Menstrual Cycle and Respiratory Symptoms in a General Nordic–Baltic Population

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***Rationale*: There is little knowledge of variations in respiratory symptoms during the menstrual cycle in a general population, and potential modifying factors are not investigated.**

***Objectives*: To investigate menstrual cycle variation in respiratory symptoms in a large general population, using chronobiology methodology, and stratifying by body mass index (BMI), smoking, and asthma status.**

***Methods*: A total of 3,926 women with regular cycles less than or equal to 28 days and not taking exogenous sex hormones answered a postal questionnaire regarding the first day of their last menstruation and respiratory symptoms in the last 3 days. Moving 4-day means were computed to smooth uneven records of daily sampling; best-fitting 28-day composite cosine curves were applied to each time series to describe rhythmicity.**

***Measurements and Main Results*: Significant rhythmic variations over the menstrual cycle were found in each symptom for all subjects and subgroups. Wheezing was higher on cycle Days 10–22, with a midcycle dip near the time of putative ovulation (approximately Days 14–16) in most subgroups. Shortness of breath was higher on days 7–21, with a dip just before midcycle in many subgroups. Cough was higher just after putative ovulation for subjects with asthma, BMI greater than or equal to 23 kg/m^2, and smokers, or just before ovulation and menses onset for low symptomatic subgroups.**

***Conclusions*: Respiratory symptoms varied significantly during the menstrual cycle and were most frequent from the midluteal to midfollicular stages, often with a dip near the time of ovulation. The patterns varied by BMI, smoking, and asthma status. These relations link respiratory symptoms with hormonal changes through the menstrual cycle and imply a potential for individualized chronotherapy for respiratory diseases.**

Keywords: menstrual cycle; RHINE; respiratory symptoms; asthma; sex hormones

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Some women experience premenstrual asthma, there are differences according to menstrual phase for various measures of respiratory health, and asthma generally varies according to hormonal status in women.

What This Study Adds to the Field

This study shows large variations in respiratory symptoms over the menstrual cycle in a general population and among individuals with asthma; the cyclical pattern differs according to subject characteristics. This implies that sex hormones are important in airway physiology, and suggests a role for individualized chronotherapy for patients with asthma.

Emerging understanding of the role of sex hormones in respiratory health represents a major advance in respiratory epidemiology the last decade (1). Sex hormones influence respiratory health throughout a woman's life-span (2–8). A considerable scientific effort addresses menstrual cycle variations in respiratory health and a recent publication by Farha and coworkers (9) showed that airflow and gas transfer varies over the menstrual cycle. Menstrual cycle variations have been described for respiratory symptoms (10–12), asthma exacerbations (11, 12), hospital admissions for asthma (13, 14), peak expiratory flow rate (15–20), bronchial hyperreactivity (BHR) (21), and gas diffusion capacity (9, 22), mainly studied in women with asthma. Parameters of inflammatory and immunologic responses, such as total IgE (23), C-reactive protein (24), IL-4 (25), and fractional exhaled nitric oxide ($F_{E_{NO}}$) (26), vary during the menstrual cycle, as does insulin levels and insulin sensitivity (27).

The understanding of menstrual cycle variations is important, given the potential to throw light on airways physiology and the potential for chronotherapy for a subgroup of women with respiratory diseases, such as asthma. However, there is little knowledge on menstrual cycle variation in respiratory symptoms in a general population, and respiratory symptoms are far more common than asthma. No study of menstrual cyclicity in respiratory outcomes addresses potential modifying factors, such as body mass index (BMI) and smoking, both related to respiratory health and sex hormones (28).

Chronobiologic methodology is generally not used in the previously cited literature on respiratory health, but provides the most sensitive approach to investigate menstrual cycle variations. It is not biologically plausible to categorize data for complex rhythmical processes; categorization implies a risk of losing important information and biasing the identification of peaks and troughs.

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The course and timing of menstruation is steered through a complex endocrine interplay between hormones originating from the hypothalamus, the pituitary gland, and the ovaries. In the 10–14 days after menses (follicular phase), there is a complex process of endocrine and paracrine sequential actions that usually leads to one mature follicle. Estrogen increases until ovulation, follicle-stimulating hormone (FSH) rises but has a short dip before a new rise around ovulation, and luteinizing hormone (LH) initiates ovulation and has a large surge around ovulation. At ovulation the basal body temperature rises 0.5°C. The luteal or secretory phase occurs in the second half of the cycle. There is a surge in circulating progesterone 4–8 days after ovulation, FSH and LH decrease, and estrogen first decreases and then has a secondary smaller peak. All hormones are approaching their nadir at menstruation except FSH, which is slowly rising. Figure 1 shows an idealized scheme of the menstrual cycle (29).

Hormonal factors are closely linked with metabolic factors and obesity. Thus, accounting for metabolic factors, such as BMI (30), is highly relevant when investigating hormonal effects on respiratory health (3, 5, 7, 31). Smoking is important for respiratory health and has antiestrogenic effects (28), and should be considered when studying hormonal factors in respiratory health. Whether people with or without asthma exhibit different menstrual cycle patterns of symptoms is not known.

