ORIGINAL INVESTIGATION

Seasonal Variation in Serum Cholesterol Levels

Treatment Implications and Possible Mechanisms

Ira S. Ockene, MD; David E. Chiriboga, MD, MPH; Edward J. Stanek III, PhD; Morton G. Harmatz, PhD; Robert Nicolosi, PhD; Gordon Saperia, MD; Arnold D. Well, PhD; Patty Freedson, PhD; Philip A. Merriam, MSPH; George Reed, PhD; Yunsheng Ma, PhD, MPH; Charles E. Matthews, PhD; James R. Hebert, ScD

Background: A variety of studies have noted seasonal variation in blood lipid levels. Although the mechanism for this phenomenon is not clear, such variation could result in larger numbers of people being diagnosed as having hypercholesterolemia during the winter.

Methods: We conducted a longitudinal study of seasonal variation in lipid levels in 517 healthy volunteers from a health maintenance organization serving central Massachusetts. Data collected during a 12-month period for each individual included baseline demographics and quarterly anthropometric, blood lipid, dietary, physical activity, light exposure, and behavioral information. Data were analyzed using sinusoidal regression modeling techniques.

Results: The average total cholesterol level was 222 mg/dL (5.75 mmol/L) in men and 213 mg/dL (5.52 mmol/L) in women. Amplitude of seasonal variation was 3.9 mg/dL (0.10 mmol/L) in men, with a peak in December, and 5.4 mg/dL (0.14 mmol/L) in women, with a peak in January. Seasonal amplitude was greater in hypercholesterolemic participants. Seasonal changes in plasma volume explained a substantial proportion of the observed variation. Overall, 22% more participants had total cholesterol levels of 240 mg/dL or greater (≥6.22 mmol/L) in the winter than in the summer.

Conclusions: This study confirms seasonal variation in blood lipid levels and suggests greater amplitude in seasonal variability in women and hypercholesterolemic individuals, with changes in plasma volume accounting for much of the variation. A relative plasma hypervolemia during the summer seems to be linked to increases in temperature and/or physical activity. These findings have implications for lipid screening guidelines. Further research is needed to better understand the effects of a relative winter hemoconcentration.

Arch Intern Med. 2004;164:863-870

SMALL LONGITUDINAL AND larger cross-sectional studies[1-6] suggest that cholesterol levels are higher in the fall and winter than in the spring and summer. Studies[7] reporting the most striking effects suggest that in areas of extreme seasonal climatic variation, such as Finland, there may be as much as a 100-mg/dL (2.59-mmol/L) seasonal variation in serum cholesterol levels. A longitudinal study[8] of plasma lipid levels in the United States reported a mean seasonal change in plasma total cholesterol concentration of 7.4 mg/dL (0.19 mmol/L). However, the study was restricted to hyperlipidemic men. A cross-sectional study[6] of seasonal variation in plasma lipid levels, using the US National Cholesterol Education Program guidelines for hyperlipidemia of 240 mg/dL or greater (≥6.22 mmol/L), reported that 25.4% of men were at or above this level in the winter, whereas only 13.5% met this cutoff point in the summer.

Despite accumulating evidence of seasonal variation in blood lipid levels, such variation is not considered in the National Cholesterol Education Program guidelines.[9-11] Seasonal variation is also rarely taken into account in the clinical management of hyperlipidemia, although the seasonal differences described in the previous paragraph would result in large differentials in the frequency of patients being labeled as hypercholesterolemic at different times of the year. The described seasonal variation also would lead to a lower percentage of patients reaching goal cholesterol levels if treatment were initiated in the summer and repeated measurement carried out in the winter.

To resolve these issues, we conducted a longitudinal study of seasonal variation in lipid levels in healthy volunteers. We also measured all of the factors thought likely to be related to such variation.

Author affiliations are given at the end of the article. The authors have no relevant financial interest in this article.

METHODS

PARTICIPANTS

Participants in the SEASONS (Seasonal Variation in Blood Lipids) Study, described in detail elsewhere,[12] were recruited primarily from the Fallon Healthcare System, a health maintenance organization serving central Massachusetts. Additional individuals of Hispanic descent residing in Worcester County, Massachusetts, were recruited in an attempt to increase the diversity of the study population. Individuals who were residents of Worcester County, who were aged 20 to 70 years, and who had telephone service were eligible to participate in the study. Eligible individuals were not taking cholesterol-lowering medications and were not actively participating in lipid-lowering or weight-control diets, did not have possible causes of secondary hyperlipidemia, and were free of chronic life-threatening illness. Participants were recruited between December 1, 1994, and February 28, 1997, and enrollment occurred throughout the calendar year. The institutional review boards of the Fallon Healthcare System and the University of Massachusetts Medical School approved all participant recruitment and data collection procedures. Each participant signed an approved informed consent form before entering the study.

PROCEDURES

Demographic data and health information were collected by self-administered questionnaire. Meteorologic data were obtained from the National Weather Service. Anthropometric data, including weight, height, and waist and hip circumferences, and fasting blood lipid values were assessed at baseline and then every 3 months, within a 3-week window on either side of the individual's quarterly appointment date, to the 1-year anniversary point (a total of 5 assessments).

Telephone-administered 24-hour recalls were used as the dietary assessment method, with interviews conducted every 3 months. At each quarterly data collection point, three 24-hour recalls were conducted on randomly selected days (including 2 weekdays and 1 weekend day). These recalls included the collection of physical activity and light-exposure data. All dietary data for the 24-hour recalls were entered into and analyzed using nutrient calculation software (Nutrition Data System NDS DOS versions 2.6 to 2.9; Nutrition Coordinating Center, University of Minnesota, St Paul).[13]

Estimates of physical activity energy expenditure (metabolic equivalent [MET] hours per day) were calculated from the 24-hour recalls for household, occupational, and leisure activities using methods described by Ainsworth and colleagues.[14] One MET hour per day is approximately equivalent to 1 kcal/kg per day. The validity of this method has been evaluated using the Baecke Physical Activity Questionnaire and whole-body accelerometers, and it has been found to be comparable to these standard methods.[15,16]

Light exposure was determined by having participants recall information about outdoor and indoor exposure to natural and artificial lighting. The validity of the light-exposure questionnaire was confirmed in a group of volunteers by comparing the 24-hour recall estimates with those obtained from a subset of 80 participants who wore a light-recording device (Actillume; Ambulatory Monitoring Inc, Ardsley, NY) for the week before the 24-hour recalls.[16]

STATISTICAL ANALYSIS

Analyses of cross-sectional and longitudinal data were conducted. Cross-sectional comparisons of baseline response by sex were made using 2-sample *t* tests (for continuous variables) and χ^2 tests (for categorical variables). Longitudinal data were analyzed using mixed models (SAS Proc Mixed; SAS Institute Inc, Cary, NC) with restricted maximum likelihood methods.[17] The primary outcome variables for the longitudinal analyses were the blood lipid measures.

