Seasonal Variations of Selected Cardiovascular Risk Factors

Gregory S. Kelly, ND

Abstract

This article reviews research on selected biomarkers of cardiovascular risk – cholesterol and other lipids, C-reactive protein (CRP), fibrinogen, homocysteine – in the attempt to determine the existence of a predictable seasonal chronobiological pattern of variation. Studies dating as far back as the 1930s have reported seasonal variations in cholesterol levels. Statistically significant seasonal changes in lipid levels have been found in individuals irrespective of the country where the research has been conducted, and irrespective of the age, sex, ethnicity, and baseline lipid levels of the study subjects. While not all studies have been in complete agreement on either the amplitude (degree of seasonal change) or month/s of highest lipid levels, a strong winter/summer difference has been found in most studies. Existing evidence for an independent effect of season in variation of CRP is weak. Studies have consistently reported significant seasonal variations in fibrinogen levels. While other biological factors clearly interact to affect fibrinogen variability, seasonality appears to be an independent source of variability. Evidence from several studies points to a lack of seasonal variability in homocysteine levels. Although seasonal variability is just one source of periodicity influencing biological function and assessments in clinical practice, for some biomarkers, including lipids and fibrinogen, it is a source of variability that warrants consideration prior to a decision to treat and in assessing response to interventions.
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Introduction

This article reviews research on selected biomarkers of cardiovascular risk – cholesterol and other lipids, C-reactive protein (CRP), fibrinogen, homocysteine – in the attempt to determine a predictable seasonal chronobiological pattern of variation.

Many health professionals are unfamiliar with the science of chronobiology – the "scientific discipline concerned with the definition, mechanisms, and significance of the so-called time structure of life forms."[1] Unlike the concept of homeostasis, which presumes a relatively constant internal state, chronobiology presumes "human bioprocesses and functions exhibit predictable variability in time, biological rhythms, at every level of organization."[1]

From a medical assessment perspective, the implication of homeostasis is that the probability of a medical or functional health assessment revealing a value outside of a normal range is essentially equal at each hour of the day and night, day of the menstrual cycle, or month of the year. Research within the field of chronobiology challenges this implication and, for many commonly assessed biomarkers, has demonstrated predictable time-sensitive variability.

In many assessment areas, time-insensitive spot checks are interpreted by reference to a time-unqualified normal range. This is potentially problematic when a physiological or functional data point

Gregory Kelly, ND – Vice President of Research and Development and Chief Medical Officer for Health Coach® Systems International Inc.; contributing editor, *Alternative Medicine Review*; past instructor at the University of Bridgeport in the College of Naturopathic Medicine; published articles on various aspects of natural medicine and contributed three chapters to the *Textbook of Natural Medicine*, 2nd edition; teaches courses on weight management, the role of stress in health and disease, chronobiology of performance and health, and mind-body medicine.
E-mail: drgreg@healthcoach.com
Phone: 888-888-8565

being assessed has a known pattern of time-specific variation because a known source of variation is being ignored. This increases the likelihood that: (1) the initial assessment might be misinterpreted, possibly missing or making a diagnosis that would not have been missed or made had the assessment been done at a different time point; or (2) the success or failure of an intervention might be judged less accurately because of lack of knowledge of how the measured variable would have changed over the time period, independent of the intervention.

***Note: MESOR and Amplitude are standardized terms used for describing chronobiological patterns. These terms are defined as:**

AMPLITUDE. One-half of the extent of the change in height of a wave (the difference between the maximum height of the wave and the rhythm-adjusted mean (MESOR) of the wave form).

MESOR. Midline Estimating Statistic of Rhythm. The value midway between the highest and the lowest values of the (cosine) function best fitting to the data.

Cholesterol and Other Lipids

Studies dating from the 1930s report seasonal variations in cholesterol levels. Statistically significant seasonal changes in lipid levels have been found in individuals irrespective of the country where the research has been conducted, and irrespective of the age, sex, ethnicity, and baseline lipid levels of the study subjects. While not all studies have been in complete agreement on either the amplitude (degree of seasonal change) or month/s of highest lipid levels, a strong winter/summer difference has been found in most studies. Due to the number of studies on seasonal lipid variations, key findings of selected independent studies are described below.

Seasonal Lipid Levels (Group Trends)

Some studies investigating possible seasonal variation have looked exclusively at total cholesterol (TC) levels. Garde et al investigated seasonal cholesterol variations in 21 healthy females with an age range of 26-44 years in Copenhagen, Denmark. Total cholesterol was highest in January-March (208.5 mg/dL) and lowest in July-September (185.3 mg/dL). The difference between the three months with the highest and the lowest TC concentrations was 12 percent.[2]

Kristal-Boneh et al, in the Israeli CORDIS study, gathered cholesterol data on employees in 21 factories (3,726 men and 1,514 women) from 1985-1987. The highest levels of TC were found in spring and lowest in summer. They reported a TC mesor of 188.8 mg/dL, with an amplitude of 13.1 mg/dL, and a peak in mid-March for men ages 20-44 years. For men ages 45-64 years, the mesor was 218.8 mg/dL, with an amplitude of 10.8 mg/dL, and a peak in late March. In the female participants ages 20-44 years, mesor, amplitude, and peak of TC were 180.6 mg/dL, 7.5 mg/dL, and mid-March, respectively.[3]

Robinson et al performed time-series analyses on data from 140,000 men and 32,000 women in the United Kingdom, and 30,000 men and 12,000 women in Japan over periods ranging from 4.0-6.5 years. In both countries and in both genders, they observed 3-5 percent higher mean TC levels in winter than in summer.[4]

McDonough monitored 1,882 male and female subjects (age range 45-72 years) in Evans County, Georgia, between August 1960 and June 1962. Males had high values of TC in February-March, a decline to lowest values in June-July, with a rise to high values again in December-January. When stratified by race, African-American males appeared to have a greater degree of seasonal change than Caucasian males. Among the female participants, seasonal changes in TC had similar annual patterns, but were only considered to be of borderline statistical significance.[5]

In addition to studies focusing exclusively on TC, many studies have monitored seasonal changes of one or more parameters – LDL cholesterol, HDL

Table 1. Mean Seasonal Lipid Levels in 34 Nuns

	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
TC	215	191	196	183	185	190	210	186	175	210	198
LDL	149	120	127	109	113	124	141	112	105	132	130
HDL	56	56	58	61	61	58	58	59	56	56	54
TG	56	77	59	68	60	45	59	68	70	70	75

