Seasonal cholesterol cycles: the Lipid Research Clinics Coronary Primary Prevention Trial placebo group

DAVID J. GORDON, M.D., PH.D., DONALD C. TROST, M.D., JOHN HYDE, M.D., PH.D., FREDrick S. WHALEY, PH.D., PETER J. HANNAH, PH.D., DAVID R. JACOBS, JR., PH.D., and LARS-GORan EKELUND, M.D.

ABSTRACT  Seasonal variation of plasma cholesterol levels was studied in 1446 hypercholesterolemic 35- to 59-year-old male participants in the Lipid Research Clinics Coronary Primary Prevention Trial placebo group. Each man's serial cholesterol data, obtained at bimonthly intervals for 2.0 to 6.5 years, were analyzed as a separate periodic time series, and distributions of cycle zeniths and amplitudes were calculated. A highly significant ($\chi^2 = 706, 2$ degrees of freedom) seasonal effect, 7.4 mg/dl higher on December 30 than on June 30, was found. This effect was similar among the 12 LRC centers, including such disparate climates as those of Minneapolis and San Diego, and tended to be larger in the southern centers. Its magnitude was independent of baseline levels of plasma cholesterol and other baseline characteristics. Observed seasonal differences in weight and diet explained less than one-third of the seasonal variation in plasma cholesterol levels. Plasma low- and high-density lipoprotein cholesterol levels, analyzed similarly, also showed significant synchronous seasonal cycles. Plasma triglyceride levels showed a weaker irregular seasonal pattern, highest in midsummer and late autumn and lowest in spring. The etiologies and mechanisms for these seasonal patterns remain largely unknown.


CYCLIC SEASONAL VARIATION in circulating cholesterol levels has been studied in a variety of settings\textsuperscript{1–4} during the past 60 years and has intrigued biologists interested in the regulation of pathways of cholesterol metabolism as well as clinicians interested in recognizing and treating hypercholesterolemia. However, since none of these studies involved frequent (i.e., several per year) serial cholesterol determinations in an adequate stable cohort over at least two annual cycles, much ambiguity remains. Although these studies convey the overall impression that cholesterol levels are higher in winter than in summer, one critical reviewer found the evidence for this "common and strongly held belief" less than compelling.\textsuperscript{1}

The present report describes the cyclic seasonal variation of plasma lipid levels observed in the placebo cohort of the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT).\textsuperscript{5–7} This cohort of 1899 hypercholesterolemic 35- to 59-year-old men, initially free of symptomatic coronary heart disease, was maintained on a standard diet and examined bimonthly for 7 to 10 years. Because of its longitudinal design, the large number of participants, the number and frequency of lipid measurements obtained for each participant, and the uniformity of methods and laboratory performance standards among the 12 LRC centers, the LRC-CPPT offered a unique opportunity to study seasonal cycles in a variety of geographic settings. In addition, the bimonthly measurement of lipoprotein cholesterol levels and body weight and the semiannual assessment of diet provided an opportunity to address some components and correlates of these cycles.
Methods

Study design and participants. The LRC-CPPT was a randomized, multicenter, double-blind, placebo-controlled clinical trial, designed to test the hypothesis that lowering elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) would reduce the subsequent combined incidence rate of coronary heart disease death and nonfatal myocardial infarction. Its participants were 35- to 59-year-old male volunteers meeting the following entry criteria: (1) plasma total cholesterol of at least 265 mg/dl with LDL-C levels of 190 mg/dl or higher, (2) plasma triglyceride levels of 300 mg/dl or less, (3) no history of myocardial infarction, angina pectoris, congestive heart failure, or cancer, (4) absence of resting electrocardiographic evidence of coronary heart disease, and (5) no known condition that might limit participation or alter lipid metabolism.

