Article

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Novel Data Analyses Explain the Seasonal Variation of Peptic Ulcers

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Abstract: Although 13 etiological theories, including the most recent *Theory of Helicobacter pylori*, have been proposed to explain the pathogenesis of peptic ulcers, the seasonal variation of the disease has remained an unsolved mystery for ≥90 years. Additionally, the major characteristics and observations/phenomena of peptic ulcers have never been fully understood. To address these challenges, a recently published Complex Causal Relationship with its accompanying methodologies was applied to analyze the existing data. Peptic ulcers were identified as a psychosomatic disease triggered by psychological stress, where *Helicobacter pylori* plays a secondary role in only the late phase of ulceration. This etiology addresses all the characteristics, observations/phenomena, controversies, and mysteries of peptic ulcers in a series of 6 articles. This fourth article focuses exclusively on the seasonal variation of peptic ulcers. The seasonal changes on the earth periodically alter multiple environmental/social factors, each of which induces psychological stress in a proportion of individuals and result in a monthly incidence of peptic ulcers. The superposition of the monthly incidences caused by climate, work, and vacation reproduces 3 typical fluctuation curves of the seasonal variation. Further discussion suggests that surrounding psychological stress, multiple environmental and social factors, such as tradition, climate, industry, vacation, and well-being policies, work together to cause the diversity of the seasonal variation. A full understanding of the seasonal variation suggests that peptic ulcers are not an infectious disease caused by *Helicobacter pylori*, but a psychosocial disease associated with multiple environmental/social factors, further validating the etiology identified by the Complex Causal Relationship.

Keywords: peptic ulcer; seasonal variation; superposition mechanism; climate; work; vacation; psychosomatic disease; psychological stress

Introduction

Since the seasonal variation of peptic ulcers (including duodenal and gastric ulcers) was noted in a textbook in 1932 [1], it has remained an unsolved mystery for 90 years. 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. The seasonal periodicity was manifested by changes in ulcer frequency by 10–20% [2]. This epidemiological pattern has been reported worldwide, including countries like China [3], South Korea [4], Turkey [5], Italy [6], Ethiopia [7], and Northern Ireland [8]. Although it was found to be a rhythmic phenomenon [1], the months with the highest and lowest frequencies varied regionally [1], and it also fluctuated differentially between the East and the West [9]. For example, unlike the seasonal variation described by Sonnenberg, in which there were two peaks, one in March and another one in October, and two troughs, one from July through August and another one from December through January, Palmas' report in 1984 suggested that the seasonal fluctuation curve in Turin, Italy showed 'a sharp decline in August, a small peak in July, and an October peak extending through November' [10]. In contrast, many studies reported 'a weak seasonal variation', in which the seasonal difference of peptic ulcers

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were not statistically significant [1]. All these suggests that the seasonal variation of peptic ulcers is a phenomenon with great diversity.

Although 13 etiological theories have been proposed to explain the pathogenesis of peptic ulcers over the past 300 years, such as *Psychosomatic Theory* [11,12], *Stress Theory* [13], *Nerve Theory* [14], and '*No Acid, No Ulcer*' [15], none of them have elucidated the seasonal variation of the disease, as well as many other characteristics and observations/ phenomena. The isolation of *Helicobacter pylori* (*H. pylori*) in 1982 was believed to be a revolutionary discovery in peptic ulcer research [16,17], and in 1987, Marshal proposed that peptic ulcers are an infectious disease caused by *H. pylori* infection [18]. As a result, currently, peptic ulcers are widely studied as an infectious disease [17,19]. This etiological theory has been designated as *Theory of H. pylori* [20]. Unfortunately, similar to all the other 12 historical theories in history, *Theory of H. pylori* cannot elucidate the seasonal variation of peptic ulcers. Two studies concluded that the seasonal changes of *H. pylori* infection were not parallel with the seasonal variation of peptic ulcers [21,22]. Therefore, the seasonal variation of peptic ulcers cannot be attributed to *H. pylori* infection. Moreover, similar to the 12 etiological theories in history, *Theory of H. pylori* cannot face the challenges from the 15 major characteristics and 81 observations/phenomena of peptic ulcers.

To address these challenges, a recently published Complex Causal Relationship (CCR) [23] was employed to analyze the existing data. Peptic ulcers were identified as a psychosomatic disease triggered by psychological stress, where *H. pylori* plays a secondary role in only the late phase of peptic ulcerations [24]. The theory based on this etiology has been designated as *Theory of Nodes* [25], which addresses all the characteristics, observations/phenomena, controversies, and mysteries of peptic ulcers in a series of 6 articles (Supplementary Table S1). In the first four articles of the series published recently [24–27], 14 characteristics and 72 observations/phenomena of peptic ulcers, including the birth-cohort phenomenon, have been explicitly elucidated. This fifth article focuses exclusively on the 73rd observation/phenomenon, the seasonal variation of peptic ulcers. Notably, the data analyses herein are also applicable to all the seasonal data on hospital admissions, mortality/morbidity rates, in- and out-patients, bleeding and perforated ulcers, relapse/recurrence, endoscopic records, age groups, and so on.