Note: Values are in mg/dL and have been rounded to nearest whole number.
Adapted From: Buxtorf JC, Baudet MF, Martin C, et al. Seasonal variations of serum lipids and apoproteins. *Ann Nutr Metab* 1988;32:68-74.

cholesterol, triglycerides (TG), and lipoprotein (a) (Lp[a]). Maes et al reported spring as the season of lowest lipid levels, compared with levels found in other seasons in the 26 healthy adults observed. Amplitude of the seasonal variations, expressed as a percentage of the mean, were 8.1 percent for TC, 12.1 percent for LDL cholesterol, and 7.3 percent for TG.[6]

Woodhouse et al gathered data on 47 elderly men and 49 elderly women from a single general practice in Cambridge, England, from January 1991 to February 1992. Peak TC and HDL cholesterol occurred in winter, while lowest values were found in the summer. Winter-summer seasonal difference for TC was 12.3 mg/dL; HDL cholesterol was 6.2 mg/dL higher in winter. LDL cholesterol was significantly higher in winter in men only (seasonal difference 10.4 mg/dL), while TG were significantly greater in late winter for women only (seasonal difference 19.5 mg/dL).[7]

Nazir et al sampled lipids in 11 males (ages 34-60 years) and 11 females (ages 25-42 years) once a month for one year. TC, LDL-, and HDL cholesterol exhibited significant reductions during the summer months, while TG showed a non-significant increase. While the group as a whole evidenced significant seasonal variation (with the exception of TG), different subjects attained maximum and minimum values in virtually every month of the year.[8]

Sharar et al found significant winter-summer differences for all lipid parameters in 94 male industrial employees who were screened twice in one year. From summer to winter the mean values of TC increased from 200.8 mg/dL to 208.6 mg/dL, LDL cholesterol increased from 125.2 mg/dL to 134.9 mg/dL, and HDL cholesterol increased from 42.7 mg/dL to 44.3 mg/dL. TG levels decreased from summer to winter from 174 mg/dL to 145 mg/dL.[9]

Frohlich et al found significant seasonal lipid patterns in eight males and eight females ages 20-41 years. LDL cholesterol peaked in January (127 mg/dL) and was lowest in July (116 mg/dL). They observed an inverse pattern of HDL cholesterol, with a peak value in August (60 mg/dL) and the lowest value in February (50 mg/dL). TG were highest in September and lowest in April.[10]

Buxtorf et al monitored cholesterol levels each month for one year in 34 healthy nuns (ages 25-75 years) living in a monastery in France. Substantial monthly lipid variations were observed. For the group as a whole, the highest TC was in November (214.9 mg/dL) and the lowest TC was in July (174.8 mg/dL). LDL cholesterol followed a similar winter-summer pattern with a November level of 149.1 mg/dL and a July level of 104.7 mg/dL. HDL cholesterol was highest in February-March (61.0 mg/dL) and reached its lowest level in September (53.8 mg/dL). TG levels were highest between June and December (in five of these six months ranging between 67.7-76.7 mg/dL) and were lowest during April (45.4 mg/dL).

Table 2. December 30th-June 30th TC Differences by Region from the Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group

	Minneapolis, MN	San Diego, CA	Seattle, WA
Total cholesterol	7.0 mg/dL	8.9 mg/dL	6.0 mg/dL

Adapted From: Gordon DJ, Hyde J, Trost DC, 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.

While these strong seasonal trends were evident in the group as a whole, there was not a smooth monthly transition. For example, while TC for the group tended to drop from November (highest) to July (lowest), before rising again in August and September, the drop was neither linear nor constant, fluctuating substantially month-to-month. In fact, the highest monthly TC levels other than November were found in May (210.4 mg/dL). Since the surrounding months were much lower (April – 190.2 mg/dL; June – 185.9 mg/dL), the reason for the mid-summer surge in this group is unclear. Table 1 illustrates the mean monthly lipid values for this group.[11]

The Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group was a U.S. multi-center trial of men, ages 35-59 years. Each subject's fasting cholesterol data was obtained at bimonthly intervals for 2.0-6.5 years. In order to investigate seasonal cholesterol levels, lipid measurements from the placebo group were analyzed. Highly significant sinusoidal seasonal cycles were found in all years of the study for TC, LDL-, and HDL cholesterol, with levels for the group peaking in the first month of winter and lowest levels occurring during summer months. An irregular, but statistically significant, seasonal pattern was also observed for plasma TG levels, with peak levels for the group occurring in the late summer through autumn and lowest levels during late spring. On average, TC was 7.6 mg/dL higher in December-January than in June-July (277.6 versus 270.0). Mean December 30th-June 30th TC differences were also relatively consistent, irrespective of the baseline TC level. Seasonal changes for men in the highest, middle, and lowest tertiles of TC were 7.6-, 6.7-, and 7.9 mg/dL, respectively. While the elevated winter TC was highly consistent within the cohort, not all participants had a winter peak. For the group as a whole the amplitude of total cholesterol was 3.7 mg/dL with a peak on December 30th. For LDL cholesterol, HDL cholesterol, and TG, amplitudes and peaks were 3.22 mg/dL (January 4th), 0.4 mg/dL (January 11th), and 1.82 mg/dL (October 16th), respectively.[12,13]

While a similar seasonal pattern was observed in the 12 Lipid Research Clinic centers, surprisingly, the largest seasonal changes were not observed in the locales with the largest seasonal changes in climate. The largest difference between winter-summer TC levels was observed in San Diego, CA. The mean TC changes per locale are noted in Table 2.[12,13]

Seasonal Variation in Blood Cholesterol Levels (SEASON) was a prospective study designed to systematically collect and analyze a number of important variables necessary to study the role of seasonality in blood lipids and relevant covariates. Participants (476 men and women) were recruited from central Massachusetts and ranged in age from 20 to 70 years. Fasting blood lipid values were assessed at baseline and then approximately every three months for one year. Samples were drawn to maximize variation in light exposure (winter – November 6th-February 4th; spring – February 5th-May 6th; summer – May 7th-August 5th; and fall – August 6th-November 5th).