We hypothesize that respiratory symptoms in a general population vary according to the menstrual cycle, and that the cyclical pattern varies according to such characteristics as BMI, smoking, and asthma status. Thus, the aims of the present study were to investigate whether respiratory symptoms in a general population vary rhythmically during the menstrual cycle and assess the magnitude of such variation; and to investigate whether the cyclical pattern of symptoms differs according to BMI, smoking, and asthma status. This was addressed in a large population-based multicentric study, where respiratory symptoms within the last 3 days were reported independently of last menses onset, and analysis for periodicity were based on chronobiologic methodology using data from each day over a 28-day cycle rather than predefined cut-points or subspans.

Some of the results of these studies have been previously reported in the form of an abstract (32).

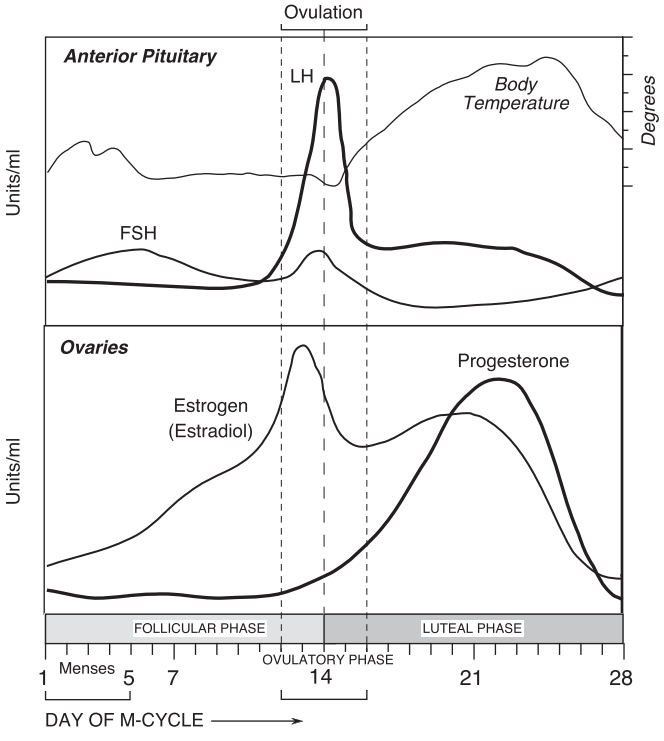

Figure 1. Generalized scheme of the hormonal and body temperature changes during a typical menstrual cycle. Day 1 = first day of menses onset; FSH = follicle-stimulating hormone; LH = luteinizing hormone. Adapted by permission from Reference 29 (Fig. 7.19).

METHODS

Respiratory Health in Northern Europe (www.rhine.nu) is a population-based multicenter postal questionnaire study, including 8,592 women (response rate 77%). Written consent was obtained from participants; local ethics committees approved the study.

Respiratory symptoms the last 3 days were defined by "yes" or "no" answers to the following questions: "Have you had wheezing or whistling in your chest at any time in the last 3 days?" "Have you been woken by an attack of shortness of breath at any time in the last 3 days?" and "Have you been woken by an attack of coughing, at any time, in the last 3 days?" Menstrual cycle day was calculated from reported date of the first day of the last menses onset to the questionnaire date. BMI was computed from reported height and weight (in kilogram per square meter). Smoking was categorized in current versus nonsmokers (never-smokers or ex-smokers). The question "Have you ever had asthma diagnosed by a doctor" defined asthma status.

To analyze a hormonally well-defined group of women with regular natural menstrual cycles, the following were excluded: pregnant (n = 260); using oral contraception (n = 1,023) or hormone-replacement therapy (n = 634); irregular menstruation (n = 1,360); oligomenorrhea (cycle length ⩾ 35 d; n = 762); postmenopausal (n = 158); age greater than 55 years (n = 138); and error in reported menses onset (n = 101).

The percentage of women reporting a symptom on each day of the menstrual cycle was calculated as N with symptom divided by N reporting on each day. We calculated 4-day moving averages to smooth the data, because of daily fluctuations in number of women on some days. The numbers of women reporting on each cycle day were evenly distributed.

Analysis of each time series for menstrual periodicity was accomplished by the single cosinor procedure (33) using percent incidence of each variable on Days 1–28 of the menstrual cycle. Single cosinor modeling involves the least-squares fitting of cosine curves with periods that are expected to characterize the dataset. This involved the approximation of each time series data by the least-squares linear regression fitting of a single component (28 d) or multiple component (28 d plus one, two, or three harmonic periods) (34). A P value for rejecting the zero-amplitude assumption was determined by an F test of variance accounted for by the fit of the single or compound period waveform versus the variance accounted for by a straight line approximation of the arithmetic mean. Rhythm detection was considered statistically significant if P was less than or equal to 0.05 for each fitted period in the cosine model separately and overall.

Rhythm characteristics determined from the best-fitting cosine include the midline estimating statistic of rhythm (mesor; the middle of the cosine, representing an adjusted 28-d average); amplitude (half the distance from the peak and trough of the best-fitting curve); and phase of the cosine (Ø, in days after 00:00 h on Day 1 of mesor). The peak of the fitted cosine, representing the calculated average time of high values in the data, is termed the "orthophase" (oØ) for a multiple-component cosine, whereas the "bathyphase" (bØ) indicates the lowest values of the cosine waveform.

