indicated current smoking.

However, 12.7% were former smokers. Participants were therefore classified into two groups: never smokers and ever smokers (current and past smokers).

Exercise—Exercise was categorized as none, low, moderate, or high, representing a cross-classification of two questions relating to occupational and leisure activities. The first question was, "Outside of your usual work or daily activities, do you usually get at least 15 minutes of vigorous exercise three or more times per week?" This was followed by a list of possible vigorous activities for the subject to check if he or she did these at least three times each week for 15 minutes on each occasion. The second question was, "Does your usual daily work or responsibilities involve vigorous activities similar to those listed in the previous question?" Possible responses were "very often," "frequently," "occasionally," "rarely," or "never." "High exercise" reflects a high occupational and/or high leisure activity status. "Moderate exercise" includes moderate leisure activity, and low or moderate occupational activity, or low leisure activity but moderate occupational activity. "Low exercise" designates subjects with both low leisure and occupational activities. The validity of questions on physical exercise among California white, non-Hispanic Adventists, has been described in detail elsewhere.[56]

Alcohol—Most subjects in this study never drink alcohol. Thus, there was very little variation and participants were classified into two groups: users and non-users.

Socioeconomic status—Socioeconomic status was assessed using attained educational level and employment status. Two levels of education were used: those with some college or less, and those who were college graduates or more. Employment status was categorized into 2 groups: employed (self employed, full time or part time employed) or unemployed (out of work, student, homemaker, volunteer worker, retired)

Marital status—Marital status was categorized into 3 groups: married, separated/divorced/widowed and never married.

Somatic diseases—Self-reported physician diagnosis of the following diseases was reported at baseline in 1976: heart attack or "coronary", stroke, hypertension, diabetes, cancer, rheumatoid arthritis, other arthritis or rheumatism, breast lump or cyst, peptic ulcer and allergic disorder. Allergic disease was defined by the following question "Have you ever been bothered enough by any of these allergic disorders to require you to seek treatment from a physician?" The alternatives were: asthma, hay fever, reaction to chemicals, medicine, bee sting or plants. Subjects were asked to mark all that applied. We categorized allergic disorders into 3 groups based on the number of allergic diseases: no allergies, one allergy, two or more allergies.

Hyperemesis gravidarum—Self-reported experience of hyperemesis gravidarum was categorized into 3 groups: 1) Never experienced in any of the pregnancies, 2) present in some of the pregnancies, and 3) present in all pregnancies.

History of surgeries—Three groups were created based on self-reported surgeries for hernia, varicose veins, hemorrhoids, peptic ulcer, gallbladder, appendix, uterus or tonsils: no surgery, 1 or 2 surgeries and 3 or more surgeries.

Medication history—Subjects reported on weekly use of the following symptom controlling medications: pain relievers, medicine for indigestion, laxatives, tranquilizers, sleeping pills or "pep" pills. Based on the response, participants were categorized into 2 groups: 1) non-users, or 2) taking one or more of these.

Statistical analysis

Comparisons between FM cases and non-cases on baseline age and BMI were performed using the Student's t-test.

All univariate and multivariate analyses were conducted using logistic regression with 25-year incidence of FM as the dependent variable. In multivariate analyses, initial models estimated individual effects adjusted for age, body mass index, education, employment and marital status. Predictor variables that met statistical significance at the $p<0.10$ level in these initial models were included in a final cumulative model.

Sensitivity analyses

Since FM is a relatively new diagnosis and it is possible that women could have been given other diagnoses for this condition in the 1970's, we did sensitivity analysis excluding 42 subjects who reported a diagnosis of rheumatism or other arthritis at baseline. This did not change the main effect of the predictor variables and therefore the final analyses included all women.

We also did a second sensitivity analysis excluding 92 subjects who, at baseline, reported taking pain medications one or more times per week. Again, the associations with FM did not change significantly and thus all women who met inclusion and exclusion criteria were included in the final analyses.

