Seasonal Changes in Incidence of Patients With Diabetes Undergoing Cardiac Surgery

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Abstract

Background: To evaluate the monthly incidence rate of patients with diabetes requiring heart surgery at a tertiary-care university hospital in East-Central Europe with a temperate climate zone. We also assessed whether additional factors affecting small blood vessels (smoking, aging, and diabetes) modulate the seasonal variability of diabetes.

Methods: Medical records were retrospectively analyzed for all 9837 consecutive adult patients who underwent surgery at our institution between 2007 and 2018. Individual seasonal variations of diabetes, smoking, and elderly patients were analyzed monthly. Potential additive or subtractive effects of the coexistence of these factors in seasonal changes in incidence rates were also examined. In the absence of a waiting list, incidence rates accurately reflect the frequency of exacerbation of cardiovascular symptoms requiring surgical intervention.

Results: Significant seasonal variations in the monthly incidence rate of diabetes ($p < 0.02$), smoking ($p < 0.001$), and elderly ($p < 0.001$) patients were observed at the cardiac surgery unit. The peak incidence of non-elderly and smoking patients with diabetes was during winter, whereas heart surgery in elderly patients without diabetes and smoking was most frequently required in summer. Concomitant occurrence of diabetes and smoking had an additive effect on the relative incidence rate of requirement for cardiac surgery ($p < 0.001$), while the simultaneous presence of older age and diabetes or smoking eliminated seasonal variations.

Conclusions: Scheduling regular cardiovascular control in accordance with periodicities in diabetes, elderly, and smoking patients more than once a year may improve patient health and social consequences.

Trial registration: NCT03967639

Background

Diabetes mellitus is a complex metabolic disease that can affect vital functions [1]. Cardiovascular complications, such as atherosclerotic cardiovascular and heart failure, are the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), which is the most common form of the disease [2–4]. Treatment of cardiovascular comorbidities comprises drug therapy; however, progression and/or exacerbation of these diabetes-related circulatory complications often require surgical intervention.

It is well established that the incidence of severe cardiovascular diseases exhibits a seasonal pattern, with more frequent relative occurrence during winter [5–9]. Several factors may contribute to these seasonal variations, such as activation of the sympathetic nervous system and increased cathecholamines [10], elevated serum cholesterol levels [11, 12], prothrombotic shift in the hemostatic system via elevated fibrinogen levels [13, 14], decreased physical activity [5], and vitamin D deficiency

[15]. Most of these pathological processes are influenced by diabetes [2, 16–19]. Consequently, seasonal augmentation of clinical signs and symptoms can be anticipated in patients with T2DM, which may require alterations in treatment strategy involving the requirement for cardiovascular surgery. Therefore, we hypothesized that the incidence rate of patients with diabetes requiring cardiac surgery exhibits seasonal variations, peaking during winter. To test this hypothesis, we evaluated the monthly incidence rate of patients with diabetes within a 12-year period at the cardiac surgery unit of a tertiary-care university hospital. We also evaluated whether factors affecting small blood vessels (smoking, aging, and obesity) modulate the seasonal variability of T2DM. Worsening and/or exacerbation of cardiovascular complications necessitating surgery can often be prevented with appropriate medical treatments in patients with diabetes. Thus, exploration of this cold-related seasonal phenomenon may elucidate novel approaches to avoid progression with appropriately timed preventive measures.

Methods

Ethics approval

Ethical approval for this study (no. 274/2018/a) was provided by the Human Research Ethics Committee of Szeged University, Hungary (chairperson, Prof. T. Wittmann) on January 21, 2019. The study was registered at clinicaltrials.gov (NCT03967639).