RESULTS

Demographic characteristics are presented in Table 1. Number of women with menstrual cycles longer than 28 days dropped abruptly and were excluded (n = 230); demographic characteristics were unaltered when excluding these (Table 1). Thus, data from 3,926 women with cycle lengths less than or equal to 28 days were analyzed. The mean age was 39 years, the median BMI was 23 kg/m^2, and 28.5% of the women were current smokers. A total of 7.7%

TABLE 1. CHARACTERISTICS OF WOMEN WITH REGULAR MENSTRUAL CYCLES AND CYCLE LENGTH UP TO 28 DAYS PARTICIPATING IN THE RHINE POPULATION-BASED STUDY

	N Responded	Characteristics
Age (mean ± SD), yr	3,926	38.9 ± 6.3 (range, 25–54)
BMI < 23 kg/m^2	3,875	49.9% (1,933/1,942)
Asthma	3,868	7.7% (298/3,570)
Current smoker	3,871	28.5% (1,104/2,767)
Wheeze in the last 3 d	3,884	5.6% (219/3,665)
Shortness of breath in the last 3 d	3,887	1.8% (70/3,817)
Cough in the last 3 d	3,884	6% (234/3,650)

Definition of abbreviations: BMI = body mass index; RHINE = Respiratory Health in Northern Europe.

reported doctor-diagnosed asthma. In the last 3 days, 5.6% had experienced wheezing, 1.8% shortness of breath, and 6.1% cough.

The cosinor analyses are presented as figures, with numerical parameters of rhythm estimates in tables. The methodology did not allow for analyses of interaction, thus stratified analyses are presented for subgroups. On inspection of cosine analyses and graphs, we noted that a 28-day plus 3 harmonic period's cosine most closely approximated the menstrual cycle waveform in the daily incidence of respiratory symptoms. Accordingly, these numerical results are listed in Table 2, and the four-component curve is shown superimposed over the 4-day smoothed daily averages in Figures 2–4.

The overall prevalence of wheeze in the last 3 days was 5.5% (rhythm adjusted mean as opposed to arithmetic mean); 6.6% when BMI was greater than or equal to 23 kg/m^2 and 4.4% when BMI was less than 23 kg/m^2, and 22.2% for women with diagnosed asthma and 5.3% for those without diagnosed asthma. Smokers had a prevalence of 10.3% as opposed to 3.6% in ex-smokers and never-smokers (Table 2 and Figure 2).

The daily incidence for wheeze over Days 1–28 of the menstrual cycle showed a significant rhythm at *P* less than or equal

TABLE 2. STATISTICAL EVALUATION BY SINGLE COSINOR MODELING OF MENSTRUAL CYCLE VARIATIONS FOR WHEEZE, SHORTNESS OF BREATH, AND COUGH

	Rhythm Parameters*					
	%R[†]	*P* Value[‡]	Mesor ± SE[§]	Amp ± SE[‖]	Orthophase Day (oØ)[¶]	Bathyphase Day (bØ)[¶]
Wheeze						
All	80.1	<0.001	5.48 ± 0.12	1.40 ± 0.20	19.1	27.2
BMI						
<23	79.5	<0.001	4.35 ± 0.14	1.63 ± 0.21	12.9	24.8
⩾23	91.7	<0.001	6.57 ± 0.13	2.83 ± 0.20	18.9	0.5
Asthma						
No	85	<0.001	5.34 ± 0.12	1.92 ± 0.20	11.7	27.8
Yes	74.5	0.001	22.19 ± 0.82	8.49 ± 1.06	21.5	27.5
Smoking						
Never+ex	87.3	<0.001	3.58 ± 0.10	1.67 ± 0.15	12	27.8
Current	87.7	<0.001	10.31 ± 0.29	4.94 ± 0.34	19.1	23.6
Shortness of breath						
All	92.1	<0.001	1.70 ± 0.07	1.16 ± 0.10	14.2	23.8
BMI						
<23	77.5	<0.001	1.23 ± 0.11	1.18 ± 0.16	12.6	22.7
⩾23	93.8	<0.001	2.07 ± 0.07	1.70 ± 0.12	16.8	24.7
Asthma						
No	91	<0.001	1.71 ± 0.08	1.31 ± 0.12	13.6	1.9
Yes	85.9	<0.001	6.83 ± 0.42	6.43 ± 0.61	7.4	24.9
Smoking						
Never+ex	88	<0.001	1.12 ± 0.08	1.17 ± 0.13	13.2	22.8
Current	94.6	<0.001	3.09 ± 0.10	2.65 ± 0.15	6.8	24.8
Cough						
All	69.4	0.005	6.02 ± 0.10	1.03 ± 0.11	25	1.4
BMI						
<23	92.2	<0.001	5.82 ± 0.13	2.28 ± 0.18	25.9	18.5
⩾23	89.9	<0.001	6.05 ± 0.15	2.86 ± 0.20	18.1	1.2
Asthma						
No	89.9	<0.001	7.78 ± 0.13	2.09 ± 0.15	25.2	20.9
Yes	59.8	0.030	14.58 ± 0.45	4.76 ± 0.72	16.5	26.9
Smoking						
Never+ex	75.9	<0.001	5.05 ± 0.13	1.44 ± 0.18	10.3	19.9
Current	78.3	<0.001	7.93 ± 0.22	2.90 ± 0.25	19.1	1.5

Definition of abbreviations: BMI = body mass index; mesor = midline estimating statistic of rhythm.

