



Seasonal Patterns in Monthly Hemoglobin A_{1c} Values

Chin-Lin Tseng^{1,2}, Michael Brimacombe^{1,2}, Minge Xie³, Mangala Rajan¹, Hongwei Wang³, John Kolassa³, Stephen Crystal⁴, Ting-Cheng Chen⁵, Leonard Pogach^{1,6}, and Monika Safford^{1,6,7}

¹ Center for Health Care Knowledge Management, Department of Veterans Affairs New Jersey Health Care System, East Orange, NJ.

² Department of Preventive Medicine and Community Health, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ.

³ Department of Statistics, Rutgers University, New Brunswick, NJ.

⁴ Health Services Research Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, NJ.

⁵ CTC Technologies, Inc., Short Hills, NJ.

⁶ Department of Medicine, University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ.

⁷ Birmingham VA Medical Center, Birmingham, AL.

Received for publication October 31, 2003; accepted for publication August 26, 2004.

The purpose of this study was to investigate seasonal variations in population monthly hemoglobin A_{1c} (A1c) values over 2 years (from October 1998 to September 2000) among US diabetic veterans. The study cohort included 285,705 veterans with 856,181 A1c tests. The authors calculated the monthly average A1c values for the overall population and for subpopulations defined by age, sex, race, insulin use, and climate regions. A1c values were higher in winter and lower in summer with a difference of 0.22. The proportion of A1c values greater than 9.0% followed a similar seasonal pattern that varied from 17.3% to 25.3%. Seasonal autoregressive models including trigonometric function terms were fit to the monthly average A1c values. There were significant seasonal effects; the seasonal variation was consistent across different subpopulations. Regions with colder winter temperatures had larger winter-summer contrasts than did those with warmer winter temperatures. The seasonal patterns followed trends similar to those of many physiologic markers, cardiovascular and other diabetes outcomes, and mortality. These findings have implications for health-care service research in quality-of-care assessment, epidemiologic studies investigating population trends and risk factors, and clinical trials or program evaluations of treatments or interventions.

diabetes mellitus; hemoglobin A, glycosylated; seasons; veterans

Abbreviation: A1c, hemoglobin A_{1c}.

Numerous human physiologic and pathophysiologic processes have been reported to vary seasonally in both healthy volunteers and people with chronic diseases. Some of these include cortisol, epinephrine, clotting factors, glucose, insulin, lipids, and blood pressure levels and heart rate variability (1–13). Many of these markers are implicated in the causal pathway for the development of common diseases; in fact, cardiovascular events, strokes, and mortality have a distinct seasonal fluctuation (14–21).

Hemoglobin A_{1c} (A1c) is associated with the risk of developing complications for one of the most common

chronic diseases: diabetes (22–24). A1c is a measure that reflects the past 90 days' average blood glucose levels. These levels have been associated with both microvascular and macrovascular risks for outcomes in diabetes (22, 24), and fluctuations in A1c levels in populations may reflect fluctuations in risk for events. A1c levels are being used to compare the quality of diabetes care for health systems, such as health plans. However, there is currently no stipulation on when during the year the chart reviews that gather the data for these comparisons are performed. If A1c levels vary by season (e.g., in some regions or in all regions, or more for

Correspondence to Dr. Chin-Lin Tseng, Department of Veterans Affairs New Jersey Health Care System, East Orange VA Medical Center, 385 Tremont Avenue, #129, East Orange, NJ 07018 (e-mail: Tseng@njneuromed.org).

some types of individuals), evaluation of quality of care using A1c levels may be biased without adequately considering the seasonal effect on A1c levels.

There have been reports of seasonal variation of A1c levels among patients with either type 1 (25) or type 2 (26) diabetes. In one study, simple comparisons were made among the four seasons on a total of 1,295 mainly Caucasian patients from a diabetes clinic (25); in the other, 39 patients from a selected geographic area were described (26). However, fluctuations in A1c levels by season or climatic change have not been reported for large populations of people with diabetes, and whether these fluctuations differ by patient characteristics such as age, sex, race/ethnicity, or severity of diabetes is not known.

We studied population monthly cross-sectional A1c levels over 2 years among 285,705 US veterans with diabetes cared for at Veterans Health Administration hospitals over the 2 years. We hypothesized that A1c levels in these mostly type 2 diabetes patients would fluctuate by month/season, with higher levels in colder months. Further, we examined whether these circannual fluctuations differed by age, sex, race, or diabetes severity; and we examined whether seasonal fluctuations were related to climate characteristics.

MATERIALS AND METHODS

Sample

We used diabetes-related pharmacy data and laboratory results from the Veterans Health Administration's Health-care Analysis Information Group in Milwaukee, Wisconsin, and Veterans Health Administration utilization data (the National Patient Clinical Dataset) from the Veterans Integrated Service Network Support Center in Austin, Texas. We selected individuals ($n = 623,461$) who met a commonly used administrative data definition of diabetes in either of the 2 years from October 1, 1998, to September 30, 2000: at least two outpatient face-to-face visits on different calendar days, or at least one inpatient stay, with an associated *International Classification of Diseases*, Ninth Revision, code 250.xx for diabetes (27) or dispensing of glycemic medications.

The 143 facilities in the Veterans Health Administration used different laboratory methods to measure A1c during the study period. Considerable variations in A1c test precision and bias have been reported in uncertified methods (28). To observe changes in population monthly A1c values not caused by variation in laboratory method, we included during the study period only the 72 facilities that used certified A1c laboratory techniques exclusively. We also excluded 1,863 A1c tests that fell outside the physiologic range (3–18 percent). This resulted in 285,705 veterans with diabetes cared for at 72 facilities with a total of 856,181 A1c tests over 2 years. Of this sample, there were 193,932 veterans in the first year and 234,361 veterans in the second year, with about 50 percent ($n = 141,588$) present in both years. For the analysis including climate information, we eliminated five facilities that had 10 or fewer months of A1c information, resulting in 272,722 patients with 823,990 A1c tests at 67 facilities.

Statistical analysis

We calculated population A1c mean values and the percentage of A1c values greater than 9.0 percent for each month over 2 years. We selected the 9.0 percent threshold since current trends in accountability are toward decreasing the threshold for poor control to 9.0 percent or even lower (29).

