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Article

Novel Data Analyses Explain the Seasonal Variation of Peptic Ulcers

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Abstract: Background: The seasonal variation of peptic ulcers is a rhythmic phenomenon reported worldwide, exhibiting diverse patterns and controversies. Unfortunately, it has remained an unresolved mystery for more than 90 years. Numerous studies have found that this phenomenon was closely associated with multiple environmental factors, but the underlying mechanism has never been elucidated. **Objectives:** This study aims to elucidate the seasonal variation of peptic ulcers and identify the role of environmental factors in the disease. **Methods:** Based on a recently identified etiology of peptic ulcers, two inverse operations in calculus, differentiation and integration, are iterated to analyze the existing data. First, the fluctuation curve in the seasonal variation is differentiated twice into the monthly incidences caused by multiple individual environmental factors, and the fluctuation curve due to each individual environmental factor is generated separately. Second, the monthly incidences caused by the individual environmental factors are integrated twice to reproduce the fluctuation curves in the seasonal variation of peptic ulcers. **Results:** The differentiations of the fluctuation curves in the season variation reveal a parallel relationship between the psychological impacts of each individual environmental factor and the monthly incidences of peptic ulcers. The integrations of the monthly incidences caused by 3 environmental factors reproduce the fluctuation curves in 3 representative seasonal patterns of peptic ulcers but make the parallel relationships invisible. **Discussion:** The parallel relationships revealed a causal role of environmental factors in peptic ulcers, whereas the reproduction of the fluctuation curves elucidated that multiple environmental factors cause the seasonal variation of peptic ulcers by Superposition Mechanism. The regional differences in environmental factors result in the diverse patterns, as well as the controversy questioning the seasonality of peptic ulcers. Significantly, the data analyses exemplify the application of a new concept, Superposition Mechanism, which might be an indispensable methodological complement to life science and medicine.

Keywords: peptic ulcers; seasonal variation; superposition mechanism; climate; work; vacation; environmental factor; psychological stress

Introduction

The seasonal variation of peptic ulcers (including duodenal and gastric ulcers) has been noted in textbooks as early as 1932 [1]. In 1992, Sonnenberg et al. described a typical seasonal pattern in the United States from 1986 to 1989, in which 'hospital admissions for peptic ulcers peaked during the first 3 months of the year, followed by a marked decline in the summer, and then experienced a second smaller peak around October' [2]. In addition, the seasonal periodicity was manifested by changes in ulcer frequency by 10-20% [2]. Over the past decades, numerous reports from China [3], South Korea [4], Turkey [5], Italy [6], Ethiopia [7], and Northern Ireland [8], etc. have confirmed the presence of this rhythmic phenomenon. However, the months with the highest and lowest incidences of peptic ulcers were found to be very different between studies[1].

Unlike the seasonal variation reported by Sonnenberg et al in 1992, Palmas et al reported another pattern in 1984, where the seasonality of active duodenal ulcers in Turin, Italy from 1970 to 1981 is characterized by 'a small peak in July, a sharp decline in August, and an October peak extending through November'[9]. Interestingly, while many studies reported that peptic ulcers were more frequent in the spring and/or autumn and less frequent in summer[1], other data presented an opposite seasonal trend with the highest incidences/peaks of peptic ulcers in the winter[4,10,11]

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and/or summer[5,8], and the lowest in the Autumn[4,8,11]. Moreover, the number of peaks in the fluctuation curves varied from one peak[4,10] to two peaks[2,12], or even 3 peaks[6,8,13]. On the other hand, although a large number of studies discovered a strong seasonal variation of peptic ulcers[2,4,7,11,12], many others reported a weak seasonal variation, where the seasonal differences were not statistically significant[5,14,15]. All these suggest that the seasonal variation of peptic ulcers is a common phenomenon with diverse patterns and controversies[1].

Approximately 13 etiological theories have been proposed to explain the pathogenesis of peptic ulcers in history, but the seasonal variation of the disease has remained a mystery for more than 90 years. In 1950, Alexander believed that peptic ulcers are caused by psychosomatic factors, such as bad habits, poor lifestyle, and unhealthy environment[16], whereas Selye proposed that psychological stress induced by personality traits and/or life events is the cause of peptic ulcers[17]. The two etiological theories were termed *Psychosomatic Theory*[18] and *Stress Theory*[17], respectively. Although both theories were supported by numerous clinical, epidemiological, and laboratory observations[17,19–23], and were demonstrated reproducible[24–31], neither of them has ever elucidated the seasonality of peptic ulcers over the past 70 years, along with many other characteristics and observations/phenomena of the diseases.

The isolation of *Helicobacter pylori* (*H. pylori*) in 1982 was believed to be a revolutionary discovery in peptic ulcer research[32]. In 1987, Marshall proposed that peptic ulcers are an infectious disease caused by *H. pylori* infection[33], and this etiological theory was termed *Theory of H. pylori*[34]. Unfortunately, *Theory of H. pylori* is not superior to any other etiological theory in history but caused more controversies and mysteries in the field. For example, it could not confront the challenges of the 15 characteristics and 75 (of a total 81) observations/phenomena of peptic ulcers, including 30 of 36 observations associated with the bacterium itself[34], but caused another epidemiological mystery, the African enigma[35]. The seasonal changes of *H. pylori* infection were demonstrated not parallel with the seasonality of peptic ulcers[36,37], suggesting that *H. pylori* infection may not play a causal role in the disease. Thus, even the most recent *Theory of H. pylori* cannot elucidate the seasonal variation of peptic ulcers.

Existing data suggests that the seasonal variation of peptic ulcers may be associated not with *H. pylori* infection[38], but with a vast variety of environmental factors, such as climate[15,39,40], work/occupation[41,42], air pollution[43], regional and ethnic differences[38], industrialization[38], vacation/holidays[44], immigration[45], religion[7], smoking and alcohol abuse[8], lifestyle and recreational habits[10]. Numerous studies have found that these environmental factors may induce psychological stress, resulting in peptic ulcers[43,46–48]. Notably, the key environmental factors, which were believed to cause the seasonal variations of peptic ulcers, have been found regionally different[5,8,9], but the underlying mechanism has never been elucidated.