The third sensitivity analysis included adding three psychosocial variables to the final model to see if they changed the main effects. The variables tested were perception of cold parenting (Y/N), raised by divorced or separated parent (Y/N) and depression at baseline (1976) (3 levels). The results remained virtually unchanged when adding these one at a time to the model and so they were not included in the final model.

Multi-collinearity was tested in each multivariate model by producing a correlation matrix and examining the tolerance and variance inflation of the independent variables in linear regression. The software Statistical Analysis Software (SAS), version 9.1 was used for analyses.

Results

Among the 3,156 women in this study, there were 136 incident cases of FM giving a 25-year period incidence of 43/1,000 or 1.72/1,000 per year.

The most common age at diagnosis was 51–60 years. A total of 60.4% of all incident cases were diagnosed between ages 51 and 70 years (Table 1). Women with incident FM tended to be younger (41.8±10 yrs vs. 45.5±10.3 yrs, $p<0.0001$) and have lower BMI at baseline compared to non-cases (22.8±3.13 vs. 23.7±3.98 kg/m^2, $p<0.005$)

Fibromyalgia and demographic factors

None of the demographic factors (age, BMI, education, employment status, marital status) were associated with FM in univariate or multivariate models (Table 2). Menopausal status was marginally and positively associated with FM and thus was included in the final model.

Fibromyalgia and health behaviors

In multivariate analyses, the risk of FM was associated with ever-smoking (OR=2.53 [95% CI: 1.52–4.23]), history of 1–2 surgeries (OR=2.08 [95% CI: 1.08–4.00]), 3 or more surgeries (OR=2.99 [95% CI:1.38–6.44]), and use of any symptom controlling medications at least once a week (tranquilizers, sleep medications, laxatives, pain killers or pep pills) (OR=1.73 [95%

CI: 1.01–2.95]) (Table 3). There was also a positive association with use of alcohol, but this did not reach statistical significance. No association was found with physical activity at baseline.

Fibromyalgia and somatic diseases/symptoms

FM was positively associated with allergies in a dose-response fashion with OR of 1.94 (95% CI: 1.19–3.14) and 3.39 (95% CI: 2.08–5.51), respectively, for one allergy and 2 or more allergies (p[trend]<0.0001). A positive association was also found with a history of peptic ulcer (OR=1.93 [95% CI: 1.05–3.56]) and with a history of hyperemesis gravidarum with OR of 2.24,(95% CI: 0.81–2.39) and 1.74 (95% CI: 1.03–2.94), respectively, for hyperemesis gravidarum in some and all of the pregnancies (p[trend]=0.03] (Table 4). No association was found with physician diagnosed hypertension, breast cysts or lumps or rheumatoid arthritis.

When the significant health behaviors and somatic variables were added into the same multivariate model, the association between FM and allergies, hyperemesis gravidarum, and ever smoking, remained virtually unchanged whereas there was no longer a significant association with number of surgeries, peptic ulcer, use of symptom control medications or menopausal status (Table 5).

DISCUSSION

To our knowledge, this is the first large study to prospectively assess somatic predictors of FM. Previous prospective studies mainly focused on the outcome of FM,[5, 23, 27] psychosocial predictors of CWP[31, 42] or health service utilization among subjects with FM.[66]

A dose-response relationship was found between prevalent allergic disease at baseline and development of FM. One cross-sectional and one case-control study have also reported an association between allergy and FM.[15, 60] Allergic conditions were three times more common in primary FM patients than in controls[60] and FM was diagnosed in 38% of chronic allergic rhinitis patients, suggesting chronic allergic rhinitis as a possible causative factor of FM.[15] Several others have reported an association between FM, allergy, and common co-morbid clinical entities, e.g. back pain, anxiety disorders, depression, irritable bowel disorder, and migraine[3, 23, 27, 66] suggesting that FM may share a common physiologic abnormality with other disease entities. This is supported by cross-sectional findings that subjects with a history of allergy were more likely to report low-back pain, be diagnosed with major depression and much more likely to have both major depression and low-back pain, compared to subjects with no history of allergy.[36]