We also calculated monthly A1c mean values for subpopulations defined by age categories, sex, and race because A1c levels are lower in older diabetic patients and higher in ethnic minorities with diabetes (30–32), and because we wanted to explore whether any observed fluctuations differed by sex. Since A1c levels are higher in people with more severe diabetes (22, 24), we also evaluated whether fluctuations may be more pronounced for those individuals with more severe diabetes, as reflected by treatment with insulin.

To evaluate any seasonal trends in population monthly A1c mean levels, we fit seasonal autoregressive models to the monthly population averaged A1c values for the overall population and within each subpopulation. First, we included a linear term (month) to describe the overall decreasing trend of the A1c values. Second, we lagged the monthly A1c average values 1 month and then 2 months. These lagged variables were simultaneously added to the linear trend to model the autocorrelation of A1c measurements. Third, to investigate potential seasonal effects, we added the trigonometric terms, sine and cosine, to the autoregressive models, using 1 year (12 months) as the period for the observed fluctuation cycle (figure 1). For model development, using the full sample, we examined the significance of each newly added variable by observing any increase in R^2 . We used the same variables as in the final model developed from the full sample to fit separate autoregressive models for each subpopulation as previously defined.

We calculated the amplitude and the phase shift parameter estimates and their 95 percent confidence intervals of the seasonal cycle using the regression coefficients from the sine and cosine variables in our final model. (Details of these methods are in the Appendix.) The amplitude calculated from our adjusted model represents the maximum deviation due to months/seasons in a year from the linear trend (i.e., adjusting for linear trend and autocorrelations of the data) as the seasonal cycle was defined by the periodic functions sine and cosine. Multiplying the amplitude by 2 yielded the maximum peak-trough A1c difference. The phase shift parameter in the adjusted model indicated the shift of the peak month relative to the standard (no phase shift) seasonal cycle defined by the sine function. We reported estimated peak and trough months in a year based on the autoregressive models.

Using the sine and/or cosine functions to model periodic fluctuations is a common practice in mathematical modeling (33). Note that, in this mathematical equation, peak and trough are by definition 6 months apart. Often, both sine and cosine terms are used to offer a flexible starting point of the cycle. (See the Appendix for further details.) The cycle period in the sine and cosine terms was chosen to be 12 months because, as indicated in figure 1, there was

a yearlong seasonal cycle of fluctuation on monthly average A1c values of all patients. This time-series approach fully uses the yearlong monthly data values to estimate the peak-trough contrast as well as the peak and trough themselves. We selected this more sophisticated method to better describe our empirical finding of a seemingly 1-year fluctuation cycle that repeated in our 2-year study period.

We also tested whether these seasonal effects varied significantly by subpopulations for different sex, race, age, and insulin-user groups. Using the full sample, we included a subpopulation indicator variable (e.g., women vs. men) in the seasonal autoregressive models as well as the interaction terms of seasonal effects and the subpopulation indicator variable; we used partial *F* tests to test whether the interaction terms contributed significantly to the R^2 values of the models.

We further evaluated a possible mechanism of our observations. If seasonal effects are caused by cold climate, we would expect to see a larger winter-summer A1c contrast in colder than warmer climates. On the other hand, if seasonal fluctuations in A1c are attributable to dietary indiscretion during the winter holidays (e.g., Thanksgiving, Christmas, and New Year's Day), we would expect to observe similar seasonal/holiday effects regardless of climate.

We used data from the National Oceanic and Atmospheric Administration (34) pertaining to the cities closest to each facility. A total of four climate-related variables were considered: the midpoints of annual low and high temperatures, average snowfall, and the high-low temperature difference. Two analytical approaches were used to test the proposed hypothesis. First, these four variables were included separately in the models to be tested for their impact on population monthly A1c values. We also included in the model interaction terms of seasonal effects (the sine/cosine pair) and each climate. The significance of any of these interaction terms would support the climate-driven hypothesis about seasonal effects. Second, we further classified facilities into five climate regions according to the midpoint of the range of their low temperatures and derived separate seasonal autoregressive models for these five regions.

RESULTS

Demographic description of the study cohort

The study sample was 97.8 percent ($n = 270,227$) male, and 70.3 percent ($n = 200,793$) were Whites, 15.3 percent ($n = 43,648$) were African Americans, 7.6 percent ($n = 21,800$) were other races/ethnicities, and 6.8 percent ($n = 19,469$) were of unknown race. Of these diabetic veterans, 12.1 percent ($n = 3,519$) were less than 50 years of age, 20.1 percent ($n = 55,356$) were aged 50–59 years, 30.8 percent ($n = 84,958$) were aged 60–69 years, 32.0 percent ($n = 88,399$) were aged 70–79 years, and 5.1 percent ($n = 14,056$) were aged 80 or more years. Insulin treatment was common, with 31.5 percent ($n = 61,146$) in the first study year and 30.5 percent ($n = 71,485$) in the second year receiving this treatment.

Seasonal patterns in the overall study population

Figure 1 shows population monthly A1c mean values and their 95 percent confidence intervals. A1c values trended downward over the study period (year 1 mean: 7.95 A1c units, range: 7.79–8.08; year 2 mean: 7.78 A1c units, range: 7.61–7.90), but values were about 0.22 A1c units higher in January to April compared with July to October. Late autumn and spring had increasing and decreasing A1c values.

Empirically (figure 1), the same downward and seasonal trends existed for the percentage of individuals with A1c values greater than 9.0 percent. There were higher percentages of A1c tests exceeding the 9.0 percent threshold in late winter months than in summer months. For example, in both years, the percentages were higher in January through March (24.86–25.25 percent in the first year; 21.14–22.36 percent in the second year) and, in both years, the percentages were among the lowest during the period from July to September (<21.0 percent in the first year; <19.5 percent in the second year). The unadjusted data revealed the largest difference to be about 5 percent for both study years: 5.18 percent (25.25 percent in February vs. 20.07 percent in September) in the first year and 5.07 percent (22.36 percent in March vs. 17.29 percent in September) in the second year.