To address the challenges, a recently published Complex Causal Relationship (CCR) with its accompanying methodology[49] was employed to analyze the existing data. *Psychosomatic Theory* and *Stress Theory* were integrated into a new etiological theory, *Theory of Nodes*, in which peptic ulcers are a psychosomatic disease triggered by psychological stress[50], whereas *H. pylori* infection is not a cause of peptic ulcers but plays a secondary role in only the late phase of ulcerations[51]. This new etiology explained all 15 characteristics and 81 observations/phenomena of peptic ulcers in a series of 6 articles, including all 36 observations associated with *H. pylori*[50–54]. All the controversies and mysteries associated with peptic ulcers, including the birth-cohort phenomenon[52] and the African enigma[53], were also resolved. This article is the fifth one of the series, focusing on the 73rd observation, the seasonal variation of peptic ulcers. Notably, since the periodic fluctuation of monthly incidences is the key feature of the seasonal patterns, this study will deliberate on elucidating the mechanism of the fluctuation curves. Moreover, the trends for duodenal and gastric ulcers are similar and thus, the mechanisms of their seasonal variation are elucidated together as peptic ulcers.

Methods

If *Theory of Nodes* proposed the correct cause of peptic ulcers, combined with the local environmental conditions, it should be able to reproduce the fluctuation curves in the seasonal

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variation of peptic ulcers. Interestingly, these fluctuation curves look very similar to the sides of an irregular shape, of which Isaac Newton calculated the area by calculus in the 1660s. Taking clues from Newton, this study iterates the two inverse operations in calculus, differentiation and integration, to reproduce the fluctuation curves in 3 representative seasonal patterns of peptic ulcers.

Based on the etiology proposed in *Theory of Nodes*[51], multiple environmental factors may induce psychological stress, resulting in a total monthly incidence of peptic ulcers. Thus, instead of studying the fluctuation curve directly, herein the data analyses first differentiate the curve into multiple total monthly incidences, each of which is then further differentiated into the monthly incidences caused by individual environmental factors. Climate, work, and vacation are selected as the model factors and the fluctuation curve caused by each factor is generated. Herein, a unified standard/assumption is adopted for all the data analyses: uncomfortable climate or heavy workload induces psychological stress and thus increases the monthly incidences of peptic ulcers, whereas vacation relieves psychological stress, thereby decreasing the monthly incidences of the disease.

Subsequently, the monthly incidences caused by all the individual environmental factors are integrated/supposed twice to reproduce the fluctuation curves in the seasonal variation. First, the monthly incidences (MI) caused by all the individual environmental factors are integrated/superposed into the total monthly incidences by the formula $MI_{Total} = MI_{work} + MI_{Climate} + MI_{Vacation}$. This way of data integration is the vertical sum of the monthly incidences by all the factors and therefore, is termed '*Vertical Superposition*'. Then all the total monthly incidences (MI_{Total}) are placed together in chronological order to produce the fluctuation curve of the total monthly incidences. This way of data packing horizontally creates a chronological view of the total monthly incidences and thus, is termed '*Horizontal Superposition*'. A successful reproduction of the fluctuation curves elucidates the underlying mechanism of the seasonal variation of peptic ulcers.

Results

As mentioned above, the seasonal patterns of peptic ulcers varied greatly between studies[1], making it a laborious task to reproduce the fluctuation curves of all the patterns. To exemplify the data analyses for local seasonality patterns, only the fluctuation curves presented in 3 representative studies are reproduced. Notably, the data analyses can also be applied to all the seasonal data, such as hospital admissions, mortality/morbidity rates, in- and out-patients, bleeding and perforated ulcers, relapse/recurrence, endoscopic records, age groups, etc.

The impacts of seasonal shifts on environments and human behaviors

Unequivocally, one of the environmental factors deeply affected by seasonal shifts on the earth is climate, which in turn influences human behaviors, such as work and lifestyle. Accordingly, the government may formulate policies or laws for the well-being of its people. The impacts of climate, work/occupations, and vacation on health have been well studied in modern research. To simplify the data analyses, herein the roles of the 3 factors in the seasonal variation of peptic ulcers are briefly reviewed.

The impacts of seasonal shifts on climate and peptic ulcers

Many reports have confirmed the roles of climate in the seasonality of peptic ulcers[4,15,39], and meteorological changes may periodically induce a series of stress as a response of the human body[40]. Extreme cold in winter or extreme heat in summer induces psychological stress[55], resulting in peptic ulcers. The Mediterranean climate was found to be predominant for the seasonal and monthly fluctuations in upper gastrointestinal bleedings in Mersin[15], a city and seaport in south-central Turkey. Two studies discovered that the peaks of peptic ulcers are most prominent in colder months[14,56]. In Ethiopia, the peak for perforated peptic ulcers was in the rainy and cold season[7]. The monthly incidences of hematemesis in gastric ulcer patients were found to be associated with mean temperature, vapor pressure, and atmospheric pressure[39]. Both acute and chronic heat stress induced hemorrhagic ulcers in rats[57]. A comprehensive examination of the

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climatological pattern and long-term trend of heat stress discovered that people living in densely populated and urbanized areas experienced severe heat stress conditions during the summer[58]. Despite a milder climate in spring, many individuals may become stressed due to hay fever[59], whereas in autumn, people may become stressed due to the upcoming cold winter[60]. All these suggest that, despite higher monthly incidences due to the extreme weather in winter or summer, climate directly or indirectly induces psychological stress in all four seasons, causing high or low monthly/seasonal incidences of peptic ulcers.