* Rhythm parameters for composite four harmonic (28 d + 14 d + 9.33 d + 7 d) cosine.

[†] %R (percent rhythm) = % of variability around flat line average (mean) reduced by cosine model.

[‡] *P* value = for rejecting the zero-amplitude assumption. Determined by an *F* test of variance accounted for by the fit of the single or compound period waveform versus the variance accounted for by a straight line approximation of the arithmetic mean. Rhythm detection was considered statistically significant if *P* less than or equal to 0.05 for each fitted period in the cosine model separately and overall, and borderline significant if *P* less than or equal to 0.10 > 0.05.

[§] Mesor = 28-day adjusted mean (middle of cosine).

[‖] Amp = amplitude of cosine model: half the distance from the peak and trough of the best-fitting curve.

[¶] Phases (Ø): orthophase (oØ) = cycle day with highest point of multiple component cosine; bathyphase (bØ) = cycle day with lowest point of multiple component cosine. Phase units = day of menstrual cycle from Day 1 of menses onset.

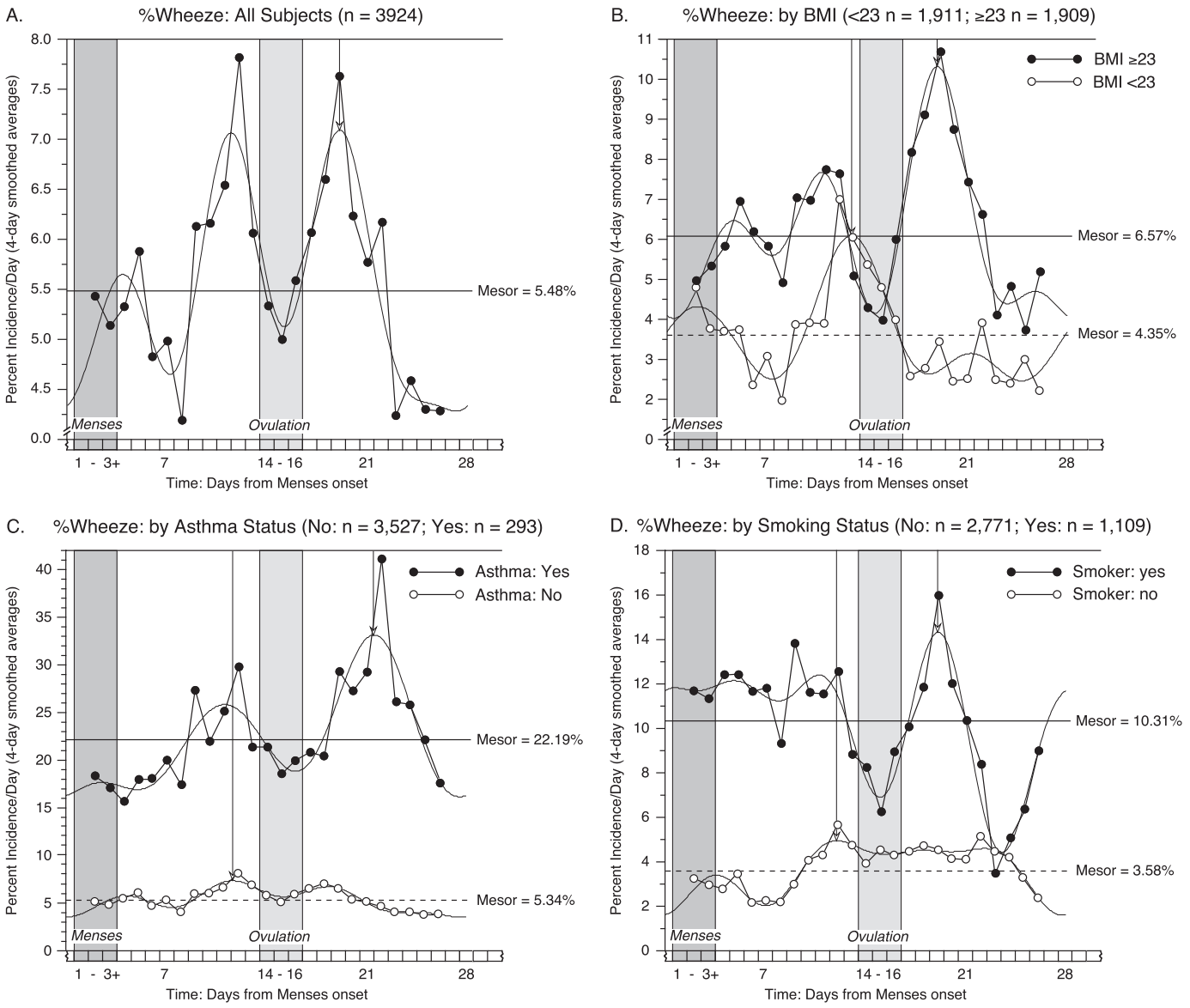

Figure 2. (*A–D*) Chronograms showing % incidence of wheezing on menstrual cycle Days 1–28 as recorded in the Respiratory Health in Northern Europe survey by 3,926 premenopausal women. Percent incidence per day smoothed over 4-day intervals and analyzed for rhythm by the least-squares fit of a composite four-component cosine. Fitted cosine (shown) significant at *P* less than or equal to 0.001 for each grouping, with peak incidence (oØ) indicated by *arrows*. All numerical results are listed in Table 2. BMI = body mass index; mesor = midline estimating statistic of rhythm.