In the SEASON study, the mean seasonal amplitude for TC was 3.9 mg/dL for men and reached its peak on December 5th. For women the mean TC

Table 3. Lipid Variations from the SEASON Study in Males

Serum lipid levels (mg/dL)	Winter	Spring	Summer	Fall	P Value
Total cholesterol	222.1	221.8	219.9	222.0	NS
LDL cholesterol	146.2	147.1	146.0	147.5	NS
HDL cholesterol	44.4	42.9	43.2	42.1	<0.001
Triglycerides	169.5	167.0	166.4	170.2	NS
LDL-HDL Ratio	3.47	3.61	3.53	3.68	<0.001

Adapted From: Ockene IS, Chiriboga DE, Stanek EJ 3rd, et al. Seasonal variation in serum cholesterol levels: treatment implications and possible mechanisms. *Arch Intern Med* 2004;164:863-870.

Table 4. Lipid Variations from the SEASON Study in Females

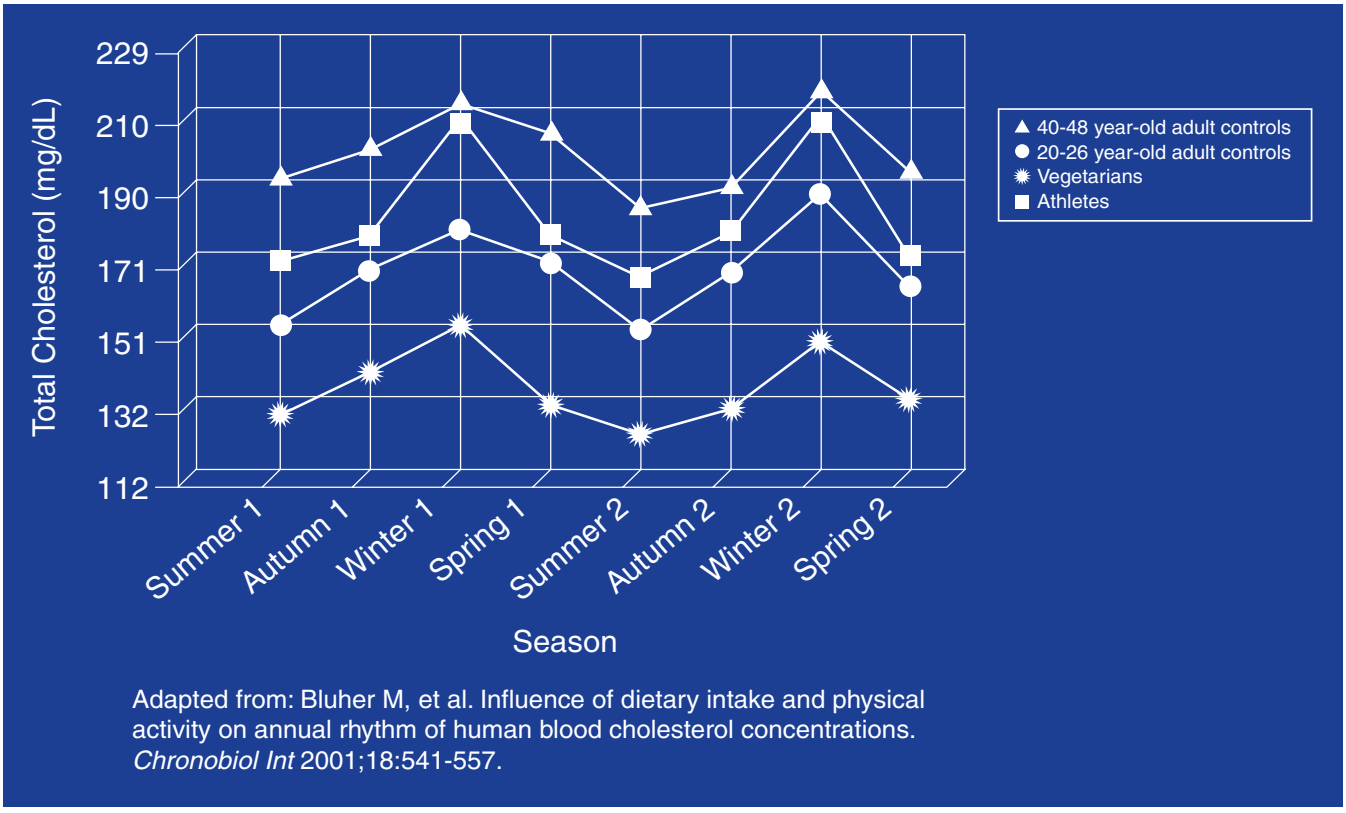
Serum lipid levels (mg/dL)	Winter	Spring	Summer	Fall	P Value
Total cholesterol	217.5	214.7	211.5	213.4	<0.001
LDL cholesterol	141.3	139.0	137.0	138.2	<0.001
HDL cholesterol	53.0	52.4	51.2	49.5	<0.001
Triglycerides	116.2	115.0	116.1	128.2	<0.001
LDL-HDL Ratio	2.82	2.79	2.82	2.95	<0.001

Adapted From: Ockene IS, Chiriboga DE, Stanek EJ 3rd, et al. Seasonal variation in serum cholesterol levels: treatment implications and possible mechanisms. *Arch Intern Med* 2004;164:863-870.

amplitude was 5.4 mg/dL with a January 3rd peak. Seasonal variation in LDL cholesterol followed a pattern similar to that observed for TC in men and women, but was of lower magnitude and statistically significant only in women. Likewise, HDL cholesterol levels peaked in the winter, with a statistically significant amplitude in both sexes. Seasonal variations in TG were present, but the amplitude was statistically significant only in women, and the peak occurred during the fall.[14] Tables 3 and 4 illustrate the lipid values in each season for males and females from the SEASON study.

Sasaki et al reported a statistically significant seasonality of HDL- and LDL cholesterol in Japanese males (age range 27-50; average 35). While changes in TC did not achieve statistical significance, HDL cholesterol was significantly higher in November and December (52 mg/dL) compared to June and September (46 mg/dL). Seasonal changes in LDL cholesterol also showed a significant seasonal pattern, with

Figure 1. Seasonal Pattern for Total Cholesterol Concentrations for Males



Adapted from: Bluher M, et al. Influence of dietary intake and physical activity on annual rhythm of human blood cholesterol concentrations. *Chronobiol Int* 2001;18:541-557.