Two methods were used to evaluate seasonal effects in the mixed models. First, the date the blood sample was obtained was used to classify each lipid measure into a season of the year, using the "light season definition," centered at the equinoxes, to maximize variation in light exposure (winter: November 6 to February 4; spring: February 5 to May 6; summer: May 7 to August 5; and fall: August 6 to November 5). Season was used as a fixed effect in the mixed-model analyses, and estimates of change in cholesterol concentration between seasons were constructed. Second, the date the blood sample was obtained was used to define sine and cosine coefficients for a sine-shaped seasonal model that assumed a period of 365 days.[18] Estimates of fixed-effect regression coefficients for the sine and cosine terms in the mixed model were transformed to estimate the amplitude and phase of the seasonal effects. A first-order Taylor series expansion was used to construct estimates of the variance of the amplitude and phase from the variance estimates of the sine and cosine coefficients (for additional information, see http://www-unix.oit.umass.edu/~seasons/se35.pdf).

Sex-specific mixed models were fit solely with seasonal effects, using participants as random effects. Subsequent models were fit that controlled for various time-dependent covariates separately, including body mass index (calculated as weight in kilograms divided by the square of height in meters), percentage of calories from saturated fat, physical activity (total and leisure), total light exposure, hemoglobin level, relative plasma volume[19] (calculated from a participant-specific mean hemoglobin value, assuming that the hemoglobin level remains constant during the year in healthy individuals), and age. We evaluated the impact of including the covariates by assessing the extent to which the estimated amplitude of the seasonal effect changed when the covariates were considered; percentage change in seasonal amplitude was used for this purpose and was obtained by comparing amplitude from the model with covariates with that of the model without covariates. Similar analyses also were conducted for participants in the upper or lower quartile distribution of blood lipid levels.

Before blood samples were obtained from participants in the SEASONS Study, up to three 24-hour recall measures were obtained of dietary intake, physical activity, and light exposure in each quarter. Because only 1 lipid measurement was made during the 3-month interval, we first estimated average covariate values for each participant during the interval. Rather than using simple 3-day averages as the estimates, we used best linear unbiased predictors from mixed models to estimate longer-term (28-day) average values,[20] assuming that the longer-term average covariate values had stronger relationships with lipids. Thus, the best linear unbiased predictor estimates of dietary intake, physical activity, and light exposure were used in analyses of lipid levels. Finally, the percentage of the study population, by sex, with total cholesterol levels of 240 mg/dL or greater (≥6.22 mmol/L) in winter and summer was obtained using the participant average at each season.

RESULTS

A total of 1254 (25%) of the 5000 individuals initially contacted by telephone met the study entry criteria and agreed to attend an initial clinic visit. Of these, 641 individuals attended the first visit and completed the baseline interview. Sixty-one individuals (10%) dropped out of the study after a single blood lipid measure, 39 (6%)

completed only 2 lipid measures, and 24 (4%) completed only 3 such measures. A participant was operationally defined as having completed the protocol if at least 4 of the potential 5 lipid measures were obtained. Using this definition, 517 individuals (81% of the enrolled population) completed the study. Comparison of these 517 participants with those who did not complete the study suggests that younger and nonwhite enrollees were more likely to drop out (data not shown). There were no statistically significant differences in occupation categories, formal education level, or current smoking status between the 2 groups.

The final analysis for this study used a subset of 476 study participants who had at least 4 quarterly cholesterol measures, of which at least 1 was obtained during the summer and at least 1 during the winter, using the light season definition.

Baseline data suggest that white, married, well-educated, and overweight people characterize the group as a whole (**Table 1**). Men had more years of formal education than women. Women were less likely to be overweight than men. More than 50% of the study participants worked in service industries or in white-collar occupations. Smokers composed approximately 16% of the study population, with no statistically significant sex differences.

The average total cholesterol level was 222 mg/dL (5.75 mmol/L) among men and 213 mg/dL (5.52 mmol/L) among women. Interassay and intra-assay coefficients of variation for total cholesterol were ±1.4% and ±1.5% and for low-density lipoprotein (LDL) cholesterol were ±1.7% and ±2.4%, respectively (in compliance with Centers for Disease Control and Prevention–accepted ranges). Unadjusted averages for each of the 4 light seasons, by sex, are given in **Table 2**. The results suggest that women are more likely to display seasonal variation in blood lipid levels than men. A winter-summer comparison indicated that in women, total, LDL, and high-density lipoprotein (HDL) cholesterol levels were statistically significantly higher in winter, whereas only HDL cholesterol levels showed a similar pattern in men.

Anthropometric and dietary data did not demonstrate statistically significant seasonal changes, whereas physical activity and light exposure did (Table 2). As a whole, the study group had a relatively low level of physical activity. Seasonal variation in physical activity was determined primarily by changes in nonoccupational (or leisure and household) activities in men and women. In men, there was a secondary peak in leisure activities during the winter, a finding described in previous work with these data.[21]

Hematologic data, particularly hemoglobin and relative plasma volume, showed statistically significant seasonal variation, suggesting a hemodilution effect during the summer and the converse during the winter. There was a positive correlation between relative blood volume and both physical activity and exposure to ambient temperature (data not shown).