to 0.001 when analyzing all women and in each of the main subcategories (Table 2 and Figure 2). Overall, the highest daily incidence of wheezing occurred with two periovulatory peaks, before and after midcycle (Days 14–16 near ovulation), with a dramatic decrease during this putative ovulatory span, and was lower before and after menses (Figure 2A). The same two-peaked pattern with a periovulatory dip was found for BMI greater than or equal to 23 kg/m^2 (Figure 2B), those with diagnosed asthma or not (Figure 2C), and among smokers and nonsmokers (Figure 2D). For women with BMI less than 23 kg/m^2, a single peak occurred before midcycle (Figure 2B).

The overall prevalence of shortness of breath was 1.7%; 2.1% when higher BMI ($\geq$23 kg/m^2) and 1.2% when lower BMI; 6.8% when diagnosed asthma and 1.7% when not; and 3.1% among smokers and 1.1% in nonsmokers (Table 2 and Figure 3).

The daily incidence for shortness of breath over Days 1–28 of the menstrual cycle showed a significant rhythm at *P* less than or equal to 0.001 when analyzing all women and in each of the main subcategories (Table 2 and Figure 3). The amplitude of the rhythmic oscillations was almost as large as the mean prevalence; this was found for all subgroups. Overall, the highest daily incidence of shortness of breath occurred with two peaks before and during midcycle (near putative ovulation on Days 14–16), and was lower before and after menses (Figure 3A). The same two-peaked pattern in shortness of breath was found for the high-prevalence groups, those with BMI greater than or equal to 23 kg/m^2 (Figure 3B), diagnosed asthma (Figure 3C), and smokers (Figure 3D). A single peak occurred just before midcycle in the lower prevalence groups, those with BMI less than 23 kg/m^2 (Figure 3B), those without asthma (Figure 3C), and nonsmokers (Figure 3D).

The overall prevalence of cough was 6%, with small differences between those with higher or lower BMI (6.1% vs. 5.8%), and larger differences according to asthma status