Table 1 presents the models predicting population monthly A1c values as variables were added in succession. Model 1 is the linear trend model, and it showed that A1c values decreased significantly in monthly units. On average, we observed a 0.015-unit monthly decrease in A1c levels. In model 2, we added the two time-lag variables (the previous 2 months' population average A1c values, respectively), and both were significant. This model showed that, after controlling for the linear trend, current average A1c values were explained by the average A1c values of 1 and 2 months earlier, as expected. In model 3, we entered the seasonal terms, revealing statistically significant seasonal variation of A1c values, as reflected in the significance of one of the sine and cosine terms. On the basis of model 3, we obtained estimates for the peak and trough months and their A1c differences. The population monthly A1c mean value peaked in late March (month 3.8), and the trough month was late September (month 9.8). The estimated winter-summer A1c contrast was 0.13 A1c units.

Seasonal patterns for various subpopulations by sex, race, age, and insulin usage

We used model 3 from table 1 to evaluate differences in seasonal variations by sex, race, age, and insulin usage (table 2). First, we confirmed that A1c values declined over the 2-year observation period for all patient types examined. However, the decline rate was larger for older individuals. Second, for all groups, we observed patterns of seasonal variation in A1c values similar to those for the whole population (figure 1), and at least one of the sine/cosine pairs was statistically significant, indicating that the observed seasonal pattern was present in all groups. All models had large R^2 values, indicating good model fit.

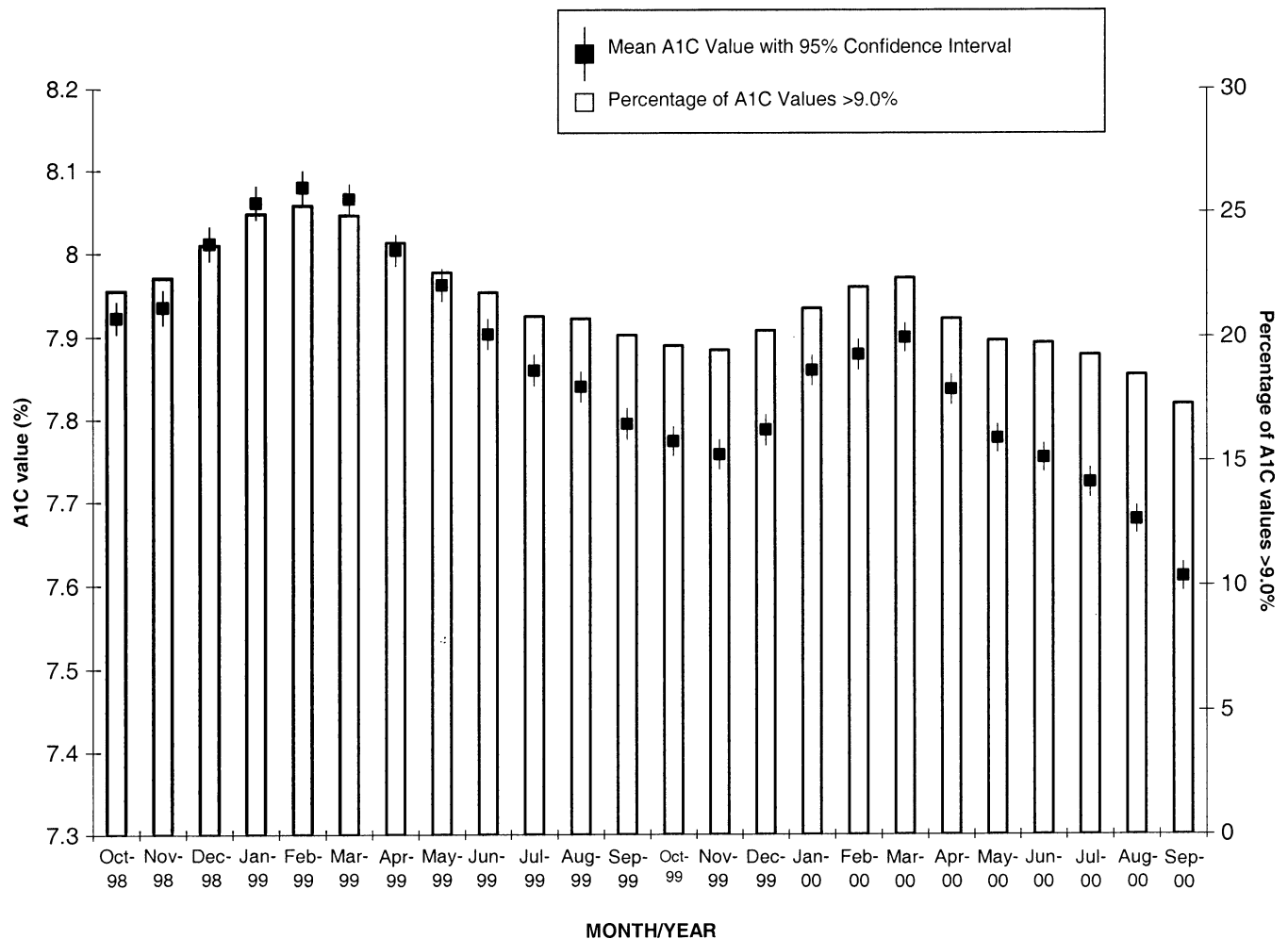


FIGURE 1. Monthly mean hemoglobin A_{1c} (A1c) values (with 95% confidence intervals) and monthly percentage of A1c values greater than 9.0%, US veterans with diabetes, 1998–2000. Month designations use only the first three letters, and year designations use only the last two digits.

Most R^2 values were larger than 0.90, with an R^2 of 0.73 for women and an R^2 of 0.86 for the “other” racial group.

The winter-summer differences ranged from 0.13 to 0.23 A1c units for the various subgroups. The peak months were also comparable for all groups, ranging between late February and early April, with most subgroups peaking in March. The range of peak month estimates was from early February (month 2.3) to mid-April (month 4.6); the trough month then would range from early August (month 8.3) to mid-October (month 10.6). For example, insulin users had an earlier peak (late February) compared with non-insulin users (early April), and those over 80 years of age also experienced a later peak (early April) compared with younger groups (early to mid-March). However, partial F tests on the interaction between seasonal terms and each of the four stratifying variables showed that the seasonal patterns (described by amplitudes and phase shifts) did not differ significantly across the subpopulations.