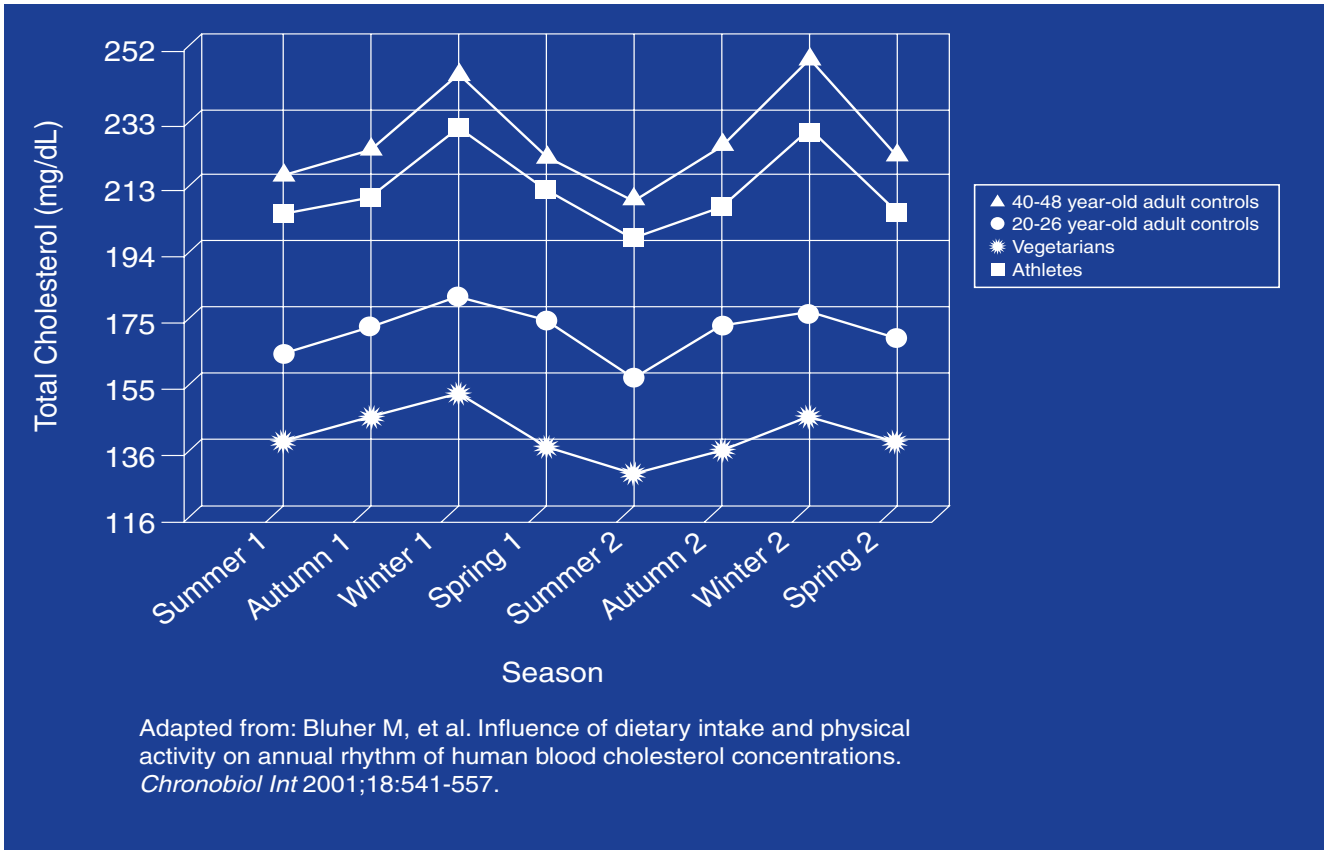
significantly higher levels in October than in April; a statistically significant seasonality of TG levels was not observed.[15]

Van Gent et al looked exclusively at HDL cholesterol levels in 1,000 residents of Leiden, Netherlands, ages 40-41 years. For the women in the study, the seasonal low point was in March (45.6 mg/dL) and the high point was in June (51.2 mg/dL). For the men, the low point was in April (39.6 mg/dL) and the high point was in June (44.4 mg/dL).[16]

Manttari et al found a significant seasonal difference over a five-year period in TC, with the lowest in August (268 mg/dL) and the highest in November (275 mg/dL), when looking at a subset of 142 dyslipidemic men ages 40-55 years, drawn from the placebo group of the Helsinki Heart Study. These researchers also noted a clear drop in HDL cholesterol in February in every year of the study, with February HDL cholesterol 4.5-percent lower than the mean of the other three sample periods (May, August, and November).[17]

In order to determine what effect diet and physical activity might have on seasonal variations in lipids, 19 vegetarians (nine males and 10 females) with a constant diet independent of the season, 14 athletes (nine males and five females) with almost constant physical activity over the year, and 114 male and female controls (ages 20-26 years and 40-48 years), were studied over a two-year period in Germany. Subjects were synchronized with respect to the sample times, duration of daylight, sleep-activity cycles, outside temperatures, and, for females, phase of the menstrual cycle. In all four groups, a seasonal rhythm of TC and HDL cholesterol concentrations was observed, which can be mathematically described by a sine curve with a maximum in winter and a minimum in summer. The seasonal rhythm in TC and HDL was independent of age, gender, body mass index, diet, or physical activity. The observed seasonal differences between the maximum and minimum were 5-10 percent for TC and 5-8 percent for HDL cholesterol (Figures 1 and 2).[18]

Figure 2. Seasonal Pattern for Total Cholesterol Concentrations for Females



Adapted from: Bluher M, et al. Influence of dietary intake and physical activity on annual rhythm of human blood cholesterol concentrations. *Chronobiol Int* 2001;18:541-557.

Seasonal Lipid Levels (Individual Trends)

A potential drawback of relying too heavily on group data is that, if select individuals demonstrate high or low lipid values in months that differ from the group average, these values would be averaged in, possibly dampening the group monthly and seasonal means. This could lead to an under- or over-estimation of the lipid variation across time that might be experienced by any single individual within the group. Since health practitioners work with individuals (rather than groups) when assessing and reassessing biomarkers, a clearer perspective in terms of what might possibly occur in a single individual might have value. Unfortunately, most of the available studies that assessed seasonal lipid variations did not report individual monthly or seasonal lipid levels.

One study, however, Thomas et al, did report monthly total cholesterol values for the group as well as for individuals (from November 1958-November 1959). Table 5 illustrates the monthly TC levels for each participant (ages 22-28 years) – prisoners in the Maryland State Penitentiary. For the group as a whole, there were significant differences in TC levels in December-January (247.6-252.5 mg/dL), compared to June-July (214.2-217.6 mg/dL).