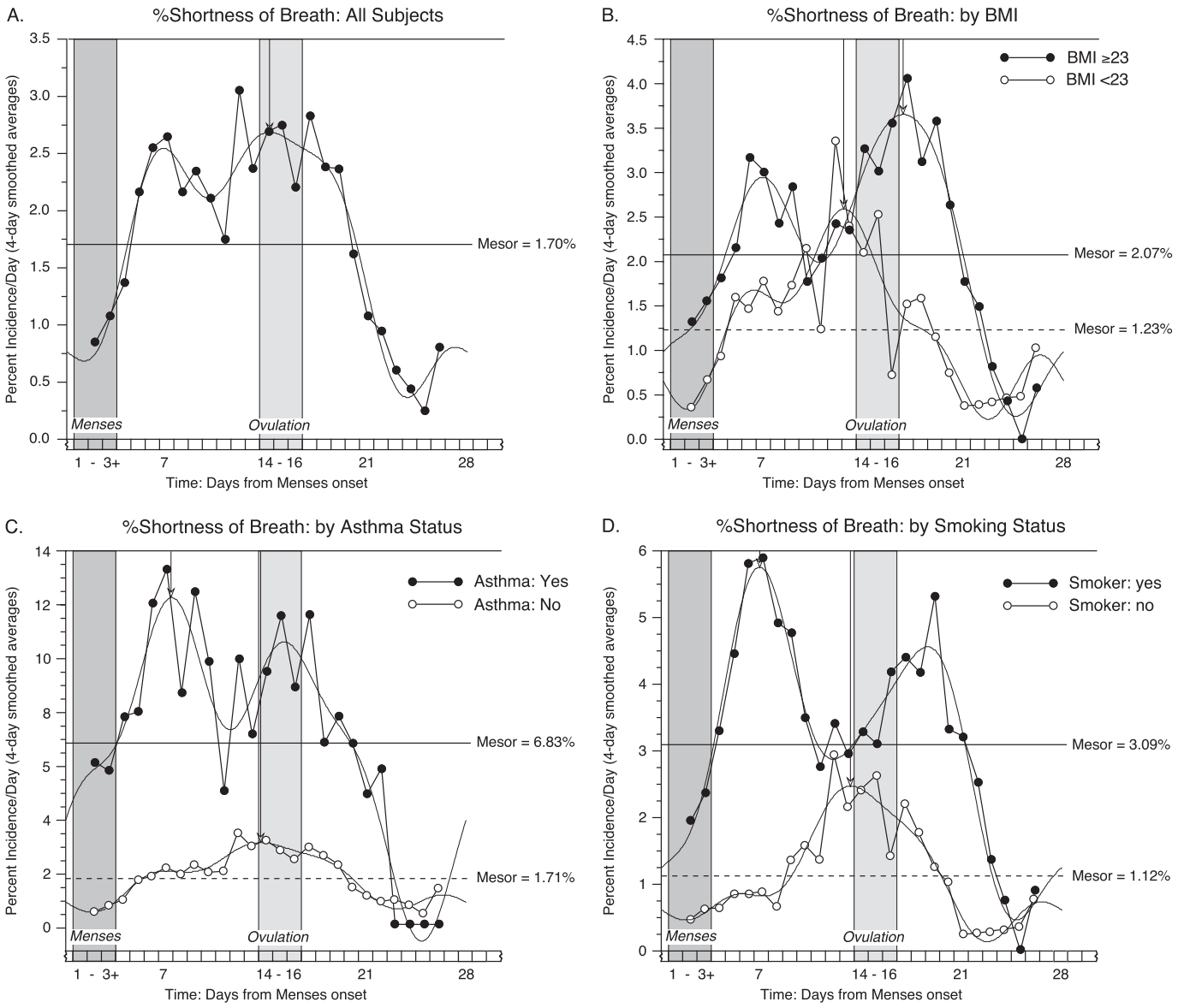

Figure 3. (*A–D*) Chronograms showing % incidence of shortness of breath on menstrual cycle Days 1–28 as recorded in the Respiratory Health in Northern Europe survey by 3,926 premenopausal women. Percent incidence per day smoothed over 4-day intervals and analyzed for rhythm by the least-squares fit of a composite four-component cosine (see METHODS). Fitted cosine (shown) significant at P less than 0.001 for each grouping, with peak incidence (oØ) indicated by *arrows*. All numerical results are listed in Table 2. BMI = body mass index; mesor = midline estimating statistic of rhythm.

(14.6% vs. 7.8%) and smoking status (7.9% vs. 5.1%) (Table 2 and Figure 4).

The daily incidence for cough over Days 1–28 of the menstrual cycle showed a significant rhythm for all women (P = 0.005), and in each of the main subcategories (Table 2 and Figure 4). Overall, the highest daily incidence of cough occurred with peaks before and after midcycle (near putative ovulation when values dropped dramatically) and before menses onset (major peak), and was lower after menses (Figure 4A). A similar three-peaked pattern in cough was noted in those without asthma (Figure 4C), and smokers/nonsmokers (Figure 4D), but a two-peaked pattern before and after midcycle was found for BMI greater than or equal to 23 kg/m^2 (Figure 4B), and those with asthma (Figure 4C). Women with BMI less than 23 kg/m^2 showed the most dissimilar pattern with highest values for cough before and after menses and lowest values during and after midcycle (Figure 4B).

DISCUSSION

We found that respiratory symptoms varied significantly during the menstrual cycle in women from a general population with regular menstruations. There were large changes in symptom incidence through the cycle for all symptoms, with amplitudes as large as the mean incidence for shortness of breath. Wheeze and shortness of breath were characterized by prominent peaks located in the midluteal and midfollicular phase, and a noticeable dip just before or during midcycle; however, the specific patterns differed between symptoms and between subgroups. Cough showed peaks before and after midcycle near putative ovulation and before menses onset, and was lower after menses. In subgroups with low incidence of symptoms there was a tendency toward a preovulatory or periovulatory peak. The cyclical pattern varied according to BMI, supporting a metabolic component in airways symptoms. There were some differences in patterns by smoking status, in accordance with known