Seasonal patterns by climate regions

Of the four selected climate variables, only the interaction of the midpoint low temperature, reflecting the coldness of the winter, and seasonal effects was statistically significant. Partial F tests (not shown) revealed that the two interaction terms (low temperature \times sine, low temperature \times cosine) were significantly associated with monthly A1c mean levels. These results suggested that colder temperatures were associated with higher fluctuation of A1c values.

We then grouped facilities according to their midpoint low temperature; these five groups were modeled separately using the autoregressive model 3, and the results are also listed in table 2. The R^2 values for these models ranged between 0.75 and 0.96. There was no significant seasonal effect in the warmest area, which had cold temperatures of greater than 50°F (>10°C). As shown, facilities in colder regions, which had winter temperatures of less than or equal

TABLE 1. Models of population average A1c† values progressively adjusting for linear trends in monthly A1c changes, autocorrelation with previous months' population A1c values, and seasonal effects temperatures, US veterans with diabetes, 1998–2000

	Population average A1c level (β coefficient (SE))		Seasonal effect (β coefficient (SE))		Winter-summer A1c contrast		Peak		Trough		R ²	
	1 month prior	2 months prior	Sine	Cosine	Intercept (β coefficient (SE))	A1c (%)	95% confidence interval	Months	95% confidence interval	Months		95% confidence interval
Model 1	-0.015 (0.002)**				8.048 (0.030)**							0.69
Model 2	-0.006 (0.002)**	1.413 (0.156)**			2.654 (0.737)**							0.96
Model 3	-0.014 (0.003)**	0.715 (0.190)**	-0.670 (0.197)*	-0.026 (0.016)	7.698 (1.568)**	0.131	0.066, 0.196	3.8	3.0, 4.5	9.8	9.0, 10.5	0.98

* $p < 0.01$; ** $p < 0.001$.

† A1c, hemoglobin A_{1c}; SE, standard error of β.

‡ Estimated regression coefficient.

§ To facilitate interpretation of the numerical values, we roughly divided a month into three time periods: early (the first third of the month, about days 1–10), middle (the middle third, about days 11–20), and late (the last third, about days 21–30 or 31). Thus, 3.8 roughly corresponds to late March, and 9.8 roughly corresponds to late September.

to 32°F ($\leq 0^\circ\text{C}$), had a larger winter-summer contrast, and facilities in warmer regions, which had winter temperatures of greater than 40°F ($>4.4^\circ\text{C}$), had a smaller winter-summer contrast. The group with an intermediate winter climate, with a winter temperature of greater than 32° to 40°F ($>0^\circ$ to 4.4°C), appeared to have the largest winter-summer contrast, with colder climates demonstrating smaller, not larger, contrasts. This suggested that the relation between the winter-summer A1c contrast and the midpoint low temperature may be nonlinear, but that the observed seasonal variation in A1c values was indeed related to colder winter temperatures.

DISCUSSION

We demonstrated that A1c levels among a population of older men with largely type 2 diabetes fluctuated seasonally in a sinusoidal pattern, demonstrating a peak in March to April and a trough in September to October. This late winter-late summer difference in A1c values was about 0.22 A1c units, which was smaller than the values reported by Maguire and Edwards (25) ($\sim 0.47\text{--}0.69$ A1c units) and by Hajime et al. (26) (0.50 A1c units). Both the shape of the curve and the timing of the peak and trough were consistent with data from Maguire and Edwards (25) and Hajime et al. (26). These two studies were of a much smaller scale, and only simple (t test) comparisons between seasons were made.

Our findings are strikingly consistent with the patterns observed for physiologic markers, as well as those for cardiovascular events and mortality, in previous studies. The seasonal sinusoidal pattern of cardiovascular events is well described in numerous populations (17–21), with peaks in colder winter months and excess mortality largely attributable to cardiovascular events (14–16). Physiologic responses to cold temperatures have been implicated in several studies (35–36).

In addition to cardiovascular events and mortality, seasonal variations in other diabetes-related outcomes have also been reported. Congestive heart failure admissions in Scotland were 16 percent higher than average for women in December and 7 percent lower in July during 1990–1996 (odds ratio = 1.14; $p < 0.001$); for men, the respective values were 6 percent more and 8 percent less (odds ratio = 1.16; $p < 0.001$) (37). Deaths followed a similar trend, with patterns in this report more pronounced for those over 75 years of age. There was also a winter peak in concomitantly coded respiratory disease, but this seasonal excess accounted for only approximately one fifth of the winter increment in congestive heart failure hospitalizations (37). French investigators reported similar peaks in December to January, with congestive heart failure deaths 15 percent higher and congestive heart failure hospitalizations 7–10 percent higher in these months for all adults hospitalized with congestive heart failure in France during 1992–1996 (38).

Some microvascular events also follow a seasonal pattern in diabetes. Of the 14,555 lower extremity amputations in New York State in 1990 and 1991, amputations were 27 percent more common in the spring only for people with diabetes (39). Similarly, initiation of dialysis for patients

TABLE 2. Number of A1c* measures, winter-summer A1c contrast, and peak and trough months for various subpopulations by patient characteristic and climate categories, US veterans with diabetes, 1998–2000