Study design and population

Medical records were retrospectively analyzed for all 9838 consecutive adult patients who underwent surgery at our institution (Cardiac Surgery Unit, Second Department of Internal Medicine and Cardiology Center at the University Hospitals of Szeged, Hungary) from January 1, 2007 to December 31, 2018. Patients underwent the entire spectra of cardiac surgeries. Our clinical practice avoided a waiting list; therefore, all operations were performed within five days after establishing the requirement for surgical intervention. Since patient records were discarded in case of emergency reoperations as a consequence of tamponade or acute bleeding, patients were included in the analyses only after a primary or redo open heart surgeries.

Cardiac surgery patients were assigned to the following groups, or combinations of groups, based on hospital medical records. Patients were defined as having T2DM if their medical history included a diagnosis of T2DM and/or hemoglobin A1c (HbA1c) > 6.5%, in accordance with the diagnostic criteria of the American Diabetes Association [20–22]. Since almost all (99.6%) patients with diabetes had T2DM, and the etiology and pathophysiological characteristics of type 1 diabetes mellitus differs from that of T2DM, only T2DM patients were included in the analyses, with an average of 8.6 years diagnosed disease period. Among T2DM patients, 25.8% were treated with insulin. Since there was no difference in cardiovascular status between T2DM patients treated with insulin or oral antidiabetics, these patients were pooled in the final analyses. Patients were assigned to the smoking group based on the definitions of the National Center for Health Statistics [23]: current smokers (smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes); everyday smokers (smoked at least 100 cigarettes in his or

her lifetime and currently smokes every day); or ex-smokers (ceased tobacco use < 12 months ago). Patient were considered to be elderly if they were older than the average life expectancy age in southern Hungary published by the Hungarian Central Statistical Office during the study period: ≥72 years for males and ≥ 79 years for females [24]. Obesity was classed according to the definition of the World Health Organization as body mass index (BMI) ≥ 30 kg/m^2 [25]. Individual seasonal effects of these factors were analyzed on a monthly basis. To identify the coexistence of these factors with potential additive or regressive effects on seasonal changes, the combined occurrence of statistically significant factors were also examined.

Monthly average temperature data

Average monthly temperature data for the study period were obtained from the database of the Hungarian Meteorological Service.

Data processing and statistical analyses

Statistically significant differences between the study groups for continuous variables were assessed by one-way analysis of variance followed by followed by Bonferroni's post-hoc tests. Pearson's Chi-squared tests were used to evaluate differences in categorical variables. Monthly incidence rates were calculated as the number of patients with a given risk factor (independently of the other two risk factors, alone, and in combination; e.g., T2DM alone; T2DM and smoking; T2DM, smoking, and elderly) divided by the total number of patients in the same month. Seasonality of the monthly aggregated incidence rates during the study period was assessed using Walter–Elwood and negative binomial regression methods [26], assuming that incidence data followed a sinusoidal curve with a periodicity of one year. Diabetes, aging, smoking, obesity, and gender were considered as possible risk factors for cardiac surgeries. Relative change (peak–mean)/mean was calculated to quantify the severity of seasonality and two compare seasonal amplitudes. Statistical analyses were performed using *R* environment (version 3.5.2) and p-values < 0.05 were considered statistically significant.

Results

Anthropometric data and clinical characteristics

The anthropometric data and main clinical characteristics of the study groups according to significant factors exhibiting seasonal variations in the overall incidence rates are summarized in Table S1 (online supplementary data). In agreement with the worldwide incidence rate (30–40%) of T2DM among patients undergoing cardiovascular surgery [27], 38.4% of patients were diagnosed T2DM in the present study. In accordance with the diagnostic criteria, HbA1c was significantly higher in patients with diabetes (7.75 ± 1.17) than in those without metabolic disorders (5.69 ± 0.4, $p < 0.001$). The preponderance of males observed in the whole study population (63.1%) was also present in each subgroup, with the exception of patients with T2DM alone (51.4%) and those without examined risk factors (52.4%). T2DM was significantly associated with higher body weight ($p < 0.001$) and BMI ($p < 0.001$), whereas smoking was

associated with lower BMI ($p < 0.001$). Compared with patients without risk factors, aortic diseases were more frequent in elderly patients ($p < 0.05$), whereas the prevalence of grown-up congenital heart diseases was lower in T2DM, smoking, and elderly patients ($p < 0.05$). Incidence of coronary disease was generally greater in T2DM and smoking patients ($p < 0.05$).