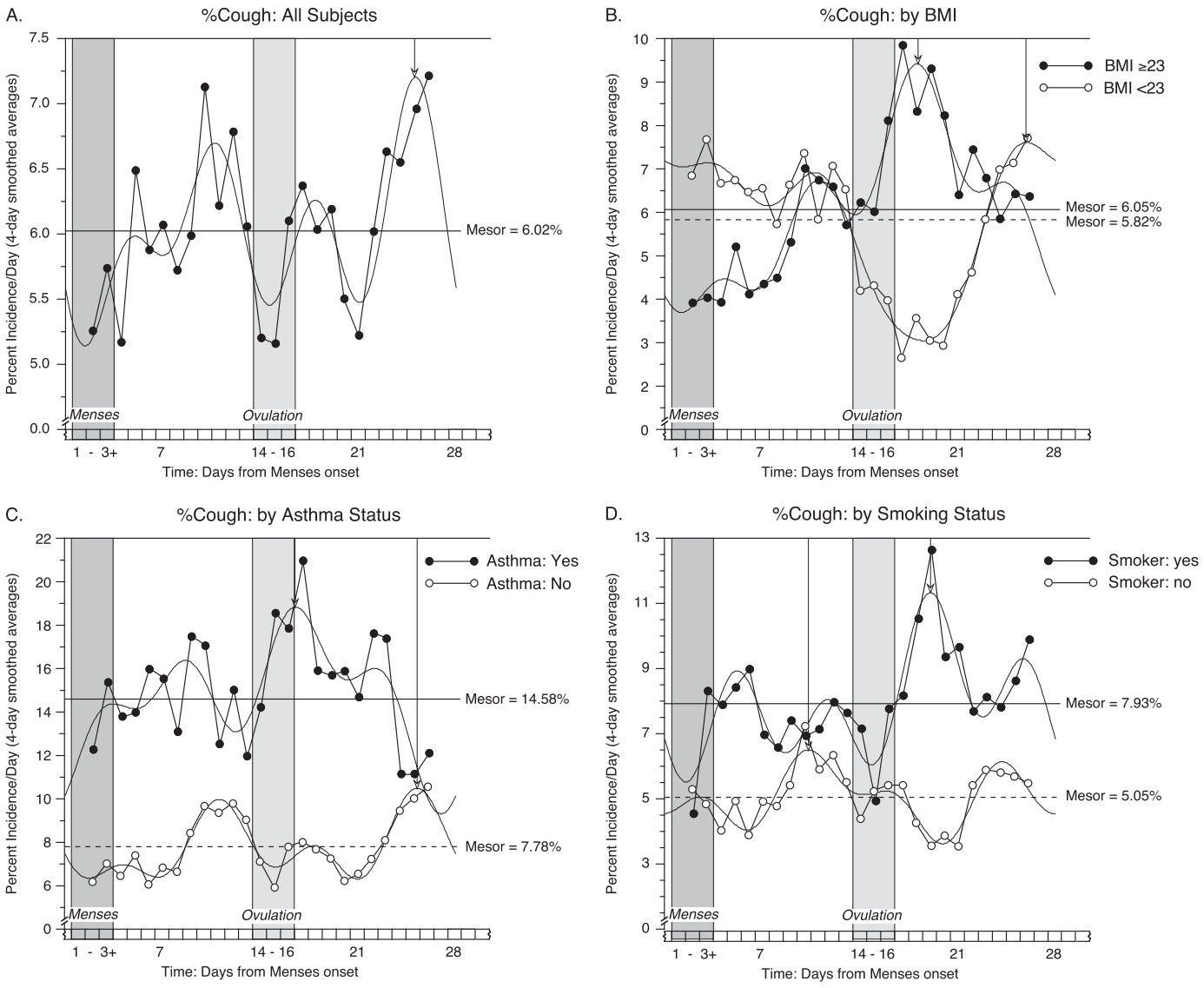

Figure 4. (*A–D*) Chronograms showing % incidence of cough on menstrual cycle Days 1–28 as recorded in the Respiratory Health in Northern Europe survey by 3,926 premenopausal women. Percent incidence per day smoothed over 4-day intervals and analyzed for rhythm by the least-squares fit of a composite four-component cosine (see METHODS). Four-component fitted cosine (shown) significant at $P = 0.005$ for all subjects, $P = 0.03$ for subjects with asthma, and P less than 0.001 for all other groupings, with peak incidence (oØ) indicated by *arrows*. All numerical results are listed in Table 2. BMI = body mass index; mesor = midline estimating statistic of rhythm.

hormonal influences of smoking. Pronounced cyclical variations were present in the subgroup of women with diagnosed asthma, suggesting a potential for individualized chronotherapy. These multioscillatory findings are based on chronobiologic methodology for analysis of percent incidence on each day of the menstrual cycle, rather than sampling restricted to specific subspans within the cycle.

It is novel that respiratory symptoms in a general population vary rhythmically during the menstrual cycle. However, this finding is consistent with a number of studies with different designs and methodology. There is evidence of menstrual cycle variation in BHR (21), lung function (9), gas diffusion capacity (9, 22), and FE_{NO} (12, 26). Among those with asthma, the literature describes menstrual cycle variations in respiratory symptoms (10–12), peak expiratory flow rate (15, 16–19), total IgE (23), asthma exacerbations (11, 35), and hospital admissions (13, 14). Menstrual cycle variations in respiratory symptoms in a general population seem biologically plausible, because such factors as edema (20), smooth muscle contractility, and inflammatory mediators (25) vary during the menstrual cycle.

Differences in menstrual cycle patterns of respiratory symptoms according to BMI and smoking have not been reported previously, to the authors' knowledge. The observation of differences according to BMI is plausible, given the close interplay between hormonal and metabolic factors, and supports previous literature showing such interplay specifically in respiratory health outcomes (3, 5–7). The use of chronobiologic methodology as in the present study is novel.

The menstrual cycle pattern in the present analysis was characterized by prominent peaks in the midluteal and midfollicular phase and a noticeable dip near midcycle. However, the pattern varied somewhat between the respiratory symptoms and differed between subgroups. Farha and coworkers (9) showed higher FEV_1 and higher diffusing capacity of carbon monoxide around menstruation and lower levels around midcycle; this was similar among subjects with asthma and healthy controls. These

findings are in accordance with the patterns presented in our study: phases of higher lung function and gas diffusion capacity in that study coincide roughly with periods of less respiratory symptoms in the present study. However, Dratva and coworkers (21) found increased prevalence of BHR perimenstrually and a small peak in BHR around ovulation in a general population; we did generally not identify peaks in symptoms in the perimenstrual phase, and both peaks and troughs around ovulation, dependent on symptom and subgroup. Increased F_{ENO} as a marker of eosinophil airway inflammation was in one study positively related to progesterone (26), a pattern not easily comparable with our findings. Several studies investigate premenstrual asthma (20, 36). Our study did not address specifically the phenotype of premenstrual asthma, but could not confirm particularly high incidences of respiratory symptoms in this general population before or during the time of menses, with the exception of cough in low symptomatic subgroups.