	No. of A1c measures	Winter-summer A1c contrast		Peak		Trough	
		A1c (%)	95% confidence interval	Month†	95% confidence interval	Month†	95% confidence interval
Sex							
Women	19,514	0.209	0.071, 0.346	4.2	3.3, 5.4	10.2	9.3, 11.4
Men	820,275	0.117	0.062, 0.173	4.0	3.3, 4.7	10.0	9.3, 10.7
Race/ethnicity							
White	609,394	0.130	0.059, 0.201	3.6	2.7, 4.5	9.6	8.7, 10.5
African American	164,663	0.126	0.049, 0.203	3.4	2.1, 4.8	9.4	8.1, 10.8
Others	56,031	0.216	0.062, 0.369	2.3	0.9, 3.7	8.3	6.9, 9.7
Unknown	56,093	0.158	0.062, 0.254	3.2	2.1, 4.2	9.2	8.1, 10.2
Age (years)							
<50	100,618	0.158	0.062, 0.253	3.3	2.1, 4.4	9.3	8.1, 10.4
50–59	179,282	0.151	0.065, 0.236	3.4	2.5, 4.4	9.4	8.5, 10.4
60–69	267,811	0.136	0.054, 0.218	3.2	2.0, 4.4	9.2	8.0, 10.4
70–79	254,486	0.152	0.083, 0.220	3.9	3.2, 4.6	9.9	9.2, 10.6
≥80	37,092	0.233	0.126, 0.339	4.6	4.0, 5.3	10.6	10.0, 11.3
Diabetes severity							
No insulin	488,599	0.138	0.078, 0.200	4.3	3.7, 5.0	10.3	9.7, 11.0
With insulin	293,984	0.218	0.106, 0.330	2.8	2.0, 3.6	8.8	8.0, 9.6
Climate categories‡,§							
Warmest (>50°F)	117,665	0.070	0.003, 0.136	3.8	2.0, 5.6	9.8	8.0, 11.6
Warm (>40° to 50°F)	204,001	0.080	0.014, 0.146	2.8	1.0, 4.5	8.8	7.0, 10.5
Intermediate (>32° to 40°F)	159,485	0.243	0.141, 0.345	3.8	3.2, 4.3	9.8	9.2, 10.3
Cold (>20° to 32°F)	229,239	0.162	0.051, 0.272	3.3	1.8, 4.7	9.3	7.8, 10.7
Coldest (5° to 20°F)	77,885	0.132	0.041, 0.224	2.2	0.6, 3.8	8.2	6.6, 9.8

* A1c, hemoglobin A_{1c}.

† To facilitate interpretation of the numerical values, we roughly divided a month into three time periods: early (the first third of the month, about days 1–10), middle (the middle third, about days 11–20), and late (the last third, about days 21–30 or 31). Thus, 4.2 roughly corresponds to early April, and 10.2 roughly corresponds to early October.

‡ We classified facilities into five climate regions according to the midpoint of the range of their annual low (winter) temperatures.

§ Temperature equivalents: >50°F (>10°C); >40° to 50°F (>4.4° to 10°C); >32° to 40°F (>0° to 4.4°C); >20° to 32°F (>–6.7° to 0°C); 5° to 20°F (–15° to –6.7°C).

with end-stage renal disease is more common in January and least common in August (40). This consistency between A1c values and outcomes in diabetes may not be surprising because of their evidenced close relation.

Previous studies of populations and healthy volunteers have demonstrated fluctuations in glucose and insulin sensitivity, with higher levels in the fall or winter in most studies (41–46). Two studies examined A1c variations in healthy volunteers, and one described no seasonal variations (47), whereas the other reported higher levels in late autumn and winter (48). To our knowledge, no US studies have examined these relations among populations of people with type 2 diabetes, although type 2 diabetes incidence did show a seasonal variation in a study from the United Kingdom (22) and in a study from Japan (26).

A1c values peaked in the late winter, presumably reflecting the lag in A1c values compared with ambient glucose levels. Glucose levels in late December, January, and February, coinciding with the coldest months of winter, would be expected to determine March A1c levels. In fact, most areas had the coldest temperatures in early February, which would be the month of greatest influence on March's A1c levels (49). Similarly, the warmer months would be expected to lead to lower glucose levels that would be reflected in fall A1c levels.

We found that all of the tested subgroups experienced seasonal variations in A1c levels similar to those of the overall population. However, some groups appeared to be more prone to seasonal variations. For example, women experienced larger winter-summer contrasts, as did the oldest

old and those of non-White and non-African-American race/ethnicity. The sizes of the fluctuations were small and not statistically significant, but these findings could have implications for population-level A1c assessments of populations composed of one or more of these groups.

The mechanism through which changes of seasons would induce changes of A1c values is unknown, but our study sheds light on one potential mechanism. A possible explanation for seasonal fluctuations in A1c levels could stem from the excess food consumed at the time of the winter holidays celebrated in the United States. Several studies have reported seasonal fluctuations in body weight (50–52), higher winter fat intake (52–55), and winter-related difficulties in achieving weight loss relative to the summer (56, 57). Physical activity has also been reported to diminish in winter months in several settings (58–64). However, several studies have demonstrated that some risk factors for cardiovascular events, especially lipids, have seasonal variation independent of age, gender, diet, body mass index, or physical activity (50, 51, 65–68). Our study supports a seasonal effect on A1c independent of a dietary indiscretion/“holiday effect,” since this would be expected to be present regardless of temperature fluctuations in the climate.

Although it is not known how changes in temperature would induce changes of A1c values, we suspect it could be a physiologic response to cold, as reflected in changes in blood pressure and heart rate variability with cold temperatures (1, 4–6, 10, 11). One study reported temperature-mediated fluctuations in venous blood glucose after a 2-hour glucose tolerance test, but glucose values were lower in cooler temperatures (69). The finding in our study, that the greatest contrast was observed for moderately cold temperatures but less so for extremes, is intriguing. Diabetes patients may well remain largely indoors with minimal exposure to cold in extremely cold climates, but they may venture outdoors more during moderately cold temperatures, resulting in higher actual exposure to cold temperatures. Further exploration of this possibility is warranted.

In this study, we found a linear decrease in A1c values with time, suggesting an overall trend for improving glycemic control. This may reflect ongoing clinical efforts to manage glycemic control, spurred by system-level changes in the Department of Veterans Affairs (70, 71). We note that, similar to studies of seasonal variations in other physiologic risk factors such as lipids, our study showed that seasonal changes were durable, regardless of overall linear downward trends (50, 51).

Our findings of seasonal variation in A1c levels and in percentages exceeding 9.0 percent (i.e., poor glycemic control) may have profound implications for various disciplines when A1c values are studied. First, for assessing the quality of diabetes care using A1c levels, it may be important to include the time of year of measurements and even the climatic region. Another example is in evaluation of health plan performance in glycemic control. If health plans A and B have similar patients but plan A performs chart reviews in the summer and plan B does them in the winter, the proportions of above-threshold A1c tests could be markedly influenced by as much as 5 percent on the basis of our study. A health plan may be inaccurately evaluated as

poor or better if the month/season when A1c tests are taken is not considered.