The impacts of seasonal shifts on work/occupations and industry

The seasonal shifts also profoundly influence the work and lifestyle of human beings, causing a 'seasonal nature' of multiple occupations. First, the workload for many industries, such as construction, tourism, agriculture, and fruit and vegetable industries, vary seasonally, resulting in periodic psychological stress[61–65]. Approximately 25% of migrant and seasonal farmworkers have ever experienced stress, depression, or anxiety in their lifetime[66]. Second, the seasonal unemployment patterns, in which companies lay off workers during adverse weather conditions that lower productivity[67], also cause seasonal psychological stress. Third, even though some occupations, such as teachers and students, are non-seasonal, they have to face the challenges of planning school events during spring and autumn, thereby becoming stressed or even burnt out[65,68]. Several factors contribute to workplace stress: workload, interpersonal conflicts, a lack of resources and internal pressures[65,69], a poor work structure or organization, an inflexible management system, and unsatisfactory working conditions[47]. Work-related psychological stress may induce peptic ulcers[46], regardless of *H. pylori* infection and NSAIDs usage[70]. Notably, occupational stress associated with industry and air pollution varied regionally[71], resulting in a region-specific seasonal pattern of peptic ulcers[72].

The impacts of seasonal shifts on vacation and peptic ulcers

Taking vacation gives the individual an opportunity to recover physically, mentally, and emotionally from a challenging or stressful job, thereby preventing and reducing chronic strain reactions to job stress[73]. Opposite to climate and work, vacationing effectively reduces work stress and burnout[74,75], causing a decrease in the incidence and relapse of peptic ulcers[9,73,75]. Many countries have formulated vacation policies based on their tradition and culture, which are seasonal. For example, in the United States, summer is the golden season for traveling and Christmas Day is a statutory holiday; therefore, most families are accustomed to taking a long vacation for relaxation, family gatherings, or activities during the two periods, leading to the relief of stress. Tom et al. found that the seasonal variation of peptic ulcers in Honolulu is primarily impacted not by climate, but by holidays[44]. Palmas also discovered that from 1979 to 1981, the fluctuations of duodenal ulcer relapse in Turin, Italy were influenced not by climate, but by stress relief due to the summer vacation[9]. Both studies suggest that the significant impact of vacation on the seasonality of peptic ulcers. Southard found that the vacation policies of the United States and European countries are quite different: the United States does not require employers to pay employees for vacation and holidays, whereas the employers of most European countries provide paid vacation and a certain number of paid holidays[76]. Consequently, Americans may have less time or a shorter duration for vacation, making it less effective in relieving stress[77]. The psychological impact of vacationing suggests that vacation policies may significantly affect the seasonal patterns of peptic ulcers.

Notably, there are many other environmental factors not listed here, which are influenced by the seasonal shifts on the earth. They periodically cause or relieve psychological stress in the population, regularly resulting in increased or decreased incidences of peptic ulcers in some months of the year and thus, play a role in the seasonal variation of peptic ulcers.

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The fluctuation curves caused by individual environmental factors

In *Theory of Nodes*, peptic ulcers are a psychosomatic disease triggered by psychological stress[50,51]. Based on this etiological theory, there are always a proportion of individuals who are genetically predisposed to peptic ulcers, and due to past life experiences/psychosomatic factors, many of them have developed hyperplasia and hypertrophy of gastrin and parietal cells in the stomach[51], or have formed a negative life-view[50]. These ready-to-ulcerate individuals may become ulcer patients if psychological stress is induced[52]. Hence, either extreme climate (too hot in July and August, or too cold in December and January) or heavy workload (due to comfortable climate in April and May or October and November) may induce psychological stress among more people, causing an increase of the monthly incidences, whereas vacation (probably in July and August or in December and January) relieve psychological stress, resulting in a decrease of the monthly incidences (Figure 1A). Therefore, once the horizontal superposition is applied, each individual environmental factor causes its own fluctuation curve, where the psychological impact of the factor is parallel with the rise and fall trends of the monthly incidence (Figure 1B). Notably, unlike the birth-cohort phenomenon, where unpredictable extraordinary environmental factors caused a wide range of fluctuations in annual mortality rates[52], the seasonal variation of peptic ulcers is caused by predictable and periodic ordinary environmental factors, exhibiting a relatively narrow range of fluctuation of monthly incidences as illustrated in Figure 1B. To amplify the fluctuation trends, herein the Monthly Incidence (MI) by each individual factor is calculated by the formula MI = Monthly Cases by the factor ÷ Average Monthly Cases by all 3 factors x 100%.