As can be seen in Table 5, the seasonal change for the group significantly under- and over-estimates seasonal changes that would be found for any given individual during these same months. As an example, subject 1 had a TC of 180 mg/dL on Dec 23rd and 165 mg/dL on June 4th (15 mg/dL difference). Conversely, subject 14 had a Dec 23rd value of 325 mg/dL and a June 4th value of 263 mg/dL (difference of 52 mg/dL). As can also be seen from the table, while the group seasonal trend was strong, the

Table 5. Individual Monthly TC Levels (mg/dL) for 24 Males

	Nov	Dec 4	Dec 23	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
1	160	186	180	178	193	186	193	148	165	175	175	193	175	205
2	186	200	193	212	170	193	170	148	160	180	170	186	170	205
3	212	193	186	193	210	180	175	170	170	170	180	180	175	278
4	200	212	225	205	180	200	218	193	200	180	193	193	175	225
5	218	212	240	240	212	218	218	175	200	205	200	186	193	240
6	205	233	248	205	212	225	233	193	205	225	212	240	180	233
7	240	255	240	205	225	255	212	200	170	200	193	233	200	225
8	205	270	212	248	218	225	180	200	218	205	218	255	193	225
9	212	255	240	263	233	255	205	233	205	200	218	263	205	270
10	233	278	263	263	205	225	233	218	225	225	205	218	248	233
11	240	278	263	315	240	255	233	225	225	233	233	225	248	248
12	225	270	305	278	240	278	240	270	255	263	248	240	233	315
13	355	365	375	345	295	315	263	270	270	225	240	287	233	305
14	315	375	325	365	295	295	325	263	263	278	263	278	233	325
15	303	295	387	365	279	335	278	248	270	305	278	305	270	295
16	278	365	278	355	345	355	295	278	263	255	295	295	325	325
17	148	180	170	186	154	160	175	154	165	170		170	170	170
18	186	200	200	212	200	160	205	180	186	193		205	154	233
19	175	210	200	225	180	180	200		186	186		212	170	225
20	212	218	260	225	200	240	218	205	212	205		225	170	218
21	200	270	218	225	200	255		186	212	212	218	200	212	233
22	218	218	270	263	180	218	255	240	295	212		205	225	
23	233	255	225	225	248	255	255	233	233	240		255	225	263
24	255	233	240	263		278	263	240	270	200		225	240	278

Adapted From: Thomas CB, Holljes HW, Eisenberg FF. Observations on seasonal variations in total serum cholesterol level among healthy young prisoners. Ann Intern Med 1961;54:413-430.

month for individual high and low TC levels can vary, with lack of a smooth linear transition. Despite these inconsistencies, a clear trend for each individual to experience some degree of seasonal variation is evident when late-fall and winter months are compared to late-spring and summer months.[19]

Seasonal Lipids: Possible Consequences

What are the consequences of failing to factor seasonal cholesterol variations into initial assessments for hyperlipidemia? Based on 1992 U.S. National Cholesterol Education Program guidelines for hyperlipidemia of 240 mg/dL or greater, Rastam et al reported that 25.4 percent of men in the sample population were at or above this level in the winter, whereas only 13.5 percent fulfilled the definition of significant hyperlipidemia in the summer. In women, the age-adjusted prevalence of high cholesterol in November/December (20.8%) was not significantly different from July/August (19.5%).[20]

Harlap et al analyzed 5,244 middle-aged men and women in Jerusalem, Israel. HDL cholesterol and TG were highest in winter and lowest in summer. TC and LDL cholesterol followed a more complex wave form, with levels high in the winter, decreasing to a low in the summer, and increasing rapidly to a second peak in the autumn. Because of the strong seasonal patterns observed, there were two- to five-fold differences in the prevalence of hypercholesterolemia, hypertriglyceridemia, and high LDL cholesterol, depending on the season lipids were assessed.[21]

Woodhouse et al gathered data on 47 elderly men and 49 elderly women from a single general practice in Cambridge, England, from January 1991 to February 1992. The proportion of subjects with total cholesterol >251 mg/dL varied from 44 percent in winter to 32 percent in summer. Similarly, the percent with levels >301 mg/dL varied from nine percent in winter to five percent in summer.[7]

Ockene et al found 22-percent more participants had TC levels of 240 mg/dL or greater in winter than in summer. Using epidemiological data and a prevalence of hypercholesterolemia in the United States of approximately 29 percent of the adult population (52 million people), the authors calculated that, using a risk cut-off for TC of 240 mg/dL, during the winter months approximately 2.86 million people might be inappropriately labeled as potentially hypercholesterolemic because of the season lipids were assessed. They suggested 800,000 individuals would likely be treated for hypercholesterolemia, at a cost of $840 million in drug treatment alone (calculated from average wholesale prices for statins) because of potential misclassification of cholesterol status due to seasonal variation.[14] While this study did not explore the inverse, it is also possible that summer assessments might inappropriately misclassify some individuals as having cholesterol within a desirable range.

C-Reactive Protein

In comparison to TC and other lipids, relatively little research has been designed to determine whether a pattern of seasonal time-specific variation exists for C-reactive protein (CRP) levels. Existing evidence for an independent effect of seasonal variation in CRP levels is weak.

Woodhouse et al studied 96 men and women, ages 65-74 years. Blood levels of CRP were tested every two months for one year. A seasonal pattern of CRP was reported, with a significant increase from a low in late-summer months of approximately 2.4 mg/L to a late-winter high point of approximately 5.7 mg/L.[22]