It is equally important in epidemiologic research (such as population studies of the prevalence rate of persons with poor A1c control, risk factors associated with poor A1c control, and trends of glycemic control) to consider such seasonal variation in the design, analysis, and interpretation of data. Studies of effect estimates in clinical trials and evaluation of intervention programs may also consider controlling for seasonality of A1c levels to reduce bias. In essence, studies may make biased or erroneous conclusions by failing to consider the month/season when the A1c values were measured. For example, in a clinical trial or a quasi-experimental study, researchers are interested in comparing the difference between pretreatment and posttreatment interventions on A1c levels. Assuming that a treatment or an intervention can actually help to decrease A1c levels, this beneficial effect can be inflated/overestimated if the pretests are in winter and the posttests are in summer or deflated/underestimated if the pretests are in summer and the posttests are in winter.

This study has several limitations. First, administrative data, the source of information in this study, can suffer from data quality and reliability problems. To minimize the variation introduced by A1c laboratory assay methods, we restricted the study to only those methods certified by the National Glycohemoglobin Standardization Program. Second, because the Veterans Health Administration serves mostly older men, our findings should be replicated in other populations. Additionally, our study of serial cross-sections could not evaluate the finding of an overall declining linear trend in A1c levels over the 2-year study period. Longitudinal designs (72) can better address this important issue, which was beyond the scope of the study.

In conclusion, we describe seasonal variations in A1c levels in a large population of older patients with largely type 2 diabetes. These effects are likely attributable to cold climate, with higher A1c levels in late winter and lower levels in late summer, with a contrast of about 0.22 A1c units. The proportion of the population with an A1c value of greater than 9.0 percent varied from 17.3 percent to 25.3 percent according to a similar pattern. A seasonal pattern appeared in all sex, race, age, and diabetes severity groups. The seasonal A1c pattern follows circannual trends similar to those reported for many diabetes outcomes. These findings may have implications for health services research in quality-of-care assessment, epidemiologic studies investigating study population trends and risk factors, and clinical trials or program evaluations examining the effects of treatments or interventions.

ACKNOWLEDGMENTS

This research has been supported by Department of Veterans Affairs health services research and development grant IIR 00-072-1 to L. P., with partial research support for M. X. received from grant NSF/SES-0241859.

REFERENCES

1. Andersen UO, Henriksen JH, Jensen G. Sources of measurement variation in blood pressure in large-scale epidemiological surveys with follow-up. The Copenhagen City Heart Study Group. *Blood Press* 2002;11:357–65.
2. 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;12:359–65.
3. Donahoo WT, Jensen DR, Shepard TY, et al. Seasonal variation in lipoprotein lipase and plasma lipids in physically active, normal weight humans. *J Clin Endocrinol Metab* 2000;85:3065–8.
4. Kristal-Boneh E, Froom P, Harari G, et al. Summer-winter differences in 24 h variability of heart rate. *J Cardiovasc Risk* 2000;7:141–6.
5. Sega R, Cesana G, Bombelli M, et al. Seasonal variations in home and ambulatory blood pressure in the PAMELA population. *Pressione Arteriose Monitorate E Loro Associazioni. J Hypertens* 1998;16:1585–92.
6. Mundal R, Kjeldsen SE, Sandvik L, et al. Seasonal covariation in physical fitness and blood pressure at rest and during exercise in healthy middle-aged men. *Blood Press* 1997;6:269–73.
7. Walker BR, Best R, Noon JP, et al. Seasonal variation in glucocorticoid activity in healthy men. *J Clin Endocrinol Metab* 1997;82:4015–19.
8. Yeh CJ, Chan P, Pan WH. Values of blood coagulating factors vary with ambient temperature: the Cardiovascular Disease Risk Factor Two-Township Study in Taiwan. *Chin J Physiol* 1996;39:111–16.
9. Kanabrocki EL, Sothorn RB, Bremner WF, et al. Weekly and yearly rhythms in plasma fibrinogen in hospitalized male military veterans. *Am J Cardiol* 1995;76:628–31.
10. Woodhouse PR, Khaw KT, Plummer M. Seasonal variation of blood pressure and its relationship to ambient temperature in an elderly population. *J Hypertens* 1993;11:1267–74.
11. Tanaka S, Konno A, Hashimoto A, et al. The influence of cold temperatures on the progression of hypertension: an epidemiological study. *J Hypertens Suppl* 1989;7:S49–51.
12. Letellier G, Desjarlais F. Study of seasonal variations for eighteen biochemical parameters over a four-year period. *Clin Biochem* 1982;15:206–11.
13. Kuroshima A, Doi K, Ohno T. Seasonal variation of plasma glucagon concentrations in men. *Jpn J Physiol* 1979;29:661–8.
14. van Rossum CT, Shipley MJ, Hemingway H, et al. Seasonal variation in cause-specific mortality: are there high-risk groups? 25-year follow-up of civil servants from the first Whitehall study. *Int J Epidemiol* 2001;30:1109–16.
15. Arntz HR, Willich SN, Schreiber C, et al. Diurnal, weekly and seasonal variation of sudden death: population-based analysis of 24,061 consecutive cases. *Eur Heart J* 2000;21:315–20.
16. Sheth T, Nair C, Muller J, et al. Increased winter mortality from acute myocardial infarction and stroke: the effect of age. *J Am Coll Cardiol* 1999;33:1916–19.
17. Spencer FA, Goldberg RJ, Becker RC, et al. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. *J Am Coll Cardiol* 1998;31:1226–33.
18. Jakovljevic D, Salomaa V, Sivenius J, et al. Seasonal variation in the occurrence of stroke in a Finnish adult population. The FINMONICA Stroke Register. Finnish Monitoring Trends and Determinants in Cardiovascular Disease. *Stroke* 1996;27:1774–9.
19. Spielberg C, Falkenhahn D, Willich SN, et al. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. *Am Heart J* 1996;132:579–85.
20. Douglas AS, Dunnigan MG, Allan TM, et al. Seasonal variation in coronary heart disease in Scotland. *J Epidemiol Community Health* 1995;49:575–82.
21. Kelly-Hayes M, Wolf PA, Kase CS, et al. Temporal patterns of stroke onset. The Framingham Study. *Stroke* 1995;26:1343–7.
22. UK Prospective Diabetes Study. IV. Characteristics of newly presenting type 2 diabetic patients: male preponderance and obesity at different ages. Multi-center Study. *Diabet Med* 1988;5:154–9.
23. Kuusisto J, Mykkanen L, Pyorala K, et al. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 1994;43:960–7.
24. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–86.
25. Maguire GA, Edwards OM. Seasonal variation in glycated haemoglobin in diabetics. *Ann Clin Biochem* 2001;38:59–60.
26. Hajime I, Suzuki H, Baba T, et al. Seasonal variation of glycemic control in type 2 diabetic patients. *Diabetes Care* 2001;24:1503–4.
27. Hebert PL, Geiss LS, Tierney EF, et al. Identifying persons with diabetes using Medicare claims data. *Am J Med Qual* 1999;14:270–7.
28. Little RR, Rohlfing CL, Wiedmeyer HM, et al. The national glycohemoglobin standardization program: a five-year progress report. *Clin Chem* 2001;47:1985–92.
29. Buse JB. Evolution in the American Diabetes Association standards of care. *Clin Diabetes* 2003;21:24–6.
30. El-Kebbi IM, Cook CB, Ziemer DC, et al. Association of younger age with poor glycemic control and obesity in urban African Americans with type 2 diabetes. *Arch Intern Med* 2003;163:69–75.
31. Saaddine JB, Engelgau MM, Beckles GL, et al. A diabetes report card for the United States: quality of care in the 1990s. *Ann Intern Med* 2002;136:565–74.
32. Zhang Q, Safford M, Ottenweller J, et al. Performance status of health care facilities changes with risk adjustment of HbA1c. *Diabetes Care* 2000;23:919–27.
33. Bloomfield P. *Fourier analysis of time series: an introduction*. New York, NY: John Wiley & Sons, Inc, 1976.
34. National Oceanic and Atmospheric Administration (NOAA)/Cooperative Institute for Research in Environmental Sciences (CIRES). US interactive climate pages. Boulder, CO: NOAA/CIRES, 2003. (www.cdc.noaa.gov/usclimate).
35. Nayha S. Cold and the risk of cardiovascular diseases. A review. *Int J Circumpolar Health* 2002;61:373–80.
36. Marchant B, Ranjadayalan K, Stevenson R, et al. Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: the influence of environmental temperature. *Br Heart J* 1993;69:385–7.
37. Stewart S, McIntyre K, Capewell S, et al. Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality. *Am Coll Cardiol* 2002;39:760–6.
38. Boulay F, Berthier F, Sisteron O, et al. Seasonal variation in chronic heart failure hospitalizations and mortality in France. *Circulation* 1999;100:280–6.