Volunteers meeting the initial entry requirements were prescribed a moderate cholesterol-lowering diet, in which the ratio of polyunsaturated fat to saturated fat was targeted at 0.8 and the daily cholesterol intake at 400 mg. Men whose LDL-C level fell below 175 mg/dl at either of two subsequent monthly screening visits were ineligible for randomization. Three months after the initial dietary instruction, eligible volunteers were randomly assigned to receive either the bile acid sequestrant resin cholesterolamine (1907 men) or a placebo (1899 men). Both randomized cohorts received ongoing dietary counseling at their bimonthly LRC-CPPT visits. Overall adherence to the prescribed diet, as measured by semiannual one-day dietary recalls, was well maintained over the duration of the trial.

Although similar seasonal cholesterol changes were observed in CPPT participants receiving cholesterolamine and placebo, the present investigation was confined to the placebo cohort. We did not use data from the first 6 months of follow-up (to allow for adjustment to the diet) or from after 7 years of follow-up. We also excluded all data obtained subsequent to a diagnosis of myocardial infarction or cancer, conditions potentially affecting lipid levels. We included in our analyses only those participants with at least three serial cholesterol measurements in each of two or more calendar years and at least nine serial cholesterol measurements altogether within this 6.5 year time frame. Most of the 1446 qualifying participants far exceeded those minimal criteria; 56% had at least 36 (out of a maximum of 40) serial cholesterol measurements, and 84% had at least 30 such measurements. Restricting the analysis to participants completing 30 or more visits tended to amplify the seasonal effect slightly by reducing background noise but did not fundamentally change our findings.

Measurements. Plasma samples were obtained from fasting participants at each bimonthly visit. Plasma cholesterol and triglyceride levels were determined with identical methods at each of the 12 LRCs. Plasma high-density lipoprotein cholesterol (HDL-C) levels were determined in plasma samples from which apo-B-containing lipoproteins had been precipitated by addition of Mn-heparin. Plasma LDL-C levels were estimated by the method of Friedewald et al.

A rigorous laboratory standardization program was maintained throughout the study to ensure comparability among the centers. With every batch of study samples, duplicate cholesterol determinations were performed on frozen serum pools having cholesterol concentrations comparable to those prevailing in study participants, which were provided by the Centers for Disease Control as standards. Mean percent deviations from the standard cholesterol values for each LRC laboratory were calculated for each such serum pool in each of six 2 month segments of each calendar year (and for all pools and years combined). Mean percent deviations for all 12 LRC centers were computed, with each center weighted in proportion to its number of study participants.

Participants were weighed at each bimonthly visit. Body mass index was calculated by dividing weight (kg) by the square of height (m). Nutrient intakes were estimated from semiannual one-day dietary recalls. Habitual physical activity, cigarette smoking, and alcohol consumption were assessed by questionnaire at intake and updated annually.

Statistical procedures. To ensure that differences among men who were examined more often at one time of year than another could not be mistaken for true seasonal cyclicity of plasma cholesterol levels within individual study participants, we used a statistical procedure specifically designed to identify and characterize cyclic patterns and to factor out irrelevant, noncyclical fluctuations. For each study participant, we computed a separate four-parameter periodic time series regression model, containing an intercept and linear, sine, and cosine terms, which permitted each man's data to be represented by a sinusoidal curve with a 1 year cycle, superimposed on a linear increasing or decreasing trend. For the participant selected arbitrarily to illustrate this process in figure 1, the best fit was provided by a seasonal cycle reaching a peak level 25 mg/dl (twice its amplitude of 12.6) higher on November 27 (its zenith) than on May 28 (its nadir), with a 3 mg/dl annual decrement from the (extrapolated) initial level of 296 mg/dl on December 21, 1973. The same four parameters (intercept, slope, amplitude, zenith) were computed in similar fashion for each of the remaining 1445 men in the cohort.