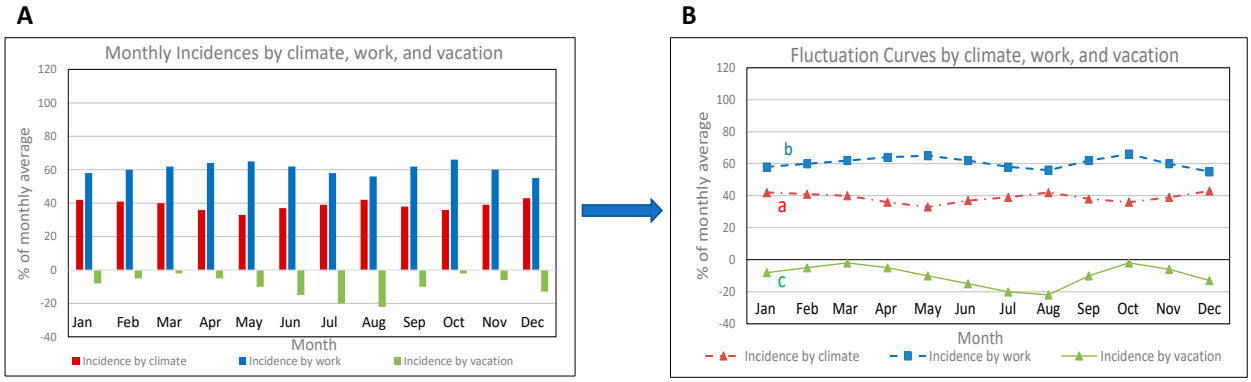

Figure 1. Climate, work, and vacation cause their own fluctuation curves independently. The data in this figure is representative of a hypothetical scenario over a year, where the total monthly incidence is caused by climate, work, and vacation. **A:** Each one, climate, work, and vacation, causes its own monthly incidence independently. **B:** The monthly incidences by each of the climate, work, or vacation were superposed horizontally to generate its own fluctuation curves, respectively. **a)** Heat in summer (July and August) and cold in winter (December and January) result in relatively higher monthly incidences than that in spring or autumn. **b)** Heavier workloads in spring (April and May) and autumn (October and November) make the monthly incidences in the two seasons higher than those in winter and summer. **c)** Opposite to climate and work, vacation reduces the monthly incidences, especially during summer vacation and Christmas time.

Reproducing the fluctuation curve of a weak seasonal variation

The CCR dictates that a life phenomenon is usually caused not by a single factor, but by multiple factors based on *Superposition Mechanism*[49,51]. Thus, the total monthly incidence of peptic ulcers in the seasonal variation is the sum (vertical superposition/integration) of the monthly incidences caused by all the individual environmental factors. However, in regions or populations without summer vacation and/or Christmas holidays, the seasonal patterns were caused primarily by climate and work. Thus, the total monthly incidence (MI_{total}) is calculated by the formula $MI_{total} = MI_{Climate} + MI_{Work}$ (Figure 2A). Then the horizontal superposition is employed to generate the fluctuation curve of the total monthly incidences (Figure 2B), which can also be derived from the integration/superposition of the curves caused by climate and work. Notably, after the

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integration/superposition, the rise or fall trends of the monthly incidences caused by climate (Figure 2B-a) are counterbalanced by the opposite trends caused by work (Figure 2B-b), making the differences between any two total monthly incidences not statistically significant to demonstrate a seasonal variation (Figure 2B-c). This flattened curve reproduced the fluctuation curves in the weak seasonal variations observed in many studies [5,14,15], and resolved the controversy questioning the seasonality of peptic ulcers[1,14]. Apparently, after the integration/superposition, the parallels between the psychological impacts of each individual environmental factor and the monthly incidences of peptic ulcers disappeared, indicating that the parallel relationships were hidden in the fluctuation curve of the weak seasonal variation. Conversely, a differentiation would uncover the parallel relationships (between the psychological impact of individual environmental factors and the monthly incidences of peptic ulcers) from the fluctuation curve of the weak seasonal variation.

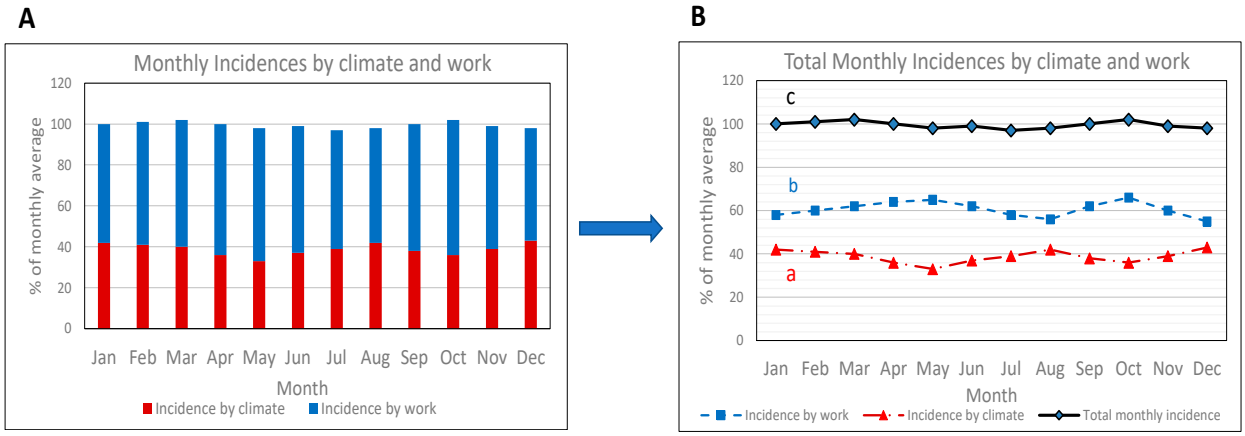

Figure 2. Reproducing the fluctuation curve of a weak seasonal variation. The data in this figure is representative of a hypothetical scenario, where a total monthly incidence is caused by climate and work without vacation. **A:** A total monthly incidence of peptic ulcers is calculated by the vertical superposition of the monthly incidences caused by climate and work. **B:** The total monthly incidences are horizontally superposed to obtain the fluctuation curve of the total monthly incidences in a year. **a)** The fluctuation curve of monthly incidences caused solely by climate. **b)** The fluctuation curve of monthly incidences caused solely by work. **c)** The fluctuation curve of total monthly incidences caused by climate and work, which can also be derived from the superposition of curve a and curve b.