There are several possible explanations for differences in the literature concerning location of peaks during the menstrual cycle, among which methodologic issues are very relevant. Different respiratory outcomes may not be comparable. Differences in study populations may be important, as indicated by differences according to asthma, BMI, and smoking as described in the present analysis. Most studies are based on analysis of predefined subspans, where the choice of cut-points may influence the results substantially; for instance, an imaginary regular cyclical variation with two peaks would reveal no differences between groups if analyzed in four equal categories. Several studies are based on reports of perceived worsening of symptoms during specific phases in the menstrual cycle, which introduce a possibility for differential reporting bias.

The course and timing of menstruation is steered through a complex endocrine interplay between hormones. The observed patterns in our study are most likely a result of such complex hormonal processes, and it does not seem plausible that one sex hormone should explain the variation in respiratory symptoms during the menstrual cycle. Both direct effects of sex steroid hormones on the airways and indirect effects of sex hormones for instance on inflammatory processes might influence respiratory symptoms, as might various other endocrine and paracrine hormones directly or indirectly involved in regulation of the menstrual cycle. Estrogens are known to have receptors in lung tissue (37), whereas progesterone acts centrally as well through an estrogen (E2)-dependent progesterone receptor-mediated mechanism to stimulate respiration (38, 39). Cyclical changes in respiratory symptoms could further be mediated through insulin resistance and inflammation, because insulin resistance (27) and C-reactive protein (24) have been shown to vary with the menstrual cycle. A role for such mechanisms is supported by our finding of differences in cyclical patterns according to BMI. Angiogenesis in the lung is another factor changing with the menstrual cycle (40) that might be suspected to contribute to cyclical patterns in respiratory symptoms. Considering the antiestrogenic effects of smoking, differences in menstrual cycle patterns of airways symptoms by smoking status, as demonstrated in the present study, seem plausible. However, the differences between observed patterns in smokers and nonsmokers cannot easily be attributed to one hormone.

The observed differences in cyclical patterns for wheeze, waking with shortness of breath, and waking with cough might reflect slight differences in underlying physiologic aspects. Wheeze and shortness of breath showed relatively similar patterns. The relative magnitude of the cyclical variation was considerably larger for shortness of breath, with amplitude as large as the mean incidence. In all subgroups, shortness of breath incidence was strikingly low in the late luteal phase, the time when progesterone peaks. The dip in incidence of wheeze on Days 14–16 coincides with putative ovulation and peaks in estrogen, LH, and FSH. Cough showed distinct and more complicated patterns as compared with wheeze and shortness of breath, which seems plausible given the broader range of triggering factors, also including upper airways and remote triggers.

Presence of airways symptoms in subjects without a doctor's diagnosis of asthma is well known and not fully understood. Unrecognized asthma and other diseases are likely to account for a considerable proportion of these symptoms. However, one may speculate whether experiencing some degree of respiratory symptoms at specific times during the menstrual cycle possibly could be physiologic.

The use of chronobiologic methodology is novel in this setting and an important strength of the present analysis. Day in cycle was calculated from day of last menses onset for each woman, and analyses were based on all days of the menstrual cycle rather than specific subsections. This methodology is sensitive for detecting variations in respiratory symptoms continuously over the menstrual cycle that could otherwise be hidden if analyzing predefined subspans. Another strength of our study derives from the questionnaire recording symptoms over the immediate last 3 days in one section, and the date of last menses onset in another section. Thus, no bias was introduced by asking women to relate respiratory symptoms to specific parts of their menstrual cycle. Furthermore, basing analyses on general population samples from several countries allows for generalization of results to a broad population. The large sample size made relevant subgroup analyses possible.

A weakness of our study is the reliance on questionnaire data for assessment of the day in the menstrual cycle. The later in the cycle since the previous menses, the less accurate the date of its onset might be remembered. However, this phenomenon should introduce a nondifferential bias and therefore attenuate our results and not strengthen them. Another difficulty in placing a woman accurately in her cycle is the finding that, among women reporting regular cycles, during 1 year approximately 20% have at least one cycle shorter than 21 days and 30% have one or more cycles longer than 35 days (41). This should also introduce a nondifferential bias and dilute associations. These sources of nondifferential error suggest that the actual menstrual cycle variation in respiratory symptoms may be very large.

Conclusions

Respiratory symptoms varied significantly during the menstrual cycle and the rhythmic oscillations were large and consistent. This was found in a cohort of almost 4,000 women analyzed with chronobiologic methodology without predefined cut-points, and based on independently reported symptoms and day of menstrual cycle, rather than perceived associations during cycle subspans. Cyclicity in respiratory symptoms was present also in the population without diagnosed asthma. Patterns varied between subgroups, thus modifying factors need to be considered in menstrual cycle variations in respiratory health. Differences according to BMI contribute to the evidence of metabolic-hormonal interplay in respiratory health. The findings suggest substantial hormonal influences in interplay with metabolic factors on airways physiology and on pathophysiologic processes in such respiratory diseases as asthma.

Pronounced cyclical variations among people with asthma but differences in patterns according to various characteristics suggest that adjustment of asthma medication to the menstrual cycle may prove feasible and efficient, but must be adapted on an individual basis. We recommend that physicians advise women with asthma to record their disease activity during several

menstrual cycles (e.g., with the asthma control test or a peak flow meter) and attempt to adapt asthma medication according to individual pattern in symptoms. Adjustment of asthma medication to the menstrual cycle may potentially improve the efficacy of asthma treatment and reduce disability and health costs related to asthma in women.

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