39. Armstrong DG, Lavery LA, van Houtum WH, et al. Seasonal variations in lower extremity amputation. *Foot Ankle Surg* 1997;36:146–50.
40. Iseki K, Morita O, Fukiyama K. Seasonal variation in the incidence of end-stage renal disease. *Am J Nephrol* 1996;16:375–81.
41. Bunout D, Barrera G, de la Maza P, et al. Seasonal variation in insulin sensitivity in healthy elderly people. *Nutrition* 2003;19:310–16.
42. Gravholt CH, Holck P, Nyholm B, et al. No seasonal variation of insulin sensitivity and glucose effectiveness in men. *Metabolism* 2000;49:32–8.
43. Nicolau GY, Haus E, Lakatua DJ, et al. Circannual rhythms of laboratory parameters in serum of elderly subjects. Evaluation by cosinor analysis. *Endocrinologie* 1986;24:281–92.
44. Behall KM, Scholfield DJ, Hallfrisch JG, et al. Seasonal variation in plasma glucose and hormone levels in adult men and women. *Am J Clin Nutr* 1984;40(suppl):1352–6.
45. Jarrett RJ, Murrells TJ, Shipley MJ, et al. Screening blood glucose values: effects of season and time of day. *Diabetologia* 1984;27:574–7.
46. Suarez L, Barrett-Connor E. Seasonal variation in fasting plasma glucose levels in man. *Diabetologia* 1982;22:250–3.
47. Simon D, Senan C, Garnier P, et al. Epidemiological features of glycated haemoglobin A1c-distribution in a healthy population. The Telecom Study. *Diabetologia* 1989;32:864–9.
48. MacDonald MJ, Liston L, Carlson I. Seasonality in glycosylated hemoglobin in normal subjects. Does seasonal incidence in insulin-dependent diabetes suggest specific etiology? *Diabetes* 1987;36:265–8.
49. Tahara Y, Shima K. Kinetics of HbA1c, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. *Diabetes Care* 1995;18:440–7.
50. Manttari M, Javela K, Koskinen P, et al. Seasonal variation in high density lipoprotein cholesterol. *Atherosclerosis* 1993;100:257–65.
51. Gordon DJ, Trost DC, Hyde J, et al. Seasonal cholesterol cycles: the Lipid Research Clinics Coronary Primary Prevention Trial placebo group. *Circulation* 1987;76:1224–31.
52. Van Staveren WA, Deurenberg P, Burema J, et al. Seasonal variation in food intake, pattern of physical activity and change in body weight in a group of young adult Dutch women consuming self-selected diets. *Int J Obes* 1986;10:133–45.
53. Tokudome Y, Kuriki K, Imaeda N, et al. Seasonal variation in consumption and plasma concentrations of fatty acids in Japanese female dietitians. *Eur J Epidemiol* 2003;18:945–53.
54. Shahar DR, Yerushalmi N, Lubin F, et al. Seasonal variations in dietary intake affect the consistency of dietary assessment. *Eur J Epidemiol* 2001;17:129–33.
55. 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.
56. Andersson I, Rosner S. The Christmas factor in obesity therapy. *Int J Obes Relat Metab Disord* 1992;16:1013–15.
57. Zahorska-Markiewicz B. Weight reduction and seasonal variation. *Int J Obes* 1980;4:139–43.
58. Pivarnik JM, Reeves MJ, Rafferty AP. Seasonal variation in adult leisure-time physical activity. *Med Sci Sports Exerc* 2003;35:1004–8.
59. Matthews CE, Freedson PS, Hebert JR, 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;153:172–83.
60. Levin S, Jacobs DR Jr, Ainsworth BE, et al. Intra-individual variation and estimates of usual physical activity. *Ann Epidemiol* 1999;9:481–8.
61. Malone CM. The prevalence of physical activity or inactivity in a rural African American community. *J Natl Black Nurses Assoc* 1997;9:58–65.
62. Mundal R, Kjeldsen SE, Sandvik L, et al. Seasonal covariation in physical fitness and blood pressure at rest and during exercise in healthy middle-aged men. *Blood Press* 1997;6:269–73.
63. Uitenbroek DG. Seasonal variation in leisure time physical activity. *Med Sci Sports Exerc* 1993;25:755–60.
64. Dannenberg AL, Keller JB, Wilson PW, et al. Leisure time physical activity in the Framingham Offspring Study. Description, seasonal variation, and risk factor correlates. *Am J Epidemiol* 1989;129:76–88.
65. Bluher M, Hentschel B, Rassoul F, et al. Influence of dietary intake and physical activity on annual rhythm of human blood cholesterol concentrations. *Chronobiol Int* 2001;18:541–57.
66. Prasad GV, Nash MM, Zaltzman JS. Seasonal variation in outpatient blood pressure in stable renal transplant recipients. *Transplantation* 2001;72:1792–4.
67. Mustad V, Derr J, Reddy CC, et al. Seasonal variation in parameters related to coronary heart disease risk in young men. *Atherosclerosis* 1996;126:117–29.
68. Buxtorf JC, Baudet MF, Martin C, et al. Seasonal variations of serum lipids and apoproteins. *Ann Nutr Metab* 1988;32:68–74.
69. Schmidt MI, Matos MC, Branchtein L, et al. Variation in glucose tolerance with ambient temperature. *Lancet* 1994;344:1054–5.
70. Sawin CT, Walder DJ, Bross DS, et al. Diabetes process and outcome measures in the Department of Veterans Affairs. *Diabetes Care* 2004;27(suppl 2):B90–4.
71. Jha AK, Perlin JB, Kizer KW, et al. Effect of the transformation of the Veterans Affairs Health Care System on the quality of care. *N Engl J Med* 2003;348:2218–27.
72. Thompson W, Wang H, Xie M, et al. Assessing quality of diabetes care by measuring longitudinal changes in hemoglobin A1c in the Veterans Health Administration. Statistical models and techniques. *J Gen Intern Med* 2004;19(suppl 1):175.
73. Bickel PJ, Doksum KA. *Mathematical statistics: basic ideas and selected topics*. Vol I. 2nd ed. Upper Saddle River, NJ: Prentice-Hall, 2000.
74. Lehmann EL. *Elements of large-sample theory*. New York, NY: Springer, 1999.