Reproducing the fluctuation curve of the seasonality observed by Sonnenberg

Vacationing has been an important part of American culture since the mid-1800s[78]. In the United States, the summer break for schools, starting from mid- to late-June and returning at the end of August, is the most popular time of the year for vacation. The Christmas break, starting from December 23 until New Year's Day (January 1st), is also a season bringing families and friends together. Both of the relaxation periods effectively reduce psychological stress[73–75], causing a significant decrease in the monthly incidences of peptic ulcers in the United States as shown in Figure 3A. In this case, the total monthly incidence (MI_{Total}) is calculated by a vertical superposition/integration of all the total monthly incidences via the formula $MI_{total} = MI_{Climate} + MI_{Work} + MI_{Vacation}$ as illustrated in Figure 3B. Although there was no obvious fluctuation after the superposition of the monthly incidences caused by climate and work (Figure 2B-c), the psychological effects of vacation (Figure 3B-c) made the differences between any two total monthly incidences statistically significant (Figure 3B-d), suggesting that the seasonal variation observed by Sonnenberg was primarily due to the vacation policy. The vacation policy predominated the fluctuation of this pattern, highlighting the impacts of social environmental factors on the prevalence of peptic ulcers. Similar to the weak seasonal variation, after the superposition, the parallel relationships between the psychological impacts of individual environmental factors and the monthly incidences of peptic ulcers in Figure 3B-a, -b & -c were hidden in Figure 3B-d, which reproduced the fluctuation curve in

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the seasonal pattern observed by Sonnenberg. Conversely, the fluctuation curve in this seasonal pattern can be differentiated into curves a, b & c to surface the hidden parallel relationships.

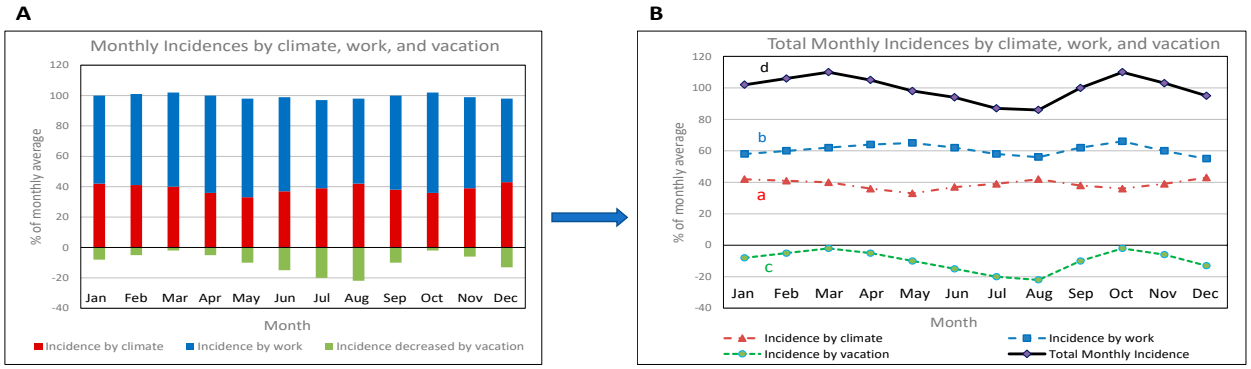

Figure 3. Reproducing the fluctuation curve of the seasonal pattern reported by Sonnenberg. The data is representative of a hypothetical scenario of the population from 1986 to 1989 observed by Sonnenberg. **A:** both climate and work cause monthly incidences of peptic ulcers, whereas vacation decreases the monthly incidences during summer break and Christmas holidays. Therefore, all the values of monthly incidences caused by vacations are negative. **B:** The total monthly incidences are horizontally superposed to form the fluctuation curve of total monthly incidences in a year. **a)** The fluctuation curve of monthly incidences caused solely by climate. **b)** The fluctuation curve of monthly incidences caused solely by work. **c)** The fluctuation curve of monthly incidences caused solely by vacation. **d)** The fluctuation curve of total monthly incidences caused by climate, work, and vacation derived from the superposition of curves a, b, and c. Note: curves a and b in this figure are the same as curves a and b in **Figure 1B** and **Figure 2B**; curve c is the same as the curve c in **Figure 1B**.

Reproducing the fluctuation curve of the seasonal variation observed by Palmas

The data analysis of the seasonal variation in Turin, Italy reported by Palmas in 1984 is similar to the analysis above on Sonnenberg's reports in 1992, resulting in Figure 4A,B. The heat in summer and cold in winter incurred the highest incidences of peptic ulcers in July and August, December and January, respectively (Figure 4B-a). The industries of Turin are characterized by manufacturing, engineering, production of confectionery and chocolate with growth in construction, tourism, and service industries[79]. It was very likely that in July, to prepare for the August vacation, many people in this city were busier than most of the other months due to heavier workloads, resulting in psychological stress in more individuals and a small July peak (Figure 4B-b). This July peak highlighted the impacts of occupational factors or local industry on the seasonal variation of peptic ulcers. Noticeably, in Italy 'during the month of August, more than half of the population leave the city to go on vacation'[80], suggesting that, while Italians attach high importance to the summer vacation in August, they may care less about the Christmas holidays. As a result, the monthly incidence in August was significantly lower than most of the other months, whereas the monthly incidence in December reduced slightly due to the Christmas break (Figure 4B-c). Similar to the two other seasonal patterns analyzed above, the parallel relationships between the psychological impacts of individual environmental factors and the monthly incidences of peptic ulcers (Figure 4B-a,-b,-c) were hidden in the integrated curve (Figure 4B-d), which reproduced the fluctuation curve of the seasonal variation in Turin, Italy reported in 1984 [9].

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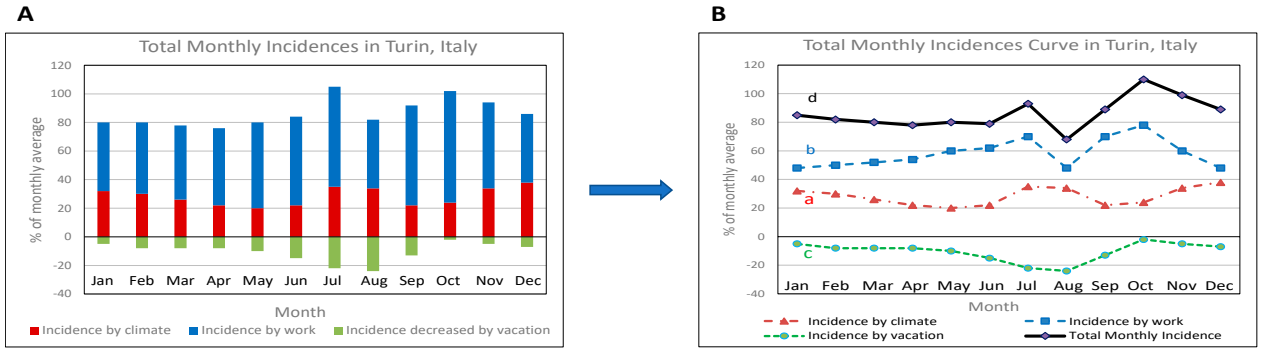