Results of the sinusoidal regression analyses show that the mean seasonal amplitude for the total serum cholesterol level was 3.9 mg/dL (0.10 mmol/L) (95% confidence interval [CI], 1.2-6.6 mg/dL [0.03-0.17 mmol/L]), with a peak on December 5 (95% CI, ±41 days), in men and 5.4 mg/dL (0.14 mmol/L) (95% CI, 2.5-8.3 mg/dL [0.06-0.21 mmol/L]), with a peak on January 3 (95% CI, ±31 days), in women (**Table 3** and **Figure**). Seasonal amplitude seemed to be of greater magnitude among participants in the upper quartile of the total cholesterol distribution (6.0 mg/dL [0.16 mmol/L]; 95% CI, 1.3-10.7 mg/dL [0.03-0.28 mmol/L] for men and 12.0 mg/dL [0.31 mmol/L]; 95% CI, 5.6-18.4 mg/dL [0.14-0.48 mmol/L] for women), but it was not statistically significantly different from the group as a whole.

Seasonal variation in LDL cholesterol levels followed a pattern similar to that observed for total cholesterol in men and women but was of lower magnitude and was statistically significant only in women (Table 3). Likewise, HDL cholesterol levels peaked in the winter, and the amplitude was statistically significant in both sexes. Seasonal variation in triglyceride levels was also present, but the amplitude was statistically significant only in women, and the peak occurred during the fall.

Results of the regression analyses suggest that changes in plasma volume seem to explain a substantial proportion of the observed seasonal variation in total and LDL cholesterol levels. After controlling for relative plasma volume, the observed seasonal variation was no longer statistically significant, except for total serum cholesterol level in women. Amplitude of seasonal change in HDL cholesterol levels, however, did not seem to be as

Table 1. Baseline Characteristics of the Seasonal Study Cohort*

Characteristic	Men (n = 244)	Women (n = 232)	*P* Value
Age, mean (SD), y	50.0 (12.3)	48.2 (11.6)	.10
Ethnicity, No. (%)			.17
White	220 (91.3)	193 (85.8)	
Hispanic	11 (4.6)	17 (7.5)	
Other	10 (4.1)	15 (6.7)	
Education, No. (%)			.005
High school or less	58 (23.9)	87 (36.7)	
Post–high school	78 (32.1)	62 (26.8)	
Bachelor degree or more	107 (44.0)	82 (36.5)	
Occupational category, No. (%)			<.001
Unemployed/retired	42 (17.1)	63 (27.2)	
Blue-collar	46 (18.9)	21 (9.0)	
Service worker	58 (23.8)	70 (30.2)	
White-collar	98 (40.2)	78 (33.6)	
Marital status, No. (%)			.004
Married	204 (83.6)	169 (72.8)	
Not married	40 (16.4)	63 (27.2)	
Body mass index classification, No. (%)†			<.001
Normal weight (17.1-24.9)	63 (25.8)	107 (46.1)	
Overweight (25-29.9)	115 (47.1)	75 (32.3)	
Obese (≥30)	66 (27.1)	50 (21.6)	
Current smoker‡			.56
No	196 (82.7)	194 (84.7)	
Yes	41 (17.3)	35 (15.3)	

*Some of the categories do not sum to the total because of missing data.
†Calculated as weight in kilograms divided by the square of height in meters.
‡Do you smoke cigarettes now?

Table 2. Selected General Characteristics by Light Season and Sex*

	Men					Women				
	Winter	Spring	Summer	Fall	*P* Value	Winter	Spring	Summer	Fall	*P* Value
Serum lipid levels, mg/dL										
Total cholesterol	222.1 (2.62)	221.8 (2.63)	219.9 (2.62)	222.0 (2.63)	NS	217.5 (2.71)†	214.7 (2.72)	211.5 (2.71)	213.4 (2.72)	<.001
LDL cholesterol	146.2 (2.28)	147.1 (2.28)	146.0 (2.27)	147.5 (2.29)	NS	141.3 (2.40)†	139.0 (2.41)	137.0 (2.40)	138.2 (2.41)	<.001
HDL cholesterol	44.4 (0.65)†	42.9 (0.65)	43.2 (0.65)	42.1 (0.65)	<.001	53.0 (0.82)†	52.4 (0.82)	51.2 (0.82)	49.5 (0.82)	<.001
Triglycerides	169.5 (10.74)	167.0 (10.77)	166.4 (10.75)	170.2 (10.79)	NS	116.2 (5.14)	115.0 (5.17)	116.1 (5.14)	128.2 (5.17)	<.001
LDL-HDL ratio	3.47 (0.08)	3.61 (0.08)	3.53 (0.08)	3.68 (0.08)	<.001	2.82 (0.07)	2.79 (0.07)	2.82 (0.07)	2.95 (0.07)	<.001
Anthropometric measures										
Body mass index‡	28.0 (0.29)	28.0 (0.29)	27.9 (0.29)	27.9 (0.29)	NS	26.82 (0.41)	26.82 (0.41)	26.77 (0.41)	26.69 (0.41)	NS
Waist circumference, cm	97.4 (0.74)	97.6 (0.74)	97.5 (0.74)	97.6 (0.74)	NS	81.74 (0.89)	81.79 (0.89)	81.94 (0.89)	81.94 (0.89)	NS
Hip circumference, cm	104.4 (0.53)	104.6 (0.53)	104.5 (0.53)	104.6 (0.53)	NS	104.27 (0.82)	104.33 (0.82)	104.20 (0.82)	104.37 (0.82)	NS
Waist-hip ratio	0.93 (0.003)	0.93 (0.003)	0.93 (0.003)	0.93 (0.003)	NS	0.78 (0.004)	0.78 (0.004)	0.78 (0.004)	0.78 (0.004)	NS
Dietary data§										
Total caloric intake, kcal/d	2255 (31.03)	2254 (31.03)	2255 (31.04)	2260 (31.04)	NS	1629 (21.33)	1619 (21.34)	1626 (21.34)	1623 (21.35)	NS
Calories from fat, %	31.89 (0.36)	31.92 (0.36)	31.92 (0.36)	31.91 (0.36)	NS	30.29 (0.29)	30.01 (0.29)	30.18 (0.29)	30.19 (0.29)	NS
Calories from saturated fat, %	11.53 (0.17)	11.49 (0.17)	11.48 (0.17)	11.47 (0.17)	NS	10.81 (0.15)‖	10.64 (0.15)	10.71 (0.15)	10.70 (0.15)	<.05
Physical activity and light-exposure data§										
Total MET h/d	12.69 (0.39)‖	12.53 (0.39)	12.87 (0.39)	12.82 (0.39)	<.001	9.88 (0.20)†	9.88 (0.20)	10.07 (0.20)	9.96 (0.20)	<.001
Leisure MET h/d	2.05 (0.10)†	2.09 (0.10)	2.18 (0.10)	2.16 (0.10)	<.001	1.48 (0.09)†	1.49 (0.09)	1.58 (0.09)	1.60 (0.09)	<.001
Occupational MET h/d	6.23 (0.38)	6.19 (0.38)	6.21 (0.38)	6.24 (0.38)	NS	3.34 (0.18)	3.39 (0.18)	3.32 (0.18)	3.35 (0.18)	NS
Household MET h/d	4.31 (0.18)‖	4.13 (0.18)	4.41 (0.18)	4.26 (0.18)	<.05	5.02 (0.14)†	4.98 (0.14)	5.09 (0.14)	4.98 (0.14)	<.001
Direct sunlight exposure, h/d	1.40 (0.09)†	1.39 (0.09)	2.52 (0.09)	2.23 (0.09)	<.001	0.67 (0.04)†	0.67 (0.04)	1.44 (0.04)	1.18 (0.04)	<.001
Hematologic data										
Hemoglobin, g/dL	15.1 (0.06)†	15.0 (0.06)	14.9 (0.06)	15.0 (0.06)	<.001	13.5 (0.06)†	13.4 (0.06)	13.3 (0.06)	13.4 (0.06)	<.001
Relative plasma volume, %	99.7 (0.14)	100.1 (0.14)	100.6 (0.14)	99.8 (0.14)	<.001	99.3 (0.17)†	100.4 (0.17)	100.7 (0.17)	100.0 (0.17)	<.001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent (1 MET h/d is roughly equivalent to 1 kcal/kg per day); NS, not significant.

SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Data are given as mean (SE).

†*P*<.001, winter-summer comparison.

‡Calculated as weight in kilograms divided by the square of height in meters.

§Data obtained from 24-hour recalls.

‖*P*<.05, winter-summer comparison.

affected by changes in plasma volume as was that of total and LDL cholesterol levels.

We observed that during the winter compared with the summer, there was a 7.0% relative increase in the number of men with cholesterol levels of 240 mg/dL or greater (≥6.22 mmol/L) (from 29.9% to 32.0%) (*P*=.42) and a 47.4% relative increase in women (from 19.0% to 28.0%) (*P*<.001) (**Table 4**). Overall, 22.2% more people had total cholesterol levels of 240 mg/dL or greater (≥6.22 mmol/L) in the winter than in the summer (*P*=.003). The corresponding values using LDL cholesterol levels of 160 mg/dL or greater (≥4.14 mmol/L) showed no increase during the winter compared with the summer in men and a 29.4% increase in women (from 22.4% to 29.0%).

COMMENT

These data demonstrate seasonal variation in blood lipid levels. The analysis of the longitudinal data fits a sinusoidal curve, with a peak in the winter and a trough in the summer. These findings are similar to those reported elsewhere in the literature,[2,5,6,8,22-29] although with lower seasonal amplitude. We also found the amplitude of seasonal variability to be greater in women than in men and in individuals in the upper quartile of the total cholesterol distribution vs those in lower quartile.

Previously, we observed seasonal variation in various covariates, including physical activity,[21] light exposure, saturated fat intake, and mood.[30] None of these covariates seemed to explain a substantial proportion of the observed seasonal variation in blood lipid levels.

After controlling for relative plasma volume, the amplitude of seasonal variation in blood lipid levels decreased statistically significantly, with a greater effect attributable to relative plasma volume in men. During the summer, the increase in environmental temperature or physical activity, or most likely a combination of the two, could be contributing to a hemodilution effect, with an accompanying apparent decrease in blood lipid levels. The underlying mechanism could be mobilization of fluid from the interstitial to the intravascular compartment due to heat acclimatization.[31-33] Plasma hypervolemia during physical training has been associated with 2 major factors: an elevation in renin activity and vasopressin lev-