The strength and significance of seasonal cholesterol variation in the cohort as a whole was assessed by adapting statistical methods for cyclic data to combine the amplitudes and zeniths of the cycles of the 1446 study participants. Briefly, each participant's seasonal cholesterol cycle was represented as a vector (A1 sin 2πθ, A1 cos 2πθ) with amplitude A1 and zenith θ1, where θ1 ranges from 0 (January 1) to 1 (December 31). A mean seasonal vector was obtained by adding the 1446 individual vectors and dividing by 1446; the amplitude (A) and orientation (θ) of this mean vector provided estimates of the amplitude and zenith of the overall seasonal cholesterol cycle in the cohort. The circular variance (V) was obtained by subtracting the ratio of A and the scalar mean of A1 from unity; this statistic differs from the variance of unbounded linear variables in that it cannot exceed unity.

These calculations may be illustrated by considering a hypothetical example in which no overall seasonal pattern is present.

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**FIGURE 1.** Periodic time series regression model for bimonthly plasma cholesterol levels (data points) of a selected CPPT participant. In the equation defining the fitted model (solid curve), t and t' represent years elapsed since December 21 and November 27, 1973, respectively.
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\[ \bar{\theta} = \text{Undefined} \]
\[ \bar{A} = 0 \]
\[ 1 - V = 0 \]
\[ \chi^2 = 0 \]

FIGURE 2. Hypothetical frequency distribution of cycle zeniths (\( \theta_i \)) in the absence of an underlying seasonal effect (i.e., under the null hypothesis). Each spike represents 1/24 times the number of men with \( \theta_i \) falling within one of 24 equal segments of the calendar year. A circle of unit radius is shaded for reference.

Under this null hypothesis, the seasonal vectors for 1446 participants would be randomly oriented, with the seasonal peaks of individual study participants equally distributed throughout the year. In figure 2, this hypothetical situation is depicted by the equal lengths of the spokes representing relative frequencies of each possible value of \( \theta_i \). Because no value of \( \theta_i \) is preferred, the individual seasonal cycles offset each other, and the mean seasonal effect has amplitude \( \bar{A} = 0 \) with undefined \( \bar{\theta} \) and circular variance \( V = 1 \). In this example, \( 1 - V \), a measure of the "strength" of the seasonal effect (i.e., the alignment of the cycles of individual participants), is zero. At the opposite extreme (not shown), \( 1 - V \) attains its maximal value, unity, when the cycles of all participants are perfectly aligned.

In general, when the number of participants (n) is large, a \( \chi^2 \) statistic with two degrees of freedom is obtained when \( 1 - V \) is squared and multiplied by 2n. In figure 2, where no overall seasonal effect exists, \( \chi^2 = 0 \); when all n cycles are in alignment (not shown), \( \chi^2 = 2n \).

The analytic method described above is based on a first-order approximation (figure 1) of the general (Fourier) model that describes any periodic phenomenon. It is conservative in that the absence of a significant first-order seasonal effect does not rule out the possibility of significant higher-order effects, whereas periodicity that is apparent in the first-order model must remain in higher-order models. In this respect, our method is analogous to the approximation of a general polynomial by its linear term.

Differences in seasonal cholesterol cycles among subgroups of participants were assessed by multivariate analysis of variance of the seasonal vector using the general linear models procedure of SAS. In this analysis, the two vector components, \( A_i \cdot \sin 2\pi \theta_i \) and \( A_i \cdot \cos 2\pi \theta_i \), were taken as dependent variables, and one or more categorical variables (LRC center, smoking, etc.) were taken as independent variables. The Hotelling-Lawley trace statistic was used as the criterion for testing the null hypothesis of homogeneity of the seasonal vector among categories of the independent variable(s).

Results

Seasonal cholesterol changes. The cyclic seasonal pattern of plasma cholesterol levels is depicted in figure 3. On the average, cholesterol levels were 7.6 mg/dl higher (277.6 vs 270.0) in December-January than in June-July. The same sinusoidal pattern was repeated in each year of the study (figure 3, left). By contrast, no repeating yearly cycle was evident at any LRC center.