A similar association was found in a prospective study where immunologically mediated disorders in childhood were strongly associated with onset of major depression in adulthood.[16] Further, persons with chronic fatigue syndrome have been found to be more likely to have a history of childhood allergic disease.[33]

Asthma subjects not treated with glucocorticoids[12] and infants genetically predisposed to allergic diseases have been reported to have alterations in the hypothalamic-pituitary-adrenal (HPA) axis with potential significant effects on the maturing immune system.[4] These findings suggest that allergic disease may prime the HPA axis to respond aberrantly to stressors, creating a potential etiologic link to FM.[4]

Several studies have reported disturbed HPA axis function in subjects with FM, including reduced 24-hour free cortisol excretion and loss of their circadian fluctuation,[18–19] exaggerated adrenocorticotropin hormone (ACTH), but blunted cortisol response to exogenous administration of human corticotrophin releasing hormone (CRH) and to insulin-induced hypoglycemia.[29] CWP has been associated with altered HPA axis function,[43] and among a group of psychologically at-risk subjects, dysfunction of the HPA axis helped distinguish between those who did and did not develop new onset CWP.[44] Holliday also report that subjects with a genetic variation in the primary stress-response system genes in the HPA axis are more prone to develop musculoskeletal pain.[35] Reduced HPA axis activity is often associated with symptoms of fatigue, myalgias, disturbed sleep, and depressed mood.[1] Thus, alteration of the HPA axis may be one of the main pathophysiologies of FM.

Central sensitization may also play a role in abnormal widespread pain sensitivity[57–58] and such dysregulation/sensitization of central sensory processing provides a pathophysiological model for the explanation of pain in FM/CWP.[14, 22, 34] The specific linkage between HPA axis alteration and central sensitization, however, is unclear. In a recent focus article, Chapman et al.[14] suggest that chronic pain conditions stem from dysregulation of a "supersystem" where nervous, endocrine and immune systems interact reciprocally through hormones, neurotransmitters and cytokines causing dysregulation of neuroendocrine-immune systems, including the HPA axis, resulting in central sensitization.

In our study, after adjusting for all potential confounders, smoking was independently associated with increased risk of FM. This association was not altered by inclusion of psychosocial predictors in our third sensitivity analysis. Both cross-sectional studies among FM/CWP patients[48, 69] as well as in population-based studies[2, 8, 37, 47] have reported higher prevalence of pain at all sites among current and ex-smokers, with several also reporting dose-response relationships. The temporal relationships between smoking and FM, however, could not be ascertained in these studies. The subjects of the present study, on the other hand, reported their smoking history in 1976, well before the diagnosis of FM. By 1976, virtually all (99.5%) were non-smokers. Thus, our findings suggest a strong effect of past smoking on later development of FM. Our results are in line with a 5-year prospective study of metal industry workers where a dose-response association was found between smoking intensity and future musculoskeletal symptoms.[40] A possible underlying mechanism could be that smoking may cause resetting of the threshold for central pain tolerance.[52] Both smokers and patients with FM have been found to have alterations of the HPA axis[19, 21, 28] affecting endogenous opioid activity in pain modulating regions of the brain.[32, 53] A single dose of nicotine is sufficient to activate the HPA axis, whereas chronic cigarette smoking results in a blunted HPA axis responsiveness to acute psycho-social stress.[19, 29, 51] A possible confounding factor in the relationship between FM and smoking is depression which is associated with both smoking[9–10] and FM.[10, 46] Adjusting for depression in our study, did not change the results, suggesting a causal association between smoking and risk of FM.