Seasonal variabilities: significant risk factors

There were no statistically significant seasonal variations for gender ($p = 0.81$) and BMI ($p = 0.75$) for incidence rates; therefore, these variables were not included in further analyses. The main types of heart disease with sufficient numbers of patients available to analyze seasonal changes revealed no statistically significant periodicity ($p = 0.30$, $p = 0.58$, $p = 0.51$, and $p = 0.75$ for aortic stenosis, mitral insufficiency, coronary artery disease, and coronary artery disease with mitral insufficiency, respectively). Conversely, statistically significant seasonal variations for the monthly aggregated data was observed for the incidence rates of T2DM ($p < 0.02$), smoking ($p < 0.001$), and elderly ($p < 0.001$) patients alone. Therefore, further analyses were based on these significant variables alone, and their pairwise and combined coexistence were also examined.

Seasonal variabilities in cardiac surgery patients

Seasonal patterns of statistically significant factors (T2DM alone, smoking alone, and aging alone) for the monthly aggregated data over the 12-year study period are shown in Fig. 1. The incidence of T2DM and smoking patients at the cardiac surgery unit peaked during the winter months and decreased in the summer. Conversely, the seasonal peak for elderly patients was observed in the summer and was lowest in the winter months.

Seasonal variations in the incidence of patients with paired combinations of the significant factors are shown in Fig. 2. No statistically significant seasonal variations were observed in elderly patients with T2DM ($p = 0.66$) or smoking ($p = 0.46$). However, the apparent seasonal variations of T2DM and smoking were additive, resulting a marked and statistically significant effect with peak occurrences of these patients in winter and lower in the summer months.

Table 1 summarizes the main parameters of the seasonal variations observed for the statistically significant individual factors (T2DM, smoking, and aging) and their combination (T2DM and smoking) that demonstrated statistically significant seasonality ($p < 0.001$). The goodness of fit of a simple harmonic trend to the data was excellent (> 0.9) for the variance of incidence rate in T2DM, elderly, and smoking T2DM patients who underwent cardiac surgery. The model fit was worse for seasonal change for smoking only patients; however, a highly significant periodic trend was still observed. The incidence of T2DM and smoking peaked in January and December, respectively, whereas elderly patients most frequently underwent cardiac surgeries in June. To express the magnitude of seasonal differences in the incidence rates of different risk factors for cardiac surgery, the amplitudes of each factor relative to the mean incidence rate ([peak - mean]/mean) and to the nadir ([peak - nadir]/nadir) were also calculated. The greatest seasonal variability was observed for the incidence rate of smoking patients with T2DM, with values indicating that the incidence rate of such patients at the cardiac surgery unit was more than

double in November compared with that in May. The magnitude of seasonal variations in the incidence rates of elderly, smoking, and T2DM patients were lower, but still demonstrated a markedly increased relative risk for cardiac surgeries in the corresponding peak periods.

Table 1

Characteristic parameters of seasonality for statistically significant variables. Maximum increase in incidence rate refers to the peak of the first derivative of the fitted seasonality curves. T2DM: type 2 diabetes mellitus; SM: smoking.

	T2DM alone	SM alone	Elderly alone	SM + T2DM
Significance	p = 0.0184	p < 0.001	p < 0.001	p < 0.001
Goodness of fit	0.92	0.51	0.95	0.97
Peak (month)	January	December	June	November
Nadir (month)	July	May	December	May
(peak – mean)/mean (%)	9.6	16.4	20.3	42.6
(peak – nadir)/nadir (%)	19.2	34.3	52.1	107.0
Maximum increase in incidence rate (month)	October	August	March	September

Table S2 (online supplementary data) demonstrates the mean arterial pressure (MAP) values at admission for the individual factors (T2DM, smoking, and aging) and their combination (T2DM and smoking), revealing statistically significant seasonal changes. The MAP was significantly lower in July than in January for each group ($p < 0.05$).