FIGURE 3. Left, Mean plasma cholesterol levels for December 1976 to November 1980, the period in which no participant had fewer than 0.5 or more than 7 years of follow-up. Each data point represents the average for all men seen in a 2 month interval, usually one value per participant. Right, Each closed circle represents the mean plasma cholesterol level (lefthand scale) for participants seen in a 2 month segment of the calendar year, averaged over all years. Each open circle represents the mean percent deviation (righthand scale) of all cholesterol determinations performed on frozen serum for quality control during the same 2 month segment of the calendar year from their standard values.
in cholesterol levels determined in the frozen serum pools used for quality control; when averaged over all years and all centers, the curve was essentially flat (figure 3, right). Thus the seasonal cycles observed in study participants could not be attributed to variations in the analytic procedures, reagents, or instruments.

To ensure that the observed seasonal changes arose from differences within rather than among study participants, the distribution of \( \theta \), estimated for each of the 1446 participants as in figure 1, was analyzed. The average participant’s cholesterol level peaked on December 30 (standard error = 2 days) with a value 7.4 mg/dl (standard error = 0.3 mg/dl) higher than on June 30. Although this mean seasonal difference (2 \( \cdot \) \( \bar{A} \)) represented only 2.7% of the mean baseline level (274 mg/dl), its timing was highly consistent throughout the cohort (figure 4). Late autumn and early winter cholesterol peaks were two to three times as common as would have been expected under the null hypothesis of no seasonal effect (shaded circle), whereas fewer than half of the expected proportion of men showed peaks in the spring or summer. The high values of \( 1 - V \) (0.49; half its theoretical maximum) and of \( \chi^2 \) (706; a value of 14 is sufficient to give \( p < .001 \)) are further statistical indicators of the strength of preference for an early winter peak. Thus, although seasonal cycles of individual participants tend to be obscured by noncyclic fluctuations in cholesterol levels (average root mean square error of regression 18.7 mg/dl), the consistency of the cyclic pattern makes it easily discernible in the cohort of 1446 men.

The mean seasonal cholesterol cycles for each LRC center are plotted in figure 5, A. Although the null hypothesis of homogeneity was rejected (\( p = .04 \)), the 12 centers were essentially similar. The amplitude of the cholesterol cycle (\( A \)) varied over a 1.8-fold range (2.9 to 5.2 mg/dl), and its zenith (\( \theta \)) varied over a 4 week range (December 15 to January 12). Surprisingly, the largest seasonal cholesterol changes were not observed in the locales subject to the largest seasonal changes in the physical environment. The mean seasonal cholesterol change varied inversely (\( r = -.60 \)) with the magnitude of the December-June difference in hours of daylight (figure 5, B) and bore no clear relationship (\( r = -.11 \)) to seasonal differences in mean ambient temperature (figure 5, C). For example, the mean December 30–June 30 plasma cholesterol difference was 8.9 mg/dl in San Diego vs 7.0 mg/dl in Minneapolis and 6.0 mg/dl in Seattle.

The seasonal cholesterol cycles of subgroups of participants defined by levels of the following additional baseline characteristics were compared: cigarette smoking, exercise, and tertiles of age, height, body mass index, total caloric intake/body weight, and plasma levels of cholesterol, triglyceride, LDL-C, and HDL-C. No significant heterogeneities were found. Of particular interest, the mean December 30–June 30 plasma cholesterol differences for men in the top, middle, and bottom tertiles of plasma cholesterol of baseline were 7.6, 6.7, and 7.9 mg/dl, respectively.

**Seasonal dietary and weight changes.** Given the known interrelationship of lipid metabolism and body weight, seasonal cycles of body mass index were investigated. Superimposed on a linearly increasing trend, a seasonal cycle, having a zenith in February-March and a nadir in August-September, was evident (figure 6). When periodic time series were compared for each participant as above, and the distributions of cycle parameters were analyzed, significant linear (0.10 kg/m²/year) and seasonal (\( \bar{\theta} = \text{Feb. 12}, A = 0.126 \text{ kg/m}^2 \)) effects were demonstrated. Thus a typical 5'10" participant gained 0.7 pounds/year and weighed 1.8 pounds more in midwinter than in midsummer each year. This seasonal effect was even stronger than that observed for plasma cholesterol (\( 1 - V = 0.57, \chi^2 = 933 \)).
The seasonal body mass index cycle trailed the cholesterol cycle by 44 days; plasma cholesterol reached its annual zenith about halfway between the times at which body mass index and its rate of increase were at their respective maxima. Although men who gained the most weight each winter tended to show the biggest seasonal increases in plasma cholesterol levels, this correlation was of only modest strength (r = .24).