APPENDIX

In time-series analyses, for observations that contain periodic components that fluctuate in a predictable way (e.g., yearly), it may be desirable to use periodic functions to describe/approximate the observations/data. The trigonometric functions sine and cosine are considered the most obvious choices.

In this 2-year study, we observed a yearly cycle of fluctuation, with higher A1c values in winter months, lower

A1c values in summer months, and decreasing values in spring (compared with winter) and increasing values in autumn (compared with summer), as shown in figure 1.

Using the population monthly A1c mean as the dependent variable, we described the periodic (seasonal) fluctuation using the sine function, which is similar to the pattern of data we observed. A standard sine curve goes through zero at $n\pi$, where n is an integer. Since 2π is a complete cycle and since we hypothesized our seasonal cycle to be 12 months as a period, so π corresponds to 6 months. Our data start from October 1998 and go to September 2000; we coded time 1 as the start of the observation period (October 1998), and to every 1-month increment was added an additional 1. Thus, September 2000 was coded as time 24. Therefore, a standard sine curve with a period of 12 months using our study period as an example would have its peak value at time 3 ($= \pi/2$, December) and lowest value (trough) at time 9 ($= 3\pi/2$, June). Our data, however, showed that the peak value was around March and the lowest value was around September; therefore, our sine function needed to take this phase shift into account. The sine function, hence, can be expressed as the following:

$$F(t) = A \times \sin(kt + \phi) \\ = A \times (\sin(kt) \times \cos\phi + \cos(kt) \times \sin\phi) \quad (1)$$

$$= a \times \sin(kt) + b \times \cos(kt), \quad (2)$$

where $k = 2\pi/T$, $T = 12$ (months), $t =$ points of time, $A =$ amplitude, and $\phi =$ phase shift (in radians).

Comparing equations 1 and 2, we can see that $a = A \times \cos\phi$ and $b = A \times \sin\phi$. So $A = \sqrt{a^2 + b^2}$ and $\phi = \tan^{-1}(b/a)$.

We also calculated the variance of amplitude and phase shifts, making use of the delta method (73, 74). Let $G = \begin{pmatrix} A \\ \phi \end{pmatrix}$, with $\text{var}(G)$ calculated as QMQ^T , where Q is the Jacobian matrix between the two parameterizations $\begin{pmatrix} A \\ \phi \end{pmatrix}$ and $\begin{pmatrix} a \\ b \end{pmatrix}$, and M is the covariance matrix of $\begin{pmatrix} a \\ b \end{pmatrix}$.

$$Q = \begin{pmatrix} \frac{\partial A}{\partial a} & \frac{\partial A}{\partial b} \\ \frac{\partial \phi}{\partial a} & \frac{\partial \phi}{\partial b} \end{pmatrix} = \begin{pmatrix} \frac{a}{\sqrt{a^2 + b^2}} & \frac{b}{\sqrt{a^2 + b^2}} \\ \frac{-b}{a^2 + b^2} & \frac{a}{a^2 + b^2} \end{pmatrix};$$

$$M = \text{var} \begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} m_1 & m_2 \\ m_3 & m_4 \end{pmatrix}.$$

So,

$$\text{var}(A) = \frac{1}{a^2 + b^2} (a^2 m_1 + ab(m_2 + m_3) + b^2 m_4);$$

$$\text{var}(\phi) = \frac{1}{(a^2 + b^2)^2} (b^2 m_1 - ab(m_2 + m_3) + a^2 m_4).$$

Note 1: shifted number of months = $12 \times \phi/(2\pi)$, where $\pi = 3.1416$.

Note 2: Because $\tan\phi = \tan(\phi + \pi)$, \tan^{-1} has multiple values (i.e., no unique answers); depending on the signs of a and b , we may need to use ϕ or $\phi + \pi$.