Discussion

The present study analyzed the medical records of all adult consecutive patients in the past 12-year period at the cardiac surgery unit in our tertiary-care university hospital. Our analyses revealed that the monthly incidence rate of diabetes, smoking, and elderly patients exhibited seasonal variation. Non-elderly patients with diabetes and/or smoking showed a peak incidence during the winter, whereas heart surgery in elderly patients without diabetes and smoking was most frequently required in the summer. Concomitant occurrence of diabetes and smoking had an additive effect on the incidence rate of the requirement for cardiac surgery, while the simultaneous presence of older age and diabetes or smoking eliminated the seasonal variation. Since the standard practice at our institution is to avoid waiting lists longer than five days, the seasonal trends observed in the present study accurately reflect the worsening and exacerbation of cardiovascular diseases requiring surgical interventions.

One of the main findings of the present study was a significant elevation of the incidence of patients with diabetes during the coldest months of the year. The sinusoidal seasonal trend suggested that the relative risk for patients with diabetes undergoing cardiac surgery during the winter period is almost 20% higher

than that in the summer (Fig. 1 and Table 1). In patients with diabetes, hyperglycemia leads to endothelial dysfunction, resulting in low-grade inflammatory, prothrombotic, proliferative, and vasoconstrictive processes [28]. These mechanisms may converge and lead to hypertension, atherosclerotic cardiovascular disease, and heart failure [2, 3, 29–31]. Hypertension may be worsened in a cold environment [5, 32–36], elevating the myocardial workload and myocardial oxygen demand, or exacerbating functional valve insufficiencies. In addition to these mechanisms, viral infections [37] and/or vitamin deficiency [38] may also be involved. This seasonality is reflected in the high incidence rate of type 1 [37, 39] and T2DM [40, 41] during the coldest months. In agreement with previous findings [36], the MAP at admission was significantly higher the present T2DM cohort in January than July over the 12-year study period (Table S2). Severe manifestation of all these pathologies requires surgical intervention more frequently during winter for coronary and heart valve diseases.

The incidence rate of smoking in patients without T2DM or old age was lower than those with T2DM alone in our population. Since the seasonal changes were similar in smoking patients and patients with T2DM only, the relative peak-to-peak seasonal variability reached 34% (Fig. 1 and Table 1). Similar to T2DM, smoking is also characterized by a blunted response to endothelium-dependent vasodilators due to a diminished bioavailability of nitric oxide [42, 43]. Therefore, the mechanisms also triggered by endothelial dysfunction and subsequent elevated vascular tone may be responsible for the seasonal changes in the incidence of smoking patients in the cardiac surgery population. Common pathophysiological processes in T2DM and smoking responsible for the periodicity in their incidence rates were confirmed by the additive effect of these factors, as it is also reflected in the MAP in the coldest season (Table S2). Therefore, the relative peak-to-peak seasonal variability reached more than 100% in smoking patients with diabetes (Fig. 2 and Table 1).

A further significant seasonal variability in the cardiac surgery cohort was observed for elderly patients without T2DM or smoking with peak-to-peak seasonal variability > 50% (Fig. 1 and Table 1). In contrast with smoking and T2DM patients, the incidence rate of elderly patients peaked in summer. This opposite trend in mortality may be attributed to compromised elasticity of large conductive arteries [44]. Stiffening of the large arteries makes elderly people susceptible to hypovolemia and hypotension [45]. The significantly lower MAP observed in July compared with January (Table S2) is in agreement with previous findings, demonstrating that exacerbation of symptoms is expected to be more frequent during the warmest season.