A significant dose-response relationship was also found between hyperemesis gravidarum and incident FM. Others have reported an association between hyperemesis gravidarum and psychiatric illness, a co-morbidity of FM.[24, 59] Psychologic factors (somatization disorder or response to stress) or hormonal changes have been proposed[11, 38, 55] while others have reported an association with overactivity of the HPA axis.[62] In our study, the association with hyperemesis gravidarum remained unchanged when adjusting for psychosocial factors, suggesting an independent effect. The pathogenesis of hyperemesis gravidarum is still unclear and more studies are needed.

Previous cross-sectional reports have found associations between FM and education,[49, 65] employment status.[66] obesity[70] and an "overactive" lifestyle.[61] We found no such associations in this prospective study. The lack of association with FM for these demographic factors in our prospective study as opposed to the findings in the cross-sectional studies, could suggest that these factors may be the results, rather than predictors, of FM.

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In demographics adjusted models, the association between incident FM and a history of surgeries, peptic ulcer, and use of symptom controlling medications are in line with the findings of others.[7, 66] Berger et al. reported that FM patients have comparatively high levels of co-morbidities and high levels of healthcare utilization.[7] In a prospective study of subjects with FM, Wolfe found high rates of lifetime as well as current utilization of all types of medical services including lifetime surgical interventions.[66] Also, significant relationships have been reported between depression, hostility and social alienation and later ulcer development.[41] Our findings became non-significant when adjusting for smoking and other diseases, suggesting that surgeries, peptic ulcer, and use of symptom controlling medication are not true risk factors for FM.

The majority (60.4%) of our incident cases were diagnosed between the ages of 51 to 70 years which is broadly in line with previous reports.[63] These 136 new cases of FM occurred among 3,136 women during 25 years follow-up with a cumulative incidence of 4.3% or 1.7/1,000 per year. This is significantly lower than studies from southern Norway which found a 5.5 year cumulative incidence of FM of 3.2% or 5.8/1,000 per year in females aged 20–49 years at baseline.[26] This high incidence rate was explained by having used a highly sensitive method for diagnosis and the fact that the study was conducted in a high risk region. Another study reported incidence rates from 10.8 (25–29 yrs) to about 20.5 (45–64 yrs) cases per 1,000 person-years for females.[63] This retrospective cohort study of a health insurance claims database, identified FM cases using the International Classification of Disease, 9th Revision, Clinical Modification (ICD9-CM). On ICD9-CM codes, however, there is no single specific code for FM. According to the coding rules, FM is coded as 729.1 which is labeled “Myositis and Myalgia, unspecified” and may therefore include other conditions as well, resulting in overestimates for FM.

The two major limitations of our study are that all variables are self-reported and some of the FM cases were diagnosed before the American College of Rheumatology (ACR) diagnostic criteria were established in 1990. Even though the diagnosis was self-reported, it was based on “doctor told” diagnosis and not self assessment. Our study population has a high level of education and easy access to health care. It is therefore likely that the validity of the physician diagnosis is fairly good compared to other population studies. Even so, our findings need to be confirmed in other studies where the diagnosis of FM is based on objective criteria rather than self-reported physician diagnosis.

In summary, after adjustment for potential confounders, ever-smoking and a history of allergies and hyperemesis gravidarum were major independent predictors of FM even after adjusting for psychosocial variables. The study findings give yet another strong rationale for avoiding smoking. Further studies are needed to assess the associations between smoking, allergies and hyperemesis gravidarum and risk of FM and to shed light on possible underlying mechanisms.

Perspective

Smoking as well as prevalent allergies, and a history of hyperemesis gravidarum seem to predict development of FM in women during 25 years of follow-up. This information may help in identifying persons at high risk of developing FM and thus initiate effective prevention strategies.