The correlation of seasonal changes in body weight and plasma cholesterol suggests a possible underlying seasonal influence of diet and/or exercise. The annual assessment of exercise habits in the CPPT was too infrequent to permit a reliable analysis of seasonal effects. However, our semiannual dietary recall questionnaires did permit a simplified assessment of seasonal variation in dietary habits. Taking October to March as “winter” and April to September as “summer,” we compared mean daily intakes of saturated fat (12.34% vs 12.15% of calories), polyunsaturated fat (8.91% vs 8.97% of calories), and cholesterol (347.0 vs 347.8 mg) for winter vs summer and used the Keys and Hegsted formulates to predict the resulting plasma cholesterol difference (figure 7). The predicted differences represented only 10.5% and 8.3%, respectively, of the observed 4.5 mg/dl winter-summer difference in plasma cholesterol levels. A regression formula based on observations in CPPT screeners, which incorporates changes in body mass index as well as dietary composition, predicted 29% of the observed seasonal plasma cholesterol differences.

Other seasonal lipid changes. Seasonal variation in plasma levels of LDL-C, HDL-C, and triglyceride were similarly assessed in the same CPPT cohort. Although a detailed discussion of these seasonal effects is beyond

**FIGURE 5.** Geographic variation of seasonal cholesterol cycles among the 12 LRC centers (numbered from south to north). A, Mean seasonal cycle vectors (A_c \cdot \sin 2\pi \theta_c, A_c \cdot \cos 2\pi \theta_c) for each center. B, The June 21–December 21 difference in number of hours of daylight at each LRC locale was calculated from its latitude \( \lambda \) by the formula \((24 \cdot 90^\circ) \cdot \arcsin (\tan \lambda \cdot \tan 23.45^\circ)\), and plotted against the amplitude of its seasonal cholesterol cycle. The least-squares regression line and Pearson correlation coefficient (r) for these 12 points are given. C, The mean July and January temperatures at each LRC locale were obtained from the U.S. National Weather Service, and their difference was plotted against the amplitude of its seasonal cholesterol cycle. The least-squares regression line and Pearson correlation coefficient (r) for these 12 points are given.

**FIGURE 6.** Mean body mass index for 2 month intervals from December 1976 to November 1980.
the scope of this article, the zenith ($\bar{0}$) and strength ($1 - V$) of each seasonal cycle are depicted, along with those for plasma total cholesterol (TOT-C) and body mass index in figure 8. The LDL-C and TOT-C effects were of similar strength, whereas the HDL-C and triglyceride cycles were relatively weak, although still significant ($p < .001$). The LDL-C, HDL-C, and triglyceride cycles were essentially synchronous. The weak midautumn triglyceride peak reflected an underlying bimodal distribution of $\theta$ (not shown) with peaks in midsummer and late autumn. Despite moderate correlations (0.2 to 0.3) of increases in triglyceride and decreases in HDL-C with increases in body mass index, the seasonal zenith of triglyceride occurred near the seasonal nadir of body mass index, whereas the seasonal zeniths of HDL-C and body mass index were but a month apart. These seemingly paradoxical findings suggest that the observed seasonal triglyceride and HDL-C changes occurred despite rather than because of seasonal weight changes.

Discussion

The analysis of the LRC-CPPT placebo cohort clearly demonstrates that plasma cholesterol levels vary in a repeating cycle, reaching on average a maximum at the end of the year and a minimum in midyear. The average amplitude of this cycle, 7.4 mg/dl from minimum to maximum, represented only about 2% to 3% of the mean plasma cholesterol level in these hypercholesterolemic men; noncyclic fluctuations (as indicated by the root mean square error of regression) were more than twice as great. Although it is possible that the seasonal effects observed in the CPPT cohort differ from those that would pertain in a population not selected for hypercholesterolemia, similar seasonal cycles were observed in the most and least hypercholesterolemic men in our study. Proportionally greater seasonal plasma cholesterol changes were observed in a cross-sectional population-based survey of 17-year-old Israeli boys and girls and might be generally anticipated in groups not prescribed a uniform diet.