Interestingly, seasonal variability disappeared if aging was associated with diabetes or smoking (Fig. 2). The lack of seasonality in these comorbidities may be attributed to the superposition of two sinusoidal waves of aging and diabetes or smoking. Since these waves have similar a period but opposite phases, the periodicity is eliminated in the resultant relative incidence rate. While the lack of season-dependent periodicity in these patients mimics an invariable monthly incidence rate, these patients are still exposed to both individual risk factors of aging, diabetes, or smoking.

There was no evidence for seasonal changes in the incidence rate of specific heart disease (i.e., aortic stenosis, mitral insufficiency, or coronary artery disease) for the whole population. Seasonal variation may be related to peripheral vasculature sensitivity to temperature changes rather than the type of cardiac disease. This suggests that diabetes, smoking, and aging are the primary season-dependent factors regardless of the nature of heart pathology. Gender and BMI do not directly affect the peripheral vasculature, as these factors exhibited no seasonal appearance.

An important feature of our findings is related to local climate. Hungary is situated in East-Central Europe and has four seasons with a continental climate. The Hungarian Meteorological Service calculated the average monthly temperature from daily averages, which varied between 0.7°C (33.3°F) in January and 23.1°C (73.6°F) in July during the 12-year study period in our region (Fig. 3). Our findings may represent the seasonal changes of cardiovascular comorbidities of diabetes, smoking, and aging in the temperate climate zone of the world where the majority of the human population resides.

Counclusions

In conclusion, analyses of the monthly incidence of diabetes, smoking, and elderly patients in the cardiac surgery unit showed seasonal variations, demonstrating a periodicity in exacerbation of cardiovascular diseases requiring surgical intervention. Matching the intensity and control rate of care to these periodicities could prevent worsening of cardiovascular status in diabetes, elderly, and smoking patients. Cardiovascular risk factors should be systematically assessed at least twice per year in diabetes, smoking, and elderly patients. Cardiovascular assessments should primarily occur during the fall–winter period in diabetes and smoking patients, and the spring–summer season in elderly people. Optimal management of patients with diabetes require more frequent cardiovascular risk assessment than the recommended annual control [2, 22], at least three times a year. Considering the seasonal trends for risk factors affecting at least half whole population may improve patient and social health care.

Abbreviations

BMI
body mass index
HbA1c
hemoglobin A1c
MAP
mean arterial pressure
SM
smoking
T2DM
type 2 diabetes

Declarations

Ethics approval and consent to participate

Ethical approval for this study (no. 274/2018/a) was provided by the Human Research Ethics Committee of Szeged University, Hungary (chairperson, Prof. T. Wittmann) on January 21, 2019. The study was registered at clinicaltrials.gov (NCT03967639).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None

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Authors' contributions

BKN: participated in the data collection and analyses, FP: contributed to the study design, data analyses, preparation of the figures and manuscript drafting, SzA: participated in the data collection and analyses, KV: participated in the data analyses of the seasonal changes, TNy: contributed to establish a model for the analyses of the seasonal changes, AM: participated in the data collection and analyses, RS: participated in the data collection and analyses, CsL: contributed to the study design, interpretation of the seasonal changes and manuscript drafting, BB: contributed to the study design, interpretation of the seasonal changes, data collection, and manuscript drafting. All authors read and approved the final manuscript.