Figure 4. Reproducing the fluctuation curve of the seasonal variation in Turin, Italy. The data is representative of a hypothetical scenario in Turin, Italy from 1979-1981. **A:** The vertical superposition of the monthly incidences due to work, climate, and vacation. The calculation is the same as in **Figure 3**. **B:** The total monthly incidences are horizontally superposed to illustrate the fluctuation curve of total monthly incidences in a year. **a)** The fluctuation curve of monthly incidences caused solely by climate. **b)** The fluctuation curve of monthly incidences caused solely by work, where the monthly incidence in July was higher than most of the other months of the year. **c)** The fluctuation curve of monthly incidences caused solely by vacations, where summer breaks in July and August significantly reduced the monthly incidences, but Christmas break only slightly reduced the monthly incidence. **d)** The fluctuation curve of total monthly incidences caused by climate, work, and vacation is derived from the superposition of curves a, b, and c.

Comparison between the birth-cohort phenomenon and seasonal variation

Both the birth-cohort phenomenon and seasonal variation are important epidemiological characteristics of peptic ulcers, but they have never been fully understood in modern medicine. *Theory of Nodes* elucidated both mysteries by the same etiology and analytical method, although they investigated the epidemic of peptic ulcers from different angles. In the birth-cohort phenomenon, the fluctuation curves highlight the impacts of extraordinary environmental factors (crucial events)[52], whereas, in the seasonal variation, the fluctuation curves reflect the consequences of ordinary environmental factors (common events). The resolution of the two mysteries reveals that both are compelling evidence for a causal role of environmental factors in peptic ulcers, further supporting the etiology proposed by *Theory of Nodes*, where peptic ulcers are a psychosomatic disease triggered by psychological stress. Table 1 lists the major similarities and differences between the two epidemiological observations.

Table 1. Similarities & differences between birth-cohort phenomenon and seasonal variation.

	Birth-cohort Phenomenon[52]	**Seasonal Variation**
Similar Features	1. Important epidemiological observations/phenomena.	
	2. Compelling evidence for a causal role of environmental factors in peptic ulcers, which cause the disease by inducing psychological stress.	
	3. Multiple environmental factors cause the phenomenon via *Superposition Mechanism*; fluctuation curves can be differentiated to reveal a parallel relationship between psychological impacts of individual environmental factors and the mortality/morbidity rates of peptic ulcers.	
	4. Without considering *H. pylori* infection.	
	5. Implicate that peptic ulcers are not an infectious disease caused by *H. pylori* infection, but a psychosomatic disease triggered by psychological stress.	
	6. Epitomize the exogenous psychological stress induced by environmental factors.	

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Different Features	1. An epidemiological observation on an annual basis, in which the mortality rates increase and decrease sharply.	1. An epidemiological observation on a monthly/seasonal basis, in which the incidences increase and decrease slightly.
	2. Fluctuation curves were primarily due to extraordinary environmental factors; the annual mortality rates fluctuate within a wide range.	2. Fluctuation curves were caused by ordinary environmental factors; the monthly incidences fluctuate within a narrow range.
	3. Less diversity: increased mortality rates are maintained by sudden and short-term extraordinary environmental factors. Not a rhythmic phenomenon.	3. More diversity: increased incidences are maintained by periodic and predictable ordinary environmental factors, causing a rhythmic phenomenon.
	4. Crucial events (extraordinary environmental factors) induce gastric ulcers in 'ready-to-ulcerate' individuals. Secondary stressors induce hyperplasia and hypertrophy of gastrin and parietal cells in the stomach, resulting in duodenal ulcers after 3-5 years.	4. Common events (ordinary environmental factors) induce both gastric and duodenal ulcers in 'ready-to-ulcerate' individuals.
	5. Needs more data covering many years and is harder to study, resulting in relatively fewer reports in the existing literature.	5. Data covering ≥ 3 years is sufficient and easier to study, resulting in many reports in the existing literature.

Discussion

The seasonal variation of peptic ulcers was reported to be closely associated with multiple environmental factors with diverse patterns and controversies, but its mechanism has remained a mystery for more than 90 years[1]. Starting from the etiological theory proposed recently[51] and combined with the local environmental conditions, this study superposed the monthly incidences of peptic ulcers caused by 3 environmental factors in two ways to reproduce the fluctuation curves in the seasonal variation. The results suggest that if peptic ulcers are considered a psychosomatic disease triggered by psychological stress, the fluctuation curves in 3 representative seasonal patterns can be reproduced. It was a definite etiology and the application of a new methodological concept that made the reproduction successful. Most importantly, the reproduction of the fluctuation curves in the seasonal variation identified a causal role of environmental factors in peptic ulcers.

The widely believed H. pylori infection may not be the cause of peptic ulcers

Unequivocally, a definite etiology is essential to elucidate the seasonal variation of peptic ulcers. However, the widely believed *H. pylori* infection as the cause of peptic ulcers is currently controversial[81–85]. Consequently, there is no starting point to analyze the data, making the seasonal variation an unresolved mystery for a long time. Interestingly, without considering *H. pylori* infection, *Theory of Nodes* reproduced the fluctuation curves in the birth-cohort phenomenon[52] and seasonal variations (this study), indicating that *H. pylori* infection may not be the cause of peptic ulcers. On the other hand, provided that *H. pylori* is the cause of peptic ulcers, its infection rates should be parallel with the fluctuation in the seasonal variation. Unfortunately, the seasonal changes of *H. pylori* infection have been demonstrated to be not in parallel with the seasonal variation of peptic ulcers[36,37], also suggesting that a causal role of *H. pylori* infection in peptic ulcers is inconclusive.