Given the relative magnitudes of cyclic and noncyclic variations in plasma cholesterol, seasonal variation does not represent a significant problem in the clinical management of individual hypercholesterolemic patients. However, seasonal effects can have practical import when large numbers of patients are involved and noncyclic fluctuations are canceled out. For example, if one proposed a screening program in which men with plasma cholesterol levels above the 75th percentile were referred to a dietitian for counseling, one might allow for the fact that the difference between the 25th and 75th percentiles of plasma cholesterol is generally only 40 to 50 mg/dl. The shift in this distribution resulting from a generalized 7.4 mg/dl seasonal shift in cholesterol levels could lead to a 30% increase in the frequency of referral in winter vs summer. Furthermore, one could not reliably assess the impact of intervention on cholesterol levels without a concurrent control group.

Although several plausible hypotheses may be proposed to explain the origins of the seasonal cholesterol cycle, our data fail to establish any single explanation. There are many biological examples of physiologic

**FIGURE 7.** Comparison of observed difference in mean plasma cholesterol levels (October to March vs April to September) with predictions based on observed seasonal differences in diet and weight. Predicted differences are based on the equations of Keys, Hegsted, and a regression model computed for 6494 LRC-CPPT screenees.

**FIGURE 8.** The zenith ($\bar{0}$) and strength ($1 - V$) of the seasonal cycles for plasma levels of total (TOT-C), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) cholesterol, plasma triglyceride (TG) levels, and body mass index (BMI) are each represented by a vector ($[1 - V]\cdot \sin 2\pi\theta,[1 - V]\cdot \cos 2\pi\theta$) in a circle of unit radius.
regulation by external environmental cues (e.g., light, temperature). A diurnal pattern of hepatic activity of the rate-limiting enzyme for cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase, is well known in rats, with fourfold higher activity at midnight than midday. Thus one may speculate that long winter nights could bring increased synthesis of cholesterol in humans. However, it is difficult to reconcile this hypothesis with the lesser amplitude of the seasonal cholesterol cycles in the northernmost LRC centers, where the summer days and winter nights are longest (figure 5, B).

Although seasonal changes in diet may also have contributed to the observed seasonal cholesterol changes, seasonal differences in weight and in reported intakes of saturated and polyunsaturated fat and cholesterol fell well short of explaining them quantitatively. Given the infrequent intervals (6 months) of dietary assessment in the CPPT and the well-known limitations of the 24 hr recall method, we may well have underestimated the true seasonal variation in diet. However, an independent study of seasonal and other influences on the dietary choices of lunchtime patrons of a National Institutes of Health cafeteria also did not suggest a clear dietary basis for seasonal variation in plasma cholesterol levels. Although patrons showed an increased preference for cold foods (salads, fruits, cottage cheese, and yogurt) in the summer months at the expense of cooked starches and vegetables, their consumption of meat entrees remained constant, and total caloric consumption was only slightly below winter levels. Seasonal fat and cholesterol intakes were not reported. One may speculate that weekend and holiday eating patterns, not addressed by this study and underrepresented in the LRC data, may have a larger seasonal influence on plasma cholesterol levels. On the other hand, large spontaneous seasonal cholesterol changes have been documented in European badgers under experimental conditions in which diet was held constant and seasonal weight gains were minimal.

In conclusion, the existence of a seasonal cholesterol cycle is now clearly established, although many fundamental questions about its origin and mechanisms remain unanswered. It is hoped that application of the methods presented here to other cohorts observed in different geographic and experimental settings will elucidate this phenomenon and increase our knowledge of the regulatory pathways for cholesterol metabolism.

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Appendix


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