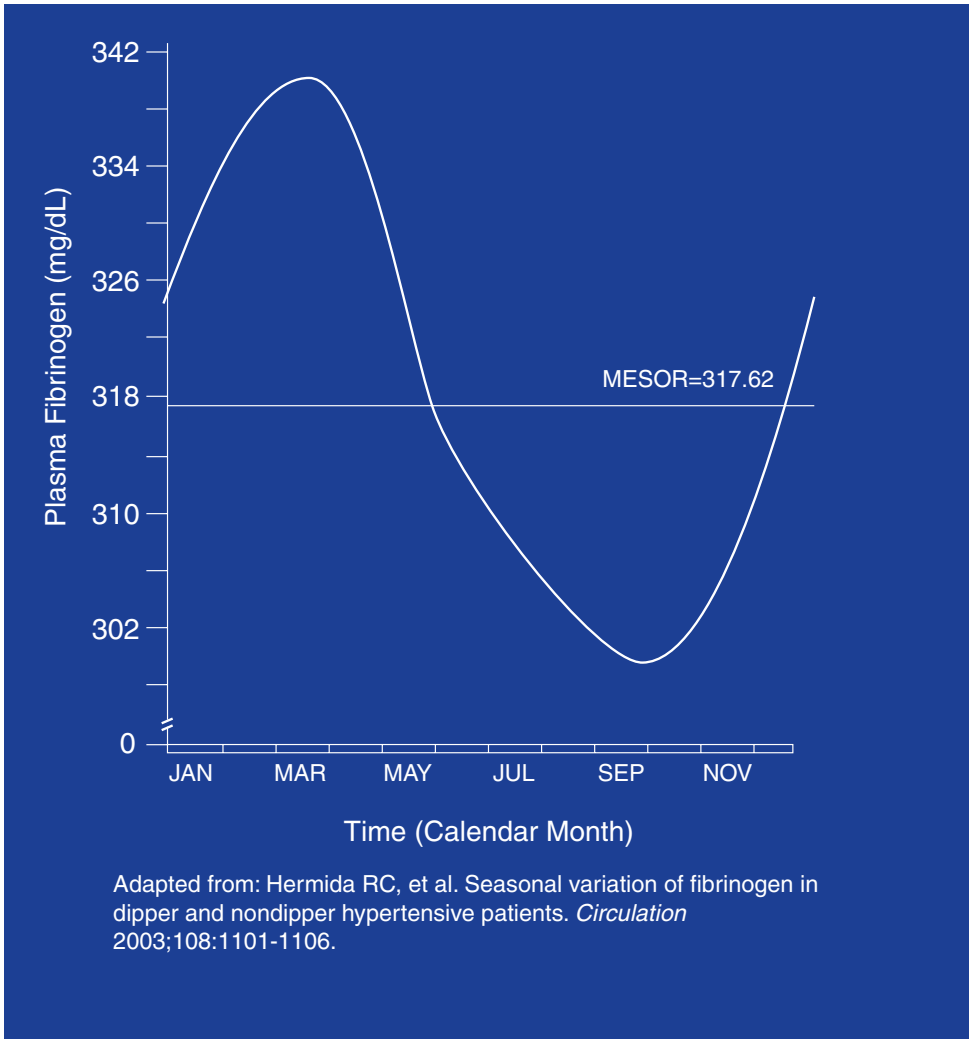
Crawford et al also sampled 24 elderly subjects (75+ years) monthly to determine whether CRP had any seasonal variation. They reported that CRP had a summer low point and reached a peak in late February. The mean summer-winter increase in the studied group was 3.71 mg/L.[23]

Horan et al investigated two populations: elderly subjects (mean age 79 years) and young adults (mean age 37 years). While the researchers observed a significant winter increase in CRP, especially in the elderly participants, this was largely (if not completely) explained by winter acute respiratory tract infections, which caused a substantial increase in CRP (370-percent increase in CRP secondary to acute infection in the elderly subjects). After multivariate analysis, season was not associated with increases in CRP.[24]

Frohlich et al analyzed data from 16 participants (eight women and eight men, ages 20-41 years) each month for one year. While a seasonal difference of 58 percent was observed, it was not statistically significant and the authors concluded there was no strong, consistent evidence for an intra-individual or inter-individual seasonal variation of CRP.[25]

Rogowski et al examined CRP for one year and found no seasonal variation in a group of 1,677 apparently healthy patients in whom the presence of infection or inflammation was excluded by a questionnaire.[26]

Figure 3. Seasonal Variation of Plasma Fibrinogen in Patients with Mild-to-Moderate Essential Hypertension



Adapted from: Hermida RC, et al. Seasonal variation of fibrinogen in dipper and nondipper hypertensive patients. *Circulation* 2003;108:1101-1106.

Fibrinogen

Studies have consistently reported significant seasonal variations in fibrinogen levels. While other biological factors clearly affect fibrinogen fluctuations, seasonality appears to be an independent source of fibrinogen variability.

Frohlich et al sampled fibrinogen from 16 healthy volunteers (eight men and eight women, ages 20-41 years) at monthly intervals for one year. A seasonal variation was found with a peak in the late winter and early spring. The seasonal change from low point in the summer to high point in early spring was 0.32 g/L.[10] Maes et al also found significant seasonal fibrinogen changes in healthy subjects. In their sample of 26 volunteers, fibrinogen values had an amplitude 28-percent higher than the mesor.[27] van der Bom et al analyzed fibrinogen data from a cohort of 2,325 participants of the Rotterdam Study and found fibrinogen levels were considerably higher in winter, with a seasonal difference of 0.34 g/L. In this study, the summer-winter increase was more pronounced in subjects over age 75 years (0.43 g/L) compared to subjects ages 55-75 years (0.29 g/L).[28]

Several other studies report similar seasonal changes in elderly subjects. In a study that compared fibrinogen levels during the coldest six months of the year with levels during the summer months in 100 subjects ages 75 and over, Stout et al reported 23-percent higher levels in the coldest six months compared with summer months.[29] In 24 subjects ages 75 and over, Crawford et al reported a mid-February peak that was 1.26 g/L greater than the values in the summer.[23] Crawford et al reported a different result in a one-year study of 54 healthy community-dwelling elderly (mean age 80.5 years) volunteers from the United Kingdom. Although a significant seasonal change was noted (0.15 g/L), the peak time shifted to May-June. The authors hypothesized that an atypically mild winter and hot summer might have been responsible for the shift in peak time of fibrinogen to late spring.[30] Woodhouse et al investigated seasonal fibrinogen changes in 96 men and women ages 65-74 years. The average winter-summer difference in fibrinogen level was 0.13 g/L.[22]

Table 6. Seasonal Variation in Plasma Total Homocysteine

	Spring	Summer	Fall	Winter
Plasma total Homocysteine, mmol/L (mean)	10.22	10.45	10.62	10.53
Plasma total Homocysteine, mmol/L (range)	6.52-20.44	6.87-20.49	6.52-20.46	5.87-22.79

Adapted From: McKinley MC, Strain JJ, McPartlin J, et al. Plasma homocysteine is not subject to seasonal variation. *Clin Chem* 2001;47:1430-1436.