Moreover, an etiology proposing the correct cause should be able to elucidate all the characteristics and observations/phenomena of the disease. However, *Theory of H. pylori* cannot elucidate the majority of the 15 characteristics and 81 observations/phenomena of peptic ulcers[34], including the birth-cohort phenomenon and seasonal variation. In contrast, *Theory of Nodes*, where peptic ulcers are not an infectious disease caused by *H. pylori* but a psychosomatic disease triggered

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by psychological stress, elucidated all 15 characteristics and 81 observations/phenomena of peptic ulcers[50–54]. The tremendous contrast further suggests that *H. pylori* infection is not the cause of peptic ulcers. *Theory of Nodes* elucidates that *H. pylori* infection proportionally increases the annual mortality rates or monthly incidences but does not affect the fluctuation trends in both the birth-cohort phenomenon and seasonal variation of peptic ulcers.

A viable analytical method is indispensable to elucidate the seasonal variation

Surrounding psychological stress induced by ordinary environmental factors, herein the data analyses elucidated the seasonal variation of peptic ulcers. Notably, as early as 1950, Selye emphasized the important role of psychological stress in peptic ulcers in his *Stress Theory*[17], but the seasonal variation has remained elusive for 70 years, suggesting that a correct etiology alone is inadequate for a full understanding of this observation. In *Theory of Nodes*, the data analyses are characterized by the repeated applications of a new methodological concept, *Superposition Mechanism*. As a result, both the birth-cohort phenomenon and season variation of peptic ulcers, as well as all the clinical, epidemiological, and laboratory observations of peptic ulcers[50–54], were elucidated. Unfortunately, due to a reductionist approach, which attempts to explain an entire system in terms of its parts[86,87], the concept of the '*Superposition Mechanism*' has never come into being in modern medicine. Consequently, even though *Stress Theory* has determined the cause of peptic ulcers, it has never elucidated the two epidemiological observations for many decades but was deemed outdated soon after the discovery of *H. pylori*[88].

The *Superposition Mechanism* showcased herein is a key methodological concept originated from the CCR, which dictates that all the small parts of the human body studied in modern medicine should be integrated into the original whole for a complete study. Therefore, *Superposition Mechanism* is a thought process opposite to the reductionist approach of modern medicine. Taking the reductionist approach alone for research, modern medicine has never explained the majority of the 15 characteristics and 81 observations/phenomena of peptic ulcers[34], including the birth-cohort phenomenon and seasonal variation. In contrast, *Theory of Nodes* applied both the reductionist approach (differentiation twice) and the *Superposition Mechanism* (integration twice) simultaneously, thereby elucidating all 15 characteristics and 81 observations/phenomena of peptic ulcers[34], including the birth-cohort phenomenon[52] and seasonal variation. The tremendous contrast suggests that the concept *Superposition Mechanism* is an indispensable methodological complement to life science and medicine. By elucidating the two mysteries (the birth-cohort phenomenon[52] and seasonal variation) simultaneously, *Theory of Nodes* exemplified the application of *Superposition Mechanism* to resolving the mysteries of life and health. It can be expected that the wide application of *Superposition Mechanism* in medical research may allow us to gain unprecedented insights into many life phenomena and human diseases.

Multiple environmental factors cause the seasonal variation by Superposition Mechanism

Numerous studies have reported that the seasonal variation of peptic ulcers was closely associated with environmental factors[5,7,43,56], but the underlying mechanism has never been elucidated in modern medicine. *Theory of Nodes* dictates that environmental factors cause peptic ulcers by inducing psychological stress. Consistent with a unified standard for psychological stress induced by environmental factors, the data analyses herein successfully reproduced the fluctuation curves in not just one, but three representative seasonal patterns, suggesting that the etiology proposed by *Theory of Nodes* is conclusive. Therefore, while elucidating the seasonal variation as well as the birth-cohort phenomenon in the fourth article of the series[52], the data analyses guided by the CCR with its accompanying methodology established a causal relationship between environmental factors and peptic ulcers.

Moreover, provided a factor is the cause of peptic ulcers, its negative or positive impacts should be parallel with the incidences to demonstrate its causal role in the occurrence of the disease. *H. pylori* infection has been demonstrated not to be parallel with the fluctuation of peptic ulcers in the seasonal variation[36,37], indicating it is not a cause of peptic ulcers. In contrast, before superposition, the

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psychological impacts of each environmental factor were parallel with their respective monthly incidences of peptic ulcers. The superposition of the fluctuation curves of multiple individual environmental factors reproduced the fluctuation curves of the seasonal variation, but the overall effect after the superposition hid the parallel relationships between individual environmental factors and the monthly incidences of peptic ulcers. Thus, due to the superposition, the rise or fall trends caused by individual environmental factors were weakened or strengthened by other coexisting environmental factors, making the parallel between individual environmental factors and peptic ulcers invisible. The differentiation operations revealed a parallel relationship between environmental factors and peptic ulcers hidden in the seasonal variation, which identified a causal role of environmental factors in peptic ulcers, whereas the integration operations reproduced the fluctuation curves, suggesting that multiple environmental factors cause the seasonal variation by *Superposition Mechanism*.