Table 3. Summary of Sinusoidal Regression Analyses

	Men					Women				
	Amplitude of Seasonal Variation, Mean (95% CI), mg/dL	Change in Seasonal Amplitude, %	Peak Day	Trough Day	95% CI for Peak and Trough Days, d	Amplitude of Seasonal Variation, Mean (95% CI), mg/dL	Change in Seasonal Amplitude, %	Peak Day	Trough Day	95% CI for Peak and Trough Days, d
Total cholesterol, unadjusted model	3.90 (1.17 to 6.64)		December 5	June 5	± 41	5.39 (2.51 to 8.27)		January 3	July 5	± 31
Controlling for										
BMI	3.71 (1.00 to 6.43)	–4.8				5.13 (2.29 to 7.98)	–4.72			
Percentage of calories from saturated fat	4.49 (1.72 to 7.26)	15.0				4.88 (1.90 to 7.85)	–9.47			
Total MET h/d	4.48 (1.69 to 7.27)	14.8				4.52 (1.51 to 7.53)	–16.14			
Total direct sunlight exposure	4.00 (0.86 to 7.14)	2.5				4.32 (0.72 to 7.92)	–19.77			
Hemoglobin level	1.77 (–0.85 to 4.39)	–54.7				3.57 (0.75 to 6.40)	–33.65			
Relative plasma volume	1.35 (–1.27 to 3.96)	–65.5				3.87 (1.08 to 6.67)	–28.06			
Age	3.92 (1.18 to 6.65)	0.3				5.50 (2.62 to 8.38)	2.21			
LDL cholesterol, unadjusted model	1.40 (–1.16 to 3.97)		November 18	May 19	± 106	3.68 (1.10 to 6.25)		December 18	June 18	± 41
Controlling for										
BMI	1.38 (–1.20 to 3.97)	–1.4				3.52 (0.96 to 6.07)	–4.32			
Percentage of calories from saturated fat	1.18 (–1.43 to 3.80)	–15.7				3.46 (0.80 to 6.12)	–5.85			
Total MET h/d	1.20 (–1.43 to 3.84)	–14.4				3.13 (0.45 to 5.80)	–15.00			
Total direct sunlight exposure	1.36 (–1.60 to 4.33)	–2.9				2.35 (–0.41 to 5.12)	–35.98			
Hemoglobin level	0.68 (–1.83 to 3.18)	–51.7				2.27 (–0.29 to 4.83)	–38.34			
Relative plasma volume	0.75 (–1.71 to 3.21)	–46.7				2.48 (–0.06 to 5.01)	–32.68			
Age	1.42 (–1.14 to 3.99)	1.4				3.78 (1.20 to 6.35)	2.70			
HDL cholesterol, unadjusted model	1.55 (0.81 to 2.30)		January 26	July 28	± 28	3.76 (2.84 to 4.68)		February 17	August 20	± 14
Controlling for										
BMI	1.72 (0.98 to 2.47)	10.8				3.83 (2.91 to 4.76)	1.93			
Percentage of calories from saturated fat	1.58 (0.82 to 2.33)	1.4				3.56 (2.63 to 4.49)	–5.23			
Total MET h/d	1.62 (0.85 to 2.38)	3.9				3.59 (2.65 to 4.53)	–4.47			
Total direct sunlight exposure	2.23 (1.32 to 3.15)	43.7				4.13 (2.99 to 5.27)	10.01			
Hemoglobin level	1.47 (0.72 to 2.22)	–5.4				3.69 (2.76 to 4.62)	–1.74			
Relative plasma volume	1.39 (0.65 to 2.13)	–10.5				3.72 (2.80 to 4.64)	–0.93			
Age	1.56 (0.82 to 2.30)	0.1				3.76 (2.84 to 4.68)	0.08			
Triglycerides, unadjusted model	8.16 (–5.38 to 21.69)		November 15	May 16	± 96	10.51 (3.83 to 17.19)		September 7	March 8	± 37
Controlling for										
BMI	5.68 (–7.55 to 18.91)	–30.4				10.92 (4.27 to 17.56)	3.92			
Percentage of calories from saturated fat	16.79 (3.90 to 29.69)	105.9				10.40 (3.58 to 17.21)	–1.03			
Total MET h/d	17.06 (4.11 to 30.00)	109.1				10.30 (3.44 to 17.16)	–2.00			
Total direct sunlight exposure	13.54 (0.22 to 26.85)	66.0				8.70 (1.11 to 16.29)	–17.20			
Hemoglobin level	5.31 (–8.74 to 19.36)	–34.9				10.62 (3.91 to 17.32)	1.07			
Relative plasma volume	6.59 (–7.11 to 20.30)	–19.2				10.66 (4.04 to 17.28)	1.44			
Age	8.06 (–5.48 to 21.60)	–1.2				10.43 (3.75 to 17.11)	–0.75			

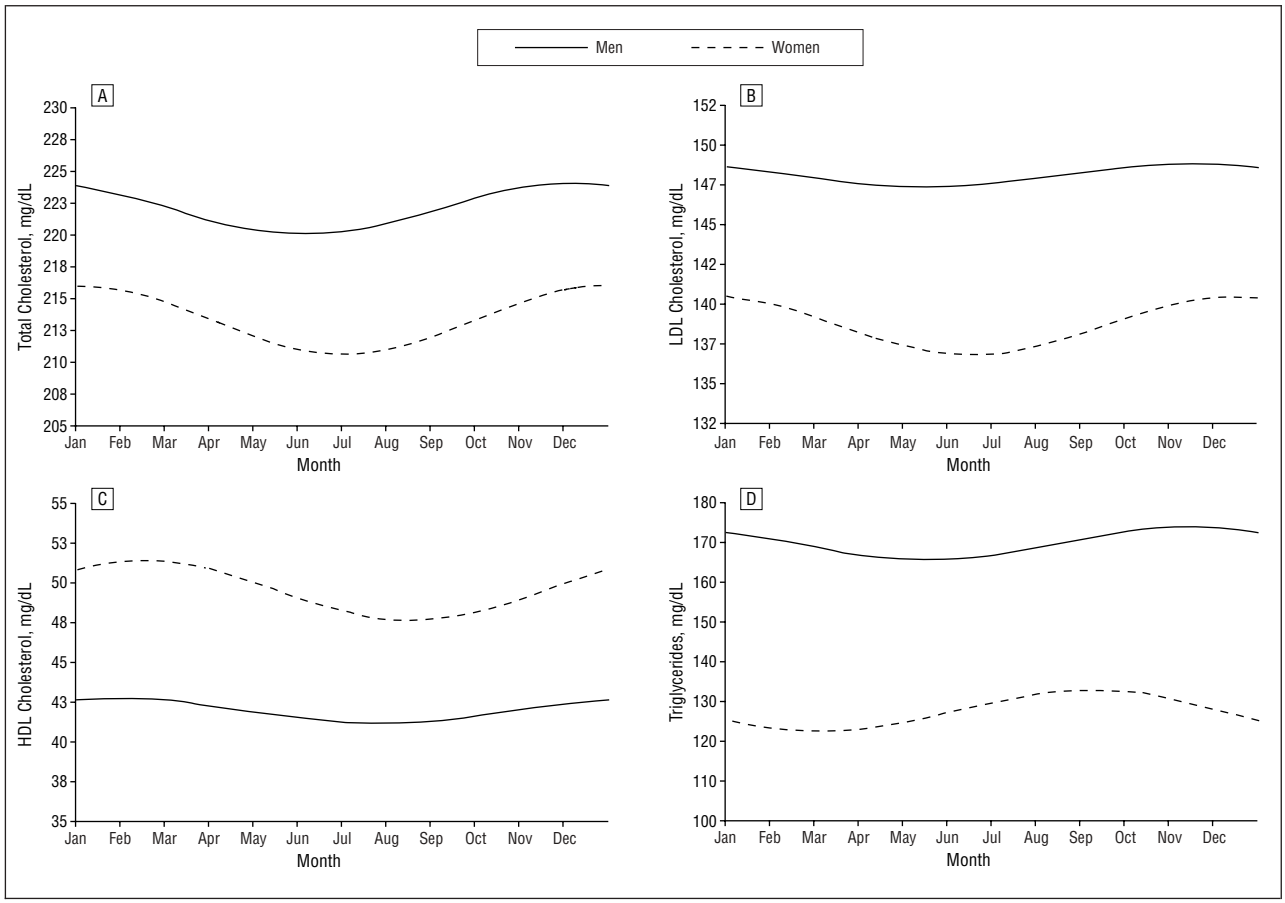
Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent.