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Table 1

Distribution of Age at Diagnosis of Fibromyalgia and Incidence of Fibromaylgia in Women, the Adventist Health Study, California, 1976–2002 (N=3,136)

Age of diagnosis	No. (%)
31–40	8 (5.9)
41–50	18 (13.2)
51–60	48 (35.3)
61–70	34 (25.1)
71–80	18 (13.2)
≥ 81	10 (7.4)
Total	136 (100)
25-yr Incidence	136 (4.3)
95% CI	3.6–5.0

Table 2

Unadjusted and Adjusted* Odds Ratios for the association between Demographic Factors and Incident Fibromyalgia in Women, the Adventist Health Study, California, 1976–2002 (N=3,136)

	Non-cases	Cases	Unadjusted		Adjusted*	
	N=3,000	N=136	OR	95% CI	OR	95% I
	n (%)	n (%)				
Baseline age (yrs)						
25–34	578 (19.3)	42 (30.8)	1.00	Referent		Referent
35–44	848 (28.3)	47 (34.6)	0.76	0.50–1.17	0.70	0.43–1.13
≥ 45	1,574 (52.4)	47 (34.6)	0.41	0.27–0.63	0.28	0.16–0.51
BMI (kg/m^2)						
< 25.0	1957 (65.2)	91 (66.9)	1.00	Referent		Referent
≥ 25.0	779 (26.0)	28 (20.6)	0.74	0.48–1.13	0.82	0.53–1.27
Education						
≤ High school graduate	630 (21.0)	25 (18.4)	1.00	Referent		Referent
Some college	1,439 (48.0)	70 (51.5)	1.23	0.77–1.95	1.13	0.69–1.87
≥ College graduate	925 (30.8)	41 (30.1)	1.12	0.67–1.86	1.00	0.57–1.77
Employed						
No	1,116 (37.2)	56 (41.2)	1.00	Referent		Referent
Yes	1,840 (61.3)	74 (54.4)	0.80	0.56–1.14	0.83	0.56–1.23
Marital status						
Married	2,557 (85.2)	113 (83.1)	1.00	Referent		Referent
Never married	173 (5.8)	8 (5.9)	1.05	0.50–2.18	0.66	0.26–1.70
Widowed/Divorced	268 (9.0)	15 (11.0)	1.27	0.73–2.20	1.29	0.69–2.42
Menopause						
No	1,644 (54.8)	78 (57.4)	1.00	Referent		Referent
Yes	1,312 (43.7)	55 (40.4)	0.88	0.62–1.26	1.64	1.00–2.68

* adjusted for age, body mass index (BMI), education, employed, marital status

Table 3

Unadjusted and Adjusted* Odds Ratios for the association between Health Behaviors and other factors and incident Fibromyalgia in Women, the Adventist Health Study, California. 1976–2002 (N=3,136)

	Non-cases	Case	Unadjusted		Adjusted*	
	N=3,000	N=136	OR	95% CI	OR	95% CI
	n (%)	N (%)				
Smoking						
Never	2,681 (89.4)	105 (77.2)	1.00	Referent	1.00	Referent
Ever	285 (9.5)	26 (19.1)	2.33	1.49–3.64	2.53	1.52–4.23
Current Alcohol use						
None	2,948 (98.3)	132 (97.1)	1.00	Referent	1.00	Referent
Some	52 (1.7)	3 (2.2)	1.72	0.61–4.82	1.72	0.60–4.97
Exercise						
None	973 (32.4)	48 (35.3)	1.00	Referent	1.00	Referent
Low	457 (15.2)	21 (15.4)	0.93	0.55–1.57	1.00	0.56–1.79
Moderate	486 (16.2)	19 (14.0)	0.79	0.46–1.36	0.85	0.46–1.58
High	1059 (35.3)	43 (31.6)	0.82	0.54–1.25	0.94	0.59–1.50
No. of surgeries						
0	509 (17.0)	14 (10.3)	1.00	Referent	1.00	Referent
1–2	1,822 (60.7)	83 (61.0)	1.66	0.93–2.94	2.08	1.08–4.00
≥ 3	631 (21.0)	32 (23.5)	1.84	0.97–3.49	2.99	1.38–6.44
Symptom control medicine‡						
No	2,586 (86.2)	108 (79.4)	1.00	Referent		Referent
Yes	346 (11.5)	19 (14.0)	1.32	0.80–2.17	1.73	1.01–2.95

* adjusted for age, BMI, education, employed, marital status

‡ "Symptom control medication" includes taking any of the following medications one or more times per week: pain relievers, medicine for indigestion, tranquilizers, sleeping pills or pep pills.