Horan et al investigated two populations – elderly subjects (mean age 79 years) and young adults (mean age 37 years) to determine whether acute infections might be responsible for seasonal fibrinogen changes. While a significant increase in fibrinogen was observed subsequent to an acute respiratory tract infection, after multivariate analysis, season remained an independent factor affecting fibrinogen levels.[24]

In addition to the seasonal variability occurring in young and elderly subjects without existing cardiovascular disease, available evidence indicates a similar seasonal pattern in persons with existing cardiovascular disease. Hermida et al investigated seasonal fibrinogen levels among 1,006 subjects (482 men and 524 women; average age 53 years; range 19-87 years); participants were diagnosed with stage 1 or 2 essential hypertension. Fibrinogen had a mesor of 317.62 mg/dL and an amplitude of 20 mg/dL; peak values were observed for the group in February (Figure 3).[31]

In a study of 82 subjects (47 free of clinical signs of coronary artery disease and 35 survivors of acute myocardial infarction), Mavri et al determined fibrinogen twice in the cold months (December and March) and twice in the warm months (June and September). Significantly higher fibrinogen levels (3.50 versus 2.95 g/L) were observed in the cold months compared with the warm months.[32]

Homocysteine

Several studies have attempted to determine whether homocysteine has a significant seasonal variability. McKinley et al recruited staff and students at the University of Ulster, Northern Ireland. A total of 22 individuals (ages 23-55 years; mean age, 33.4 years) completed the longitudinal study; the group comprised eight males (mean age, 32.6 years) and 14 females (mean age, 33.9 years). Because of the role of certain vitamins in homocysteine metabolism, persons taking any supplements containing B vitamins or consuming fortified foods were excluded from participation. Fasting blood samples were taken at the end of each season: May (spring), August (summer), November (autumn), and February (winter). In this study, plasma total homocysteine concentrations showed no statistically significant variation (Table 6).[33]

Clarke et al investigated the seasonal variation in total homocysteine in a group of elderly subjects, ages 65-74 years, recruited from Cambridge, England. One hundred participants were assessed at two-month intervals for 14 months beginning in January 1991 and ending in February 1992; data on 96 were available for analysis. Although blood draws were non-fasting, all visits occurred at the same time of day and on the same day of the week, minimizing circadian and circaseptan (weekly) rhythm variations. Unlike the study by McKinley et al, this study did not exclude vitamin users or consumers of fortified foods. Plasma total homocysteine concentrations were relatively stable throughout the year, demonstrating little

seasonal variation. The median total homocysteine was 0.32 mMol/L – three-percent higher in summer compared with winter.[34]

Conclusions

In order for health professionals to take advantage of distinctions that exist within the field of chronobiology, an understanding of how biological rhythms influence assessments, interventions, and, ultimately, responses to treatment programs is necessary. In order to most accurately assess function and reassess improvement subsequent to an intervention, it is not always sufficient to accurately determine which assessments to monitor. It is also imperative to accurately determine when to conduct the assessment, taking into account the influence of biological time structure.

Quoting from a pioneer of chronobiology, Franz Halberg, when speaking about rhythms with a known variation of 24 hours, "It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M (MESOR, a rhythm-adjusted mean) as given for the three statuses in this patient, an estimate of A (circadian amplitude) itself, and finally an estimate of acrophase. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient."[35]

Without adequate knowledge of aspects of physiology that demonstrate periodic rhythms, it becomes difficult to quantify objectively "healthy" versus "unhealthy," and even more difficult to accurately assess whether an intervention moves a person in one direction or another, independent of the periodic rhythms.

In the cardiovascular biomarkers reviewed, the consistent and robust rhythms in lipids and fibrinogen suggest a true seasonal periodicity in many individuals. Total cholesterol, as well as values of other blood lipids and fibrinogen, in any given individual at any particular point in time, is the result of numerous interacting sources of variation (both technical and biological). Seasonal changes in lipid levels and fibrinogen appear to be a reasonably consistent source of biological variation.

Current evidence indicates CRP might have a seasonal trend in some groups of individuals (possibly the elderly); however, this apparent seasonal increase might be at least in part explained by a higher incidence of acute infections during winter months. Currently available evidence does not support the existence of significant seasonal variation in young adults. While existing evidence suggests homocysteine levels do not have a significant seasonal variation, ideally this will be confirmed in larger studies of different age groups and in different geographical locations.

Clinicians should take season into account when diagnosing hyperlipidemia (and possibly hypertriglyceridemia) and when evaluating apparent success or failure of lipid-lowering interventions; the same holds true for fibrinogen.

Although no time-dependent criteria, taking season into account, currently exists for diagnosing hyperlipidemia, hypertriglyceridemia, or high fibrinogen, it seems reasonable to factor into clinical decision making known sources of biological variation. At a minimum, use of information on seasonal variation should be used to assist with the clinical decision making process. If doubt exists, more than one time point of measurement (preferably coinciding with the time points where levels tend to be lowest and highest) might be a prudent starting point prior to making a clinical conclusion that an individual warrants or does not warrant treatment.

Given the strong seasonal rhythms of lipids and fibrinogen, treatment programs aimed at improving levels of these biomarkers are likely to be judged more or less efficacious than they are in reality, if timing of initial assessment and eventual reassessment does not factor in seasonality. As an example, a lipid-lowering therapy initiated in the summer, subsequent to an assessment revealing high lipids, would be expected to show lower benefit if reassessed in the late fall or winter. Conversely, a greater benefit might be mistakenly credited to a therapy begun in winter months and reassessed in late spring or summer. In many instances reassessment for these biomarkers occurs within 3-6 months after initiating a treatment program. This time interval might be too short to adequately judge effectiveness. While from a patient perspective it might not be as gratifying to

wait a full year (and delay knowledge of whether a treatment program is working or not), this might be required to adequately assess the degree of treatment success or failure.

Despite the longstanding evidence of statistically significant seasonal variation in blood lipid levels, this information has not been included in National Cholesterol Education Program guidelines or in trials designed to assess interventions for improving lipid levels. Studies to assess the risk of cardiovascular endpoints looking at lipid levels in different seasons of the year also have not been conducted. The existing assumption within medical science is that elevated cholesterol has an equal association with risk, independent of the season in which it was measured. Unfortunately, it is not currently known whether this assumption is accurate or not. Questions, such as whether a TC level of 250 mg/dL in the winter has the same risk association with cardiovascular endpoints as a similar value in the summer, have not been assessed in research studies. The optimal seasonal changes in lipid or fibrinogen levels are also unknown. Is there a degree of change that is protective or that amplifies risk? Is there a timing of when change occurs, (example: a drop from winter to summer as opposed to either no change or an increase from winter to summer) that has an association with risk reduction or increase? These questions have not been answered to date and warrant further investigation.