els during exercise, which facilitates sodium and water retention, and a progressive, chronic increase in plasma albumin content, which provides increased blood-water binding capacity.[34-36] The fact that the HDL cholesterol concentration was not as affected by changes in plasma volume could be related to the complex interactions between seasonal changes in physical activity. Reductions in HDL cholesterol levels in the warmer months as a consequence of hypervolemia may have been counterbalanced by increased HDL cholesterol concentrations resulting from increased physical activity levels in the summer.

From the clinician's perspective, seasonal variation in blood lipid levels does occur, although such seasonality seems to be determined primarily by hemodilution in the summer and hemoconcentration in the winter. This leads to the following question: Is it the actual blood lipid concentration, at any given time, hemodilution or not, that is the most important factor in determining the rate of cholesterol deposition in the arteries, or is it the absolute amount of cholesterol carried in the blood that determines the pathophysiologic effects?[37]

If the former interpretation is correct, the measured cholesterol level does not require adjustment. However, patients whose lipid measures were considered borderline for therapy in the summer may require another measurement in the winter.

On the other hand, if the pathophysiologic effect is based on the absolute amount of cholesterol (ie, cholesterol concentration adjusted for the hemodilution effect), then there would be a bias toward inappropriately classifying individuals as hypercholesterolemic during the



Unadjusted seasonal variation in serum lipid levels by sex: total cholesterol (A), low-density lipoprotein (LDL) cholesterol (B), high-density lipoprotein (HDL) cholesterol (C), and triglycerides (D). To convert total, LDL, and HDL cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259; triglycerides from milligrams per deciliter to millimoles per liter, multiply by 0.0113.

Table 4. Misclassification of Total and LDL Cholesterol Levels in Summer vs Winter

	Participants, No.	Summer, %	Winter, %	Relative Difference, %	*P* Value*
Total cholesterol levels ≥240 mg/dL (≥6.22 mmol/L)					
All participants	476	24.58	30.04	22.21	.003
Men	232	29.9	32.0	7.0	.42
Women	244	19.0	28.0	47.4	<.001
LDL cholesterol levels ≥160 mg/dL (≥4.14 mmol/L)					
All participants	457	28.23	31.51	11.62	.06
Men	229	34.06	34.06	0.00	>.99
Women	228	22.37	28.95	29.41	.005

Abbreviation: LDL, low-density lipoprotein.
*McNemar test for the difference between summer and winter.

winter months.[6] The same would pertain to patients who initiate drug therapy during the winter.

The prevalence of hypercholesterolemia in the United States is approximately 29% of the adult population, or 52 million people.[38] Assuming an equal distribution of new diagnoses during the year, approximately 13 million people should be diagnosed as having hypercholesterolemia during the winter months. Our calculations suggest that during the winter months there may be an excess of 22% of individuals diagnosed as having hypercholesterolemia. This figure would translate into approximately 2.86 million people potentially being labeled as hypercholesterolemic, mainly because of relative winter hemoconcentration, and into 800 000 people likely being treated for hypercholesterolemia (≈$840 million in drug treatment alone [≈$1050/y per person], as calculated from average wholesale prices for statins[39]) as a result of misclassification of cholesterol status due to seasonal variation.

More patients are probably diagnosed as having high blood lipid levels during the winter as related to the distribution of cardiac events during the calendar year, with more coronary events occurring during the winter months,[40] further increasing the diagnostic and treatment selection biases.

In this study, the greatest amplitude of seasonal change in blood lipid levels was observed in people in the upper quartile of the cholesterol distribution, particularly women. In this subgroup, another concern would be apparent treatment failure, evidenced when patients start treatment for hypercholesterolemia during the summer and are reevaluated during the winter, when hemoconcentration might be "artificially" increasing serum lipid levels. Using LDL cholesterol as the reference for treatment of hypercholesterolemia, as per the National Cholesterol Education Program–Adult Treatment Panel III guidelines,[11] decreases the level of misclassification because of the lower magnitude of order of LDL cholesterol compared with that of total cholesterol. This observation would further reinforce the need to focus on LDL cholesterol levels rather than on total cholesterol levels for treatment purposes.

The seasonal variability in blood lipid levels observed in this study is of lower magnitude than that reported previously in countries such as Finland.[7] However, it is also smaller than that reported in more recent studies in the United States.[6] Many factors might be playing a role in the observed decrease in the amplitude of the seasonality of blood lipid levels, including changes in food availability, light exposure, environmental temperature, and physical activity[41,42] that have occurred over time. These changes tend to blunt the usual human exposure to seasonal changes in environment, food supply, and physical activity.[43] It is also possible that the demanding nature of the study tended to bias our participants toward individuals who have lifestyles that are relatively more constant during the year. A third possibility could be that most studies on seasonal variation in cholesterol levels are based on a cross-sectional study design. Seasonal variation in relative plasma volume may provide a plausible explanation for seasonal differences in cardiac events.[44-46] The clinical relevance of this finding is apparent, as may be an understanding of the mechanism of action. There are reports of statistically significant increases in fibrinogen levels and tissue plasminogen activator activity during the winter months,[47-49] which could be related to plasma volume contraction in response to cold exposure, determining a "clustering of peak values of haemostatic coronary risk factors."[50,51] During the summer months, however, the body would benefit from a relative hemodilution, explained in part by a complex interaction of exposure to increased temperature and physical activity, which would determine a "hypocoagulable state" as a result of relative hemodilution. At the same time, the relative decrease in winter cardiac deaths during the past several decades has been associated with the availability of central heating.[45] Therefore, seasonal changes in relative plasma volume presumably related to an interaction between exposure to increased temperature and physical activity could help explain seasonal differences in cardiac events. Changes in plasma volume may also represent another mechanism through which regular exercise exerts its cardioprotective effect.