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None

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Figures

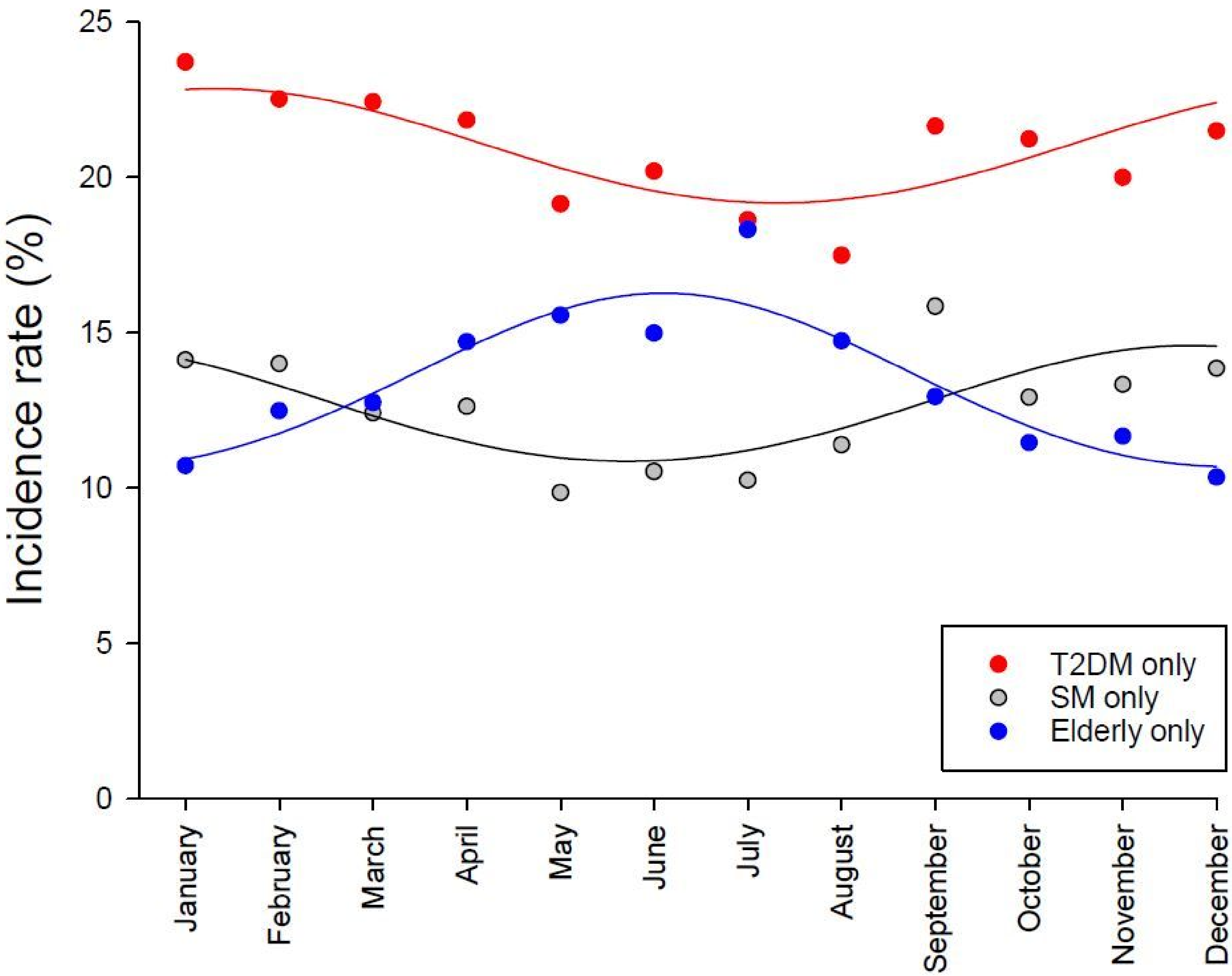

Figure 1

Seasonal changes in the incidence rates of type 2 diabetes mellitus (T2DM only), smoking (SM only), and aging (Elderly only) for the monthly aggregated data over the 12-year study period (January 1, 2007 to December 31, 2018).