Significantly herein, the data analyses can be repeatedly applied to elucidate the seasonal variation of many other diseases. Interestingly, Sonnenberg and colleagues found that the seasonal variation is not a feature particular to peptic ulcers, but widely observed in many diseases, and they speculated that the major factors responsible for the seasonality of human diseases might be very similar, but none of the mechanisms have ever been understood[2]. The mechanism herein may make peptic ulcers the first disease, of which the seasonal variation is elucidated. The seasonal variations of many diseases likely share a similar mechanism, where the seasonal shifts on the earth periodically affect multiple environmental factors, causing this rhythmic phenomenon by *Superposition Mechanism*. Therefore, both the etiology and methodology showcased herein might be important references for a full understanding of the seasonal variation of many diseases.

Regional differences in environmental factors lead to diverse patterns and controversy

Combined with the local environmental conditions, the data analyses reproduced the fluctuation curves in 3 representative studies, suggesting the powerful impact of regional differences in environmental factors on the seasonal variation of peptic ulcers. Interestingly, the seasonal pattern in Emilia-Romagna, Italy reported in 2010[6] is similar to the one in Turin, Italy reported in 1984[9], but the July peak disappeared. This nuance may highlight the impacts of regional differences in a single environmental factor on the seasonal patterns of peptic ulcers, as Turin and Emilia-Romagna are two adjacent regions in the same country with similar climate and vacation policies. It is very likely that the industrial/occupational structure differences between the two regions caused this nuance. In July, while people in Turin were busy in the construction, tourism, and service industries[79], people in Emilia-Romagna were relatively relaxed due to their agricultural and manufacturing (automobile, motor, and mechanics) industries[89]. The possible mechanism of this nuance merits an in-depth study, as it may implicate the predominant role of a single environmental factor in the seasonality of peptic ulcers. Moreover, Bekele et al. and Nomura et al. concluded that the seasonality of peptic ulcers in the regions they studied was associated with climate[7,39], whereas Tom's comparative study did not find any relationship between climate and the seasonality of hemorrhaging ulcer incidences in Hawaii[44]. All these suggest that the regional differences in environmental factors account for the diverse seasonal patterns of peptic ulcers.

The discussions above suggest that the seasonal variation of peptic ulcers should be studied on a case-by-case basis, and we should have an intimate knowledge of the local environmental factors, such as the geographical environment, historical tradition, unique climate, industry categories, vacation, and well-being policies, and all the social and natural environmental factors that may induce or relieve psychological stress. Notably, some epidemiological observations may focus on a special population, resulting in a specific seasonal pattern. For example, in the seasonal variation of peptic ulcers reported by Sonnenberg in 1992, the data was collected from the Department of Veterans Affairs[2], where all the patients are U.S. military veterans from Veterans Affairs Hospitals. This may make the seasonal pattern quite different from the other patterns observed at other locations in the United States. It is worth mentioning that the mechanism elucidated herein suggests that despite the counterbalance between the incidences, one or two environmental factors, such as the industrial

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structure or vacation policy, may predominantly determine the seasonal pattern of a region. However, the *Superposition Mechanism* suggests that each environmental factor contributes to the total monthly incidence of peptic ulcers and therefore, is a part of the mechanism, reflecting the high complexity of the seasonal variation of peptic ulcers. It cannot be ruled out that in some regions, the rise or fall trends caused by some environmental factors were counterbalanced by other environmental factors, resulting in a weak seasonal pattern or controversy questioning the seasonality of peptic ulcers.

Limitations

First, the data available for the local environmental conditions associated with the 3 representative seasonal patterns is quite limited as they are retroactive studies reported decades ago. Herein the data analyses were based on widely known tradition, culture, or national policies, and the impacts of occupational and industrial structure on health were based on speculation. In addition, facing a large number of studies reporting weak seasonal patterns, the data analyses could only give an example of the counterbalancing effects between two environmental factors. However, the interactions between multiple environmental factors are complex and diverse, and a specific analysis based on detailed local environmental conditions is essential to elucidate a particular seasonal pattern.

Second, this study is descriptive research without mathematical operations and it did not rely heavily on statistical significance[90]. Herein the statistical significance is determined not by p-values, but by changes in the range of fluctuation instead. After the superposition of the monthly incidence caused by two or three environmental factors, the narrow range of fluctuation with a flattened curve is considered statistically insignificant, making it more likely to be a weak seasonal variation, whereas a widened range of fluctuation with an uneven curve is considered statistically significant, making it more likely to be a strong seasonal variation. However, in the case of elucidating a specific seasonal pattern with mathematical operations based on the mechanism proposed herein, searching for statistical significance is still essential for data analyses.

Third, environmental factors are not the only source of psychological stress that induces peptic ulcers. As elucidated previously[50,51], there are two sources of stress: endogenous and exogenous. Endogenous stress is induced by the internal factors of the individual, such as personality traits, personal threat, and goal frustration[50,51]. Exogenous stress is induced by external environmental factors, such as life events, climate, and occupational factors as discussed above. The environmental factors discussed herein represent the exogenous source of psychological stress. Since the monthly incidences caused by endogenous stress stay fairly constant; therefore, they won't affect the fluctuations in the seasonal variation of peptic ulcers, which were predominated by environmental factors as elucidated herein.

Conclusions

The seasonal variation of peptic ulcers can be elucidated if the diseases are considered a psychosomatic disease triggered by psychological stress and a new methodological concept, *Superposition Mechanism*, is employed to analyse the existing data. The seasonal shifts on the earth periodically alter multiple environmental factors, each of which induces psychological stress in a proportion of individuals, resulting in a monthly incidence of peptic ulcers. It is not the seasonal changes of *H. pylori* infection, but the psychological impacts of each individual environmental factor that are parallel with the incidences of peptic ulcers, supporting a causal role of environmental factors in the disease. Multiple environmental factors cause the seasonal variation of peptic ulcers by *Superposition Mechanism*, and the regional differences in environmental factors result in diverse seasonal patterns, as well as the controversy on this topic. Notably, the mechanism elucidated herein validated a new concept, *Superposition Mechanism*, which may represent a significant methodological advance towards a full understanding of many life phenomena and human diseases.

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