In conclusion, this study demonstrates seasonal variation in blood lipid levels, with a peak in the winter and a trough in the summer. Our findings suggest that there is greater amplitude in seasonal variability in women and in people with hypercholesterolemia. However, changes in relative plasma volume seem to explain a substantial proportion of the observed seasonal difference in blood lipid levels. Changes in temperature and/or physical activity in winter and summer seem to be related to concomitant changes in relative plasma volume.

The information provided by this study could assist in the continuous development of guidelines for the treatment of hypercholesterolemia; however, we do not believe that season-specific guidelines would be justified. Further research is needed to better understand the mechanism through which physical activity and temperature control systems could aid in the prevention of coronary heart disease morbidity and mortality.

Accepted for publication May 30, 2003.

From the Division of Cardiovascular Medicine, Department of Medicine (Dr Ockene), the Preventive Medicine Program, Department of Family Medicine and Community Health (Dr Chiriboga), and the Division of Preventive and Behavioral Medicine, Department of Medicine (Mr Merriam and Drs Reed and Ma), University of Massachusetts Medical School, Worcester; the Departments of Biostatistics and Epidemiology (Dr Stanek) and Exercise Science (Dr Freedson), School of Public Health and Health Sciences, and the Department of Psychology (Drs Harmatz and Well), University of Massachusetts, Amherst; the Department of Health and Clinical Sciences, University of Massachusetts, Lowell (Dr Nicolosi); Division of Cardiovascular Medicine, St Vincent Hospital at Worcester Medical Center, Worcester (Dr Saperia); Vanderbilt Center for Health Services Research, Department of Medicine, Vanderbilt University, Nashville, Tenn (Dr Matthews); and the Department of Epidemiology and Biostatistics, Norman J. Arnold School of Public Health, University of South Carolina, Columbia (Dr Hebert).

The SEASONS Study was supported by grant R01-HL52745 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

We thank Laura Robidoux and Priscilla Cirillo, RN, for assisting with study recruitment and data collection; Kelly Scribner, BS, for coordinating the 24-hour recalls; SEASONS dietitians Susan Nelson, MS, RD, Christine Singelton, RD, Pat Jeans, RD, Karen Lafayette, RD, Deborah Lamb, RD, Stephanie Olson, RD, Eileen Capstraw, RD, and Barbara Olendzki, MPH, RD, for conducting the recalls; and Thomas Hurley, MS, for his organizational and data management expertise.

Corresponding author: Ira S. Ockene, MD, Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical Center, Worcester, MA 01655 (e-mail: Ira.Ockene@umassmed.edu).

REFERENCES

1. Thomas C, Holljes H, Eisenberg F. Observations on seasonal variations in total serum cholesterol level among healthy young prisoners. *Ann Intern Med.* 1961; 54:413-430.
2. Fyfe T, Dunnigan M, Hamilton E, Rae R. Seasonal variation in serum lipids, and incidence and mortality of ischaemic heart disease. *J Atheroscler Res.* 1968;8: 591-596.
3. Thelle D, Førde O, Try K, Lehmann E. The Tromsø Heart Study: methods and main results of the cross-sectional study. *Acta Med Scand.* 1976;200:107-118.