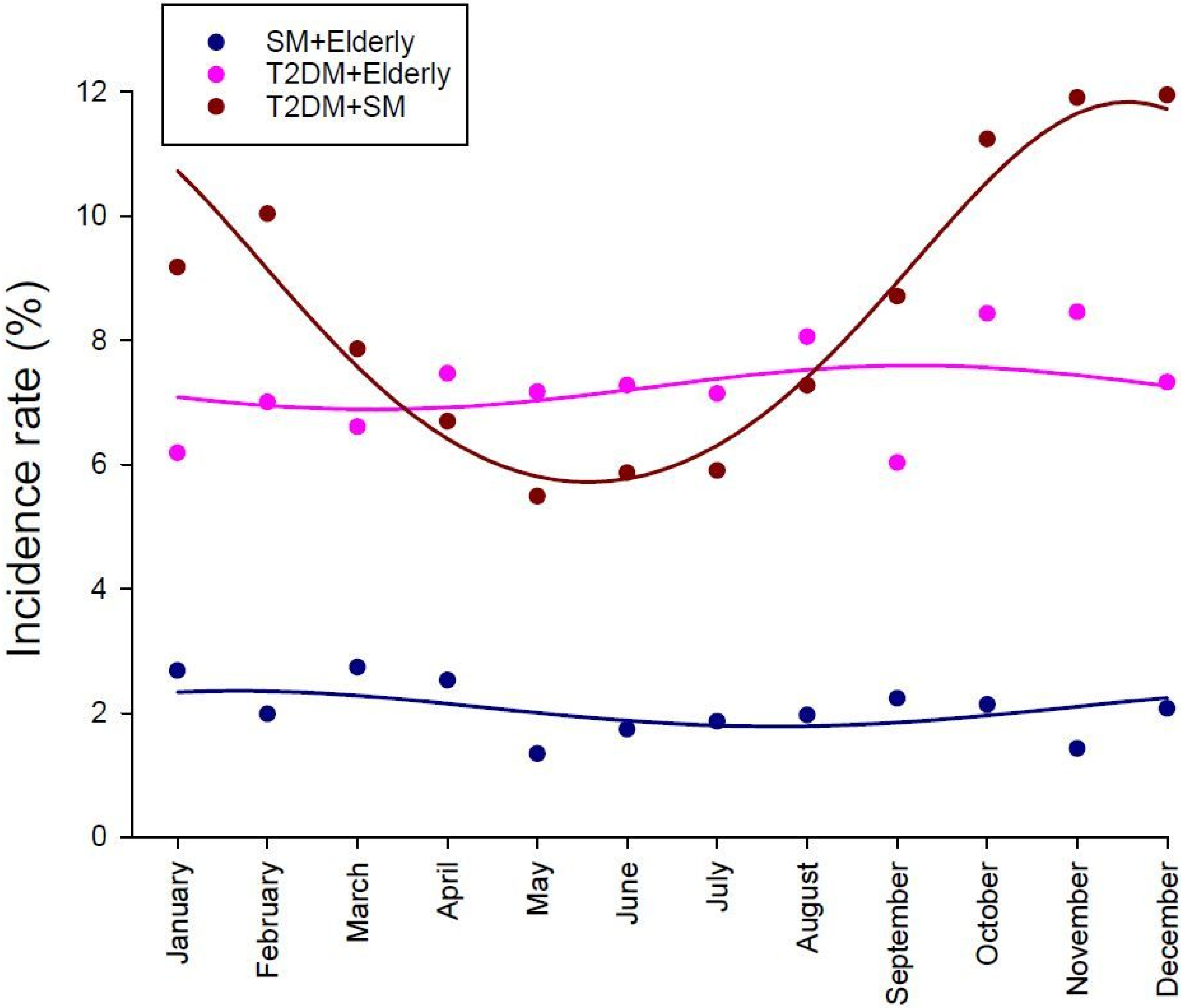

Figure 2

Seasonal changes in the combined incidence rates of smoking and aging (SM + Elderly), type 2 diabetes mellitus and aging (T2DM + Elderly), and type 2 diabetes mellitus and smoking (T2DM + SM) for the monthly aggregated data over the 12-year study period (January 1, 2007 to December 31, 2018).