While seasonal variability is just one source of periodicity influencing biological function and assessments conducted in clinical practice, for some biomarkers, including lipids and fibrinogen, it is a source of variability that warrants consideration prior to a decision to treat and in assessing response to interventions.

References

1. Smolensky MH, D'Alonzo GE. Medical chronobiology: concepts and applications. *Am Rev Respir Dis* 1993;147:S2-S19.
2. Garde AH, Hansen AM, Skovgaard LT, Christensen JM. Seasonal and biological variation of blood concentrations of total cholesterol, dehydroepiandrosterone sulfate, hemoglobin A(1c), IgA, prolactin, and free testosterone in healthy women. *Clin Chem* 2000;46:551-559.
3. Kristal-Boneh E, Harari G, Green MS. Circannual variations in blood cholesterol levels. *Chronobiol Int* 1993;10:37-42.
4. Robinson D, Hinohara S, Bevan EA, Takahashi T. Seasonal variation in serum cholesterol levels in health screening populations from the U.K. and Japan. *J Med Syst* 1993;17:207-211.
5. McDonough JR, Hames CG. Influence of race, sex and occupation on seasonal changes in serum cholesterol. *Am J Epidemiol* 1967;85:356-364.
6. Maes M, Weeckx S, Wauters A, et al. Biological variability in serum vitamin E concentrations: relation to serum lipids. *Clin Chem* 1996;42:1824-1831.
7. Woodhouse PR, Khaw KT, Plummer M. Seasonal variation of serum lipids in an elderly population. *Age Ageing* 1993;22:273-278.
8. Nazir DJ, Roberts RS, Hill SA, McQueen MJ. Monthly intra-individual variation in lipids over a 1-year period in 22 normal subjects. *Clin Biochem* 1999;32:381-389.
9. Shahar DR, Froom P, Harari G, et al. Changes in dietary intake account for seasonal changes in cardiovascular disease risk factors. *Eur J Clin Nutr* 1999;53:395-400.
10. Frohlich M, Sund M, Russ S, et al. Seasonal variations of rheological and hemostatic parameters and acute-phase reactants in young, healthy subjects. *Arterioscler Thromb Vasc Biol* 1997;17:2692-2697.
11. Buxtorf JC, Baudet MF, Martin C, et al. Seasonal variations of serum lipids and apoproteins. *Ann Nutr Metab* 1988;32:68-74.
12. Gordon DJ, Hyde J, Trost DC, 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.
13. Gordon DJ, Trost DC, Hyde J, et al. Seasonal cholesterol cycles: the Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group. *Circulation* 1987;76:1224-1231.
14. Ockene IS, Chiriboga DE, Stanek EJ 3rd, et al. Seasonal variation in serum cholesterol levels: treatment implications and possible mechanisms. *Arch Intern Med* 2004;164:863-870.
15. Sasaki J, Kumagae G, Sata T, et al. Seasonal variation of serum high density lipoprotein cholesterol levels in men. *Atherosclerosis* 1983;48:167-172.
16. Van Gent CM, Van der Voort H, Hessel LW. High-density lipoprotein cholesterol, monthly variation and association with cardiovascular risk factors in 1000 forty-year-old Dutch citizens. *Clin Chim Acta* 1978;88:155-162.

17. Manttari M, Javela K, Koskinen P, et al. Seasonal variation in high density lipoprotein cholesterol. *Atherosclerosis* 1993;100:257-265.
18. 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.
19. Thomas CB, Holljes HW, Eisenberg FF. Observations on seasonal variations in total serum cholesterol level among healthy young prisoners. *Ann Intern Med* 1961;54:413-430.
20. Rastam L, Hannan PJ, Luepker RV, et al. Seasonal variation in plasma cholesterol distributions: implications for screening and referral. *Am J Prev Med* 1992;8:360-366.
21. Harlap S, Kark JD, Baras M, et al. Seasonal changes in plasma lipid and lipoprotein levels in Jerusalem. *Isr J Med Sci* 1982;18:1158-1165.
22. Woodhouse PR, Khaw KT, Plummer M, et al. Seasonal variation of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994;343:435-439.
23. Crawford VL, Sweeney O, Coyle PV, et al. The relationship between elevated fibrinogen and markers of infection: a comparison of seasonal cycles. *QJM* 2000;93:745-750.
24. Horan JT, Francis CW, Falsey AR, et al. Prothrombotic changes in hemostatic parameters and C-reactive protein in the elderly with winter acute respiratory tract infections. *Thromb Haemost* 2001;85:245-249.
25. Frohlich M, Sund M, Thorand B, et al. Lack of seasonal variation in C-reactive protein. *Clin Chem* 2002;48:575-577.
26. Rogowski O, Toker S, Shapira I, et al. Values of high-sensitivity C-reactive protein in each month of the year in apparently healthy individuals. *Am J Cardiol* 2005;95:152-155.
27. Maes M, Scharpe S, Cooreman W, et al. Components of biological, including seasonal, variation in hematological measurements and plasma fibrinogen concentrations in normal humans. *Experientia* 1995;51:141-149.
28. van der Bom JG, de Maat MP, Bots ML, et al. Seasonal variation in fibrinogen in the Rotterdam Study. *Thromb Haemost* 1997;78:1059-1062.
29. Stout RW, Crawford V. Seasonal variations in fibrinogen concentrations among elderly people. *Lancet* 1991;338:9-13.
30. Crawford VL, McNerlan SE, Stout RW. Seasonal changes in platelets, fibrinogen and factor VII in elderly people. *Age Ageing* 2003;32:661-665.
31. Hermida RC, Calvo C, Ayala DE, et al. Seasonal variation of fibrinogen in dipper and nondipper hypertensive patients. *Circulation* 2003;108:1101-1106.
32. Mavri A, Guzic-Salobir B, Salobir-Pajnic B, et al. Seasonal variation of some metabolic and haemostatic risk factors in subjects with and without coronary artery disease. *Blood Coagul Fibrinolysis* 2001;12:359-365.
33. McKinley MC, Strain JJ, McPartlin J, et al. Plasma homocysteine is not subject to seasonal variation. *Clin Chem* 2001;47:1430-1436.
34. Clarke R, Woodhouse P, Ulvik A, et al. Variability and determinants of total homocysteine concentrations in plasma in an elderly population. *Clin Chem* 1998;44:102-107.
35. Halberg F, Cornelissen G, Katinas G, et al. Transdisciplinary unifying implications of circadian findings in the 1950s. *J Circadian Rhythms* 2003;1:2.