4. Buxtorf JC, Baudet MF, Martin C, Richard JL, Jacotot B. Seasonal variations of serum lipids and apoproteins. *Ann Nutr Metab.* 1988;32:68-74.
5. Cucu F, Purice S, Schioiu-Costache L, et al. Seasonal variations of serum cholesterol detected in the Bucharest Multifactorial Prevention Trial of Coronary Heart Disease: ten years follow-up (1971-1982). *Rom J Intern Med.* 1991;29:15-21.
6. Rastam L, Hannan PJ, Luepker RV, Mittelmark MB, Murray DM, Slater JS. Seasonal variation in plasma cholesterol distributions: implications for screening and referral. *Am J Prev Med.* 1992;8:360-366.
7. Keys A, Karvonen M, Fidanza F. Serum-cholesterol studies in Finland. *Lancet.* 1958;2:175-178.
8. Gordon D, Hyde J, Trost D, et al. Cyclic seasonal variation in plasma lipid and lipoprotein levels: the Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group. *J Clin Epidemiol.* 1988;41:679-689.
9. National Cholesterol Education Program. *Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.* Bethesda, Md: National Heart, Lung, and Blood Institute; 1988. NIH publication 88-2925.
10. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA.* 1993;269:3015-3023.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
12. Merriam P, Ockene I, Hebert J, Rosal M, Matthews C. Seasonal variation of blood cholesterol levels: study methodology. *J Biol Rhythms.* 1999;14:330-339.
13. Buzzard M, Price K, Warren R. Considerations for selecting nutrient-calculation software: evaluation of the nutrient database. *Am J Clin Nutr.* 1991;54:7-9.
14. Ainsworth B, Haskell W, Leon A, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;25:71-80.
15. Baecke J, Burema J, Frijters J. A short questionnaire for the measurement of habitual physical activity in epidmiological studies. *Am J Clin Nutr.* 1982;36:936-942.
16. Matthews C, Freedson P, Hebert J, Stanek E III, Merriam P, Ockene I. Comparing physical activity assessment methods in the Seasonal Variation of Blood Cholesterol Study. *Med Sci Sports Exerc.* 2000;32:976-984.
17. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS System for Mixed Models.* Cary, NC: SAS Institute Inc; 1996.
18. Koopmans LH. *The Spectral Analysis of Time Series.* New York, NY: Academic Press; 1974.
19. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol.* 1974;37:247-248.
20. Stanek EJ III, Well A, Ockene I. Why not routinely use best linear unbiased predictors (BLUPs) as estimates of cholesterol, per cent fat from kcal and physical activity? *Stat Med.* 1999;18:2943-2959.
21. Matthews C, Freedson P, Hebert J, et al. Seasonal variation in household, occupational, and leisure time physical activity: longitudinal analyses from the Seasonal Variation of Blood Cholesterol Study. *Am J Epidemiol.* 2001;153:172-183.
22. Robinson D, Bevan E, Hinohara S, Takahashi T. Seasonal variation in serum cholesterol levels: evidence from the UK and Japan. *Atherosclerosis.* 1992;95:15-24.
23. Bluher M, Hentschel B, Rassoul F, Richter V. Influence of dietary intake and physical activity on annual rhythm of human blood cholesterol concentrations. *Chronobiol Int.* 2001;18:541-557.
24. Gordon D, Trost D, Hyde J, et al. Seasonal cholesterol cycles: the Lipid Research Clinics Coronary Primary Prevention Trial placebo group. *Circulation.* 1987;76:1224-1231.
25. Forde OH, Thelle DS. The Tromso Heart Study: a multiple regression analysis of the relationship between coronary risk factors and some physical and social variables. *Scand J Soc Med.* 1980;8:49-54.
26. Fujimura A, Ohashi K, Ebihara A, Hirose T. Seasonal variation in serum total concentrations of cholesterol and protein in elderly subjects. *Clin Chim Acta.* 1992;212:85-87.
27. Warnick GR, Albers JJ. Physiological and analytical variation in cholesterol and triglycerides. *Lipids.* 1976;11:203-208.
28. Woodhouse PR, Khaw KT, Plummer M. Seasonal variation of serum lipids in an elderly population. *Age Ageing.* 1993;22:273-278.
29. Donahoo W, Jensen D, Shepard T, Eckel R. Seasonal variation in lipoprotein lipase and plasma lipids in physically active, normal weight humans. *J Clin Endocrinol Metab.* 2000;85:3065-3068.
30. Harmatz M, Well A, Overtree C, Kawamura K, Rosal M, Ockene I. Seasonal variation of depression and other moods: a longitudinal approach. *J Biol Rhythms.* 2000;15:344-350.
31. Kristal-Boneh E, Froom P, Harari G, Shapiro Y, Green M. Seasonal changes in red blood cell parameters. *Br J Haematol.* 1993;85:603-607.
32. Kristal-Boneh E, Harari G, Green MS. Circannual variations in blood cholesterol levels. *Chronobiol Int.* 1993;10:37-42.
33. Maw GJ, Mackenzie IL, Taylor NA. Can skin temperature manipulation, with minimal core temperature change, influence plasma volume in resting humans? *Eur J Appl Physiol.* 2000;81:159-162.
34. Convertino VA, Greenleaf JE, Bernauer EM. Role of thermal and exercise factors in the mechanism of hypervolemia. *J Appl Physiol.* 1980;48:657-664.
35. Convertino VA, Brock PJ, Keil LC, Bemauer EM, Greenleaf JE. Exercise training–induced hypervolemia: role of plasma albumin, renin, and vasopressin. *J Appl Physiol.* 1980;48:665-669.
36. Convertino VA. Fluid shifts and hydration state: effects of long-term exercise. *Can J Sport Sci.* 1987;12(suppl):136S-139S.
37. Cooper GR, Myers GL. Clinical issues in cholesterol testing. *J Med Assoc Ga.* 1991;80:301-303.
38. Sempos C, Cleeman J, Carroll M, et al. Prevalence of high blood cholesterol among US adults: an update based on guidelines from the second report of the National Cholesterol Education Program Adult Treatment Panel. *JAMA.* 1993;269:3009-3014.
39. Cardinale V, Chi J, eds. *Drug Topics Red Book.* Montvale, NJ: Medical Economics Co; 2001.
40. Enquselassie F, Dobson A, Alexander H, Steele P. Seasons, temperature and coronary disease. *Int J Epidemiol.* 1993;22:632-636.
41. Goran MI, Treuth MS. Energy expenditure, physical activity, and obesity in children. *Pediatr Clin North Am.* 2001;48:931-953.
42. Egger GJ, Vogels N, Westerterp KR. Estimating historical changes in physical activity levels. *Med J Aust.* 2001;175:635-636.
43. Yamada Y, Hirata H, Fujimura K, et al. Disappearance of differences in nutrient intake across two local cultures in Japan: a comparison between Tokyo and Kyoto. *Tohoku J Exp Med.* 1996;179:235-245.
44. Aylin P, Morris S, Wakefield J, Grossinho A, Jarup L, Elliott P. Temperature, housing, deprivation and their relationship to excess winter mortality in Great Britain, 1986-1996. *Int J Epidemiol.* 2001;30:1100-1108.
45. Seretakis D, Lagiou P, Lipworth L, Signorello L, Rothman K, Trichopoulos D. Changing seasonality of mortality from coronary heart disease. *JAMA.* 1997;278:1012-1014.
46. Lerchl A. Changes in the seasonality of mortality in Germany from 1946 to 1995: the role of temperature. *Int J Biometeorol.* 1998;42:84-88.
47. Ivanov J, Weisel R, Mickleborough L, Hilton J, McLaughlin P. Rewarming hypovolemia after aortocoronary bypass surgery. *Crit Care Med.* 1984;12:1049-1054.
48. Vogelaere P, Brasseur M, Quirion A, Leclercq R, Laurencelle L, Bekaert S. Hematological variations at rest and during maximal and submaximal exercise in a cold (0°C) environment. *Int J Biometeorol.* 1990;34:1-14.
49. Brock H, Rapf B, Necek S, et al. Comparison of postoperative volume therapy in heart surgery patients. *Anaesthesist.* 1995;44:486-492.
50. Mavri A, Guzic-Salobir B, Salobir-Pajnic B, Keber I, Stare J, Stegnar M. Seasonal variation of some metabolic and haemostatic risk factors in subjects with and without coronary artery disease. *Blood Coagul Fibrinolysis.* 2001;12:359-365.
51. van der Bom J, de Maat M, Bots M, Hofman A, Kluft C, Grobbee D. Seasonal variation in fibrinogen in the Rotterdam Study. *Thromb Haemost.* 1997;78:1059-1062.