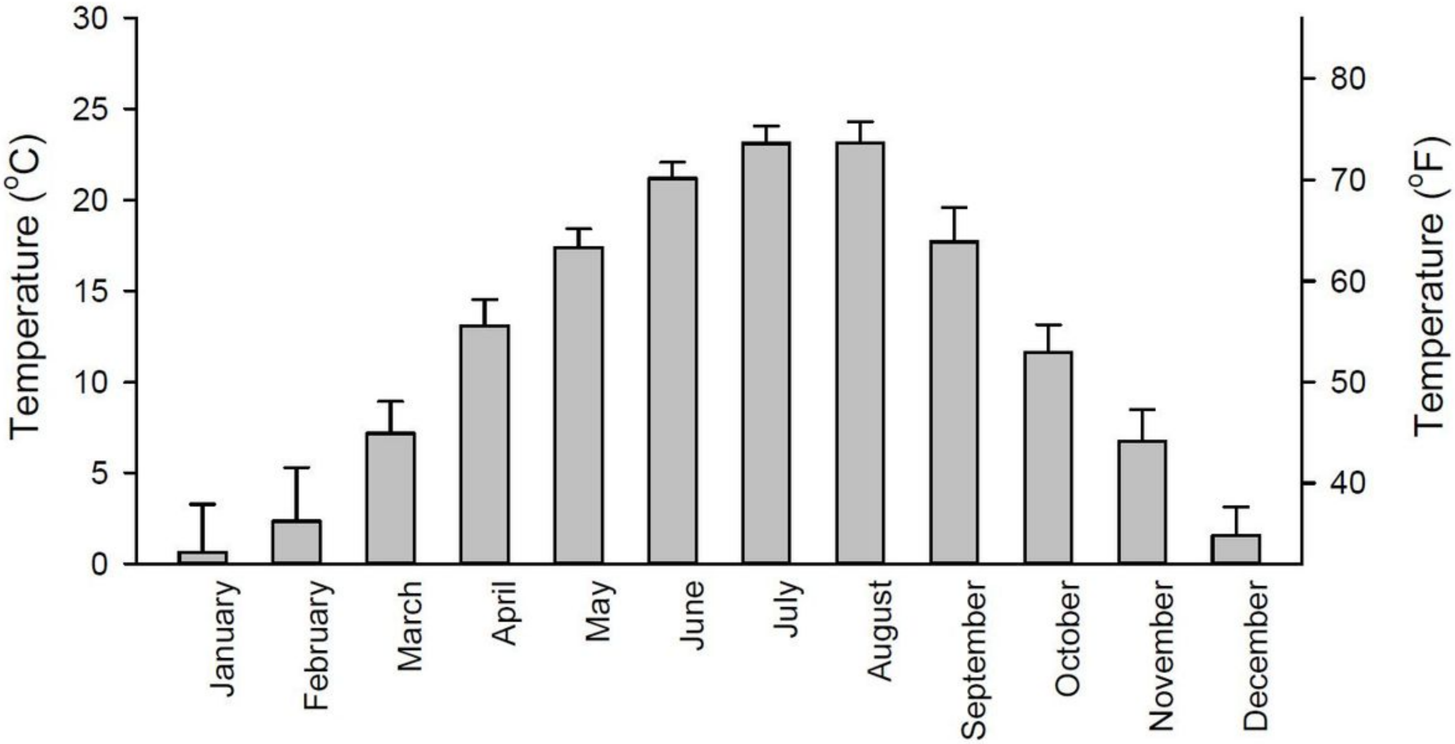

Figure 3

Monthly temperature (mean and SD) calculated from the daily averages according to the Hungarian Meteorological Service for the 12-year study period (January 1, 2007 to December 31, 2018) in South-East Hungary.

Supplementary Files

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