Table 4

Unadjusted and Adjusted* Odds Ratios for the association between various Somatic Disease Factors and incident Fibromyalgia in Women, the Adventist Health Study, California. 1976–2002 (N=3,136)

	Non-cases	No.	Unadjusted		Adjusted*	
	N=3,000	N=136	OR	95% CI	OR	95% CI
	n (%)	n (%)				
No. of allergies§						
0	1,461 (48.7)	42 (30.9)	1.00	Referent	1.00	Referent
1	899 (30.0)	43 (31.6)	1.66	1.08–2.57	1.94	1.19–3.14
≥ 2	570 (19.0)	47 (34.6)	2.87	1.87–4.40	3.39	2.08–5.51
			P(trend)<0.0001		P(trend)<0.0001	
Peptic ulcer						
No	2,697 (89.9)	113 (83.1)	1.00	Referent	1.00	Referent
Yes	210 (7.0)	17 (12.5)	1.93	1.14–3.28	1.93	1.05–3.56
Hyperemesis gravidarum						
Never	1,710 (57.0)	65 (47.8)	1.00	Referent	1.00	Referent
Some pregnancis	450 (15.0)	24 (17.6)	1.39	0.86–2.24	2.24	0.81–2.39
All pregnancies	383 (12.8)	27 (19.9)	1.77	1.11–2.82	1.74	1.03–2.94
			P(trend)=0.01		P(trend)=0.03	
Hypertension						
No	2,544 (84.8)	112 (82.4)	1.00	Referent	1.00	Referent
Yes	379 (12.6)	18 (13.2)	1.08	0.65–1.80	1.65	0.93–2.90
Breast cyst or lump						
No	2,338 (79.6)	97 (71.3)	1.00	Referent	1.00	Referent
Yes	586 (19.5)	32 (23.5)	1.32	0.87–1.98	1.28	0.80–2.04
Rheumatic arthritis						
No	2,810 (93.7)	124 (91.2)	1.00	Referent	1.00	Referent
Yes	87 (2.9)	4 (2.9)	1.04	0.38–2.88	1.15	0.35–3.76

* adjusted for age, BMI, , education, work for pay, marital status

§ "allergies" include any allergic diseases, such as asthma, hay fever, allergy to medicine, chemicals, bees, plants.

Table 5

Multivariate Adjusted* Odds Ratios for the association between lifestyle and Somatic Factors and incident Fibromyalgia among 3,136 white, non-hispanic women in the the Adventist Health Study, California, 1976–2002.

	Full Model	
	OR	**95% CI**
No. of allergies		
0	1.00	Referent
1	1.61	0.92–2.83
≥ 2	3.99	2.31–6.88
	P(trend)<0.0001	
Peptic ulcer		
No	1.00	Referent
Yes	0.92	0.42–2.01
Hyperemesis gravidarum		
Never	1.00	Referent
Some pregnancies	1.32	0.75–2.32
All pregnancies	1.73	0.99–3.03
	P(trend)=0.049	
Smoking		
Never	1.00	Referent
Ever	2.37	1.33–4.23
No. of surgeries		
0	1.00	Referent
1–2	1.71	0.84–3.46
≥ 3	1.39	0.56–3.47
	P(trend)=0.36	
Taking symptom control medication		
No	1.00	Referent
Yes	1.17	0.63–2.17
Menopause		
No	1.00	Referent
Yes	1.46	0.78–2.75

*Adjusted for age, BMI, education, work for pay, marital status and all variables in Table 5.