Methods

Six steps are taken to elucidate the seasonal variations of peptic ulcers. First, based on the etiology identified earlier in *Theory of Nodes* [24], the impacts of seasonal changes on human society are explored. Second, the fluctuation curves of the monthly incidences caused by 3 representative environmental factors are illustrated. Third, vertical and horizontal superpositions [26] are applied to draw the fluctuation curve and thus, the weak seasonal variation is elucidated. Fourth, the superposition mechanism is iterated to reproduce the fluctuation curve of the seasonal variations in the United States reported by Sonnenberg et al. in 1992. Fifth, the fluctuation curve of the seasonal variations in Turin, Italy, reported by Palmas in 1984, is also duplicated. Lastly, the similarities and differences between the birth-cohort phenomena and seasonal variation of peptic ulcers are curated into a table.

Results

In *Theory of Nodes*, the higher annual morbidity/mortality rates of peptic ulcers in the birth-cohort phenomenon are maintained primarily by crucial events, which happen suddenly and unpredictably [26]. In contrast, the monthly incidences in the seasonal variation are caused by common events, which occur periodically and predictably. As a result, the monthly incidences in seasonal variation fluctuate within a relatively narrow range, causing no statistical significance in many studies. Notably, since the periodic fluctuation of monthly incidences is the signature feature of the seasonal patten of peptic ulcers, this analysis will deliberate on reproducing the fluctuation curves. Moreover, because the trends for duodenal and gastric ulcers are similar, they are analyzed together as peptic ulcers. In addition, as the seasonal variation is a diverse phenomenon, herein only the fluctuation curves of the 3 most typical patterns in the literature are reproduced.

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1. The impacts of seasonal change on human society

Existing data suggests that seasonal variation may not be associated with *H. pylori* infection [9], but with multiple environmental/social factors, such as climate [28,29,30], work/ occupation stress [31,32], air pollution [33], regional and ethnic differences [9], industrialization [9], vacation/holidays [34], immigration [35], religion [7], smoking and alcohol abuse [8], and lifestyle and recreational habits [36]. Notably, the key factors, which were believed to determine the seasonal variations, were found to be regionally different [5,8,10]. In *Theory of Nodes*, the periodic alterations of multiple environmental/social factors due to the seasonal changes that directly or indirectly induce psychological stress in the population, result in peptic ulcers. To simplify the data analyses, only the 3 most important factors in the literature, climate, work, and vacation/holidays, were applied to reproduce the fluctuation curves of 3 typical seasonal patterns of peptic ulcers. In fact, the impacts of climate, work, and vacationing on human society have been well studied in modern medicine.

Multiple reports have studied the roles of climate in the seasonal variation of peptic ulcers [4,28,29]. The Mediterranean climate was found to be predominant for the seasonal and monthly fluctuations in upper gastrointestinal bleedings in Mersin [29]. Two studies discovered that the peaks of peptic ulcer disease are most prominent in colder months [37,38]. In Ethiopia, the peak for perforated peptic ulcers was during 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 [28]. Animal studies showed that both acute and chronic heat stress can induce hemorrhagic ulcers in rats [39]. A comprehensive examination of the climatological pattern and long-term trends of heat stress found that people living in densely populated and urbanized areas experienced severe heat stress conditions during the summer [40]. Meteorological changes may induce a series of stress as a response of the human body [30]. Extreme coldness in winter or extreme heat in summer induces psychological stress [41]. Despite a milder climate in spring, many individuals may become stressed due to hay fever [42]; whereas in autumn, people may become stressed due to the upcoming cold winter [43]. These findings suggest that, despite relatively higher monthly incidences in winter and summer in many regions, climate may induce stress in all seasons, causing monthly incidences of peptic ulcers.

The seasonal change also profoundly influences the work and lifestyle of human society, causing a 'seasonal nature' of multiple occupations. First, the workload for seasonal occupations, such as construction, tourism, agricultural, fruit and vegetable industry, varies based on the season, resulting in periodic psychological stress [44–48]. Approximately 25% of migrant and seasonal farmworkers have experienced stress, depression, or anxiety in their lifetime [49]. Second, the seasonal unemployment patterns, in which companies lay off workers during adverse weather conditions that lower productivity [50], also cause seasonal psychological stress. Third, even though many 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 in the two seasons [48,51]. A number of factors contribute to workplace stress: workload, interpersonal conflicts, a lack of resources and internal pressures [48,52], a poor work structure or organization, inflexible management system, and unsatisfactory working conditions [53]. Work-related psychological stress may induce peptic ulcers, regardless of *H pylori* infection or NSAIDs usage [54]. Notably, occupational stress associated with industry and air pollution varied regionally [55], resulting in region-specific seasonal patterns of peptic ulcers [56].

Taking vacation may provide individuals an opportunity to recover from job demands and to replenish resources that were stressed during work, thereby preventing and reducing chronic strain reactions to job stress [57]. Opposite to climate and work, vacation can effectively reduce work stress and burnout [58,59], causing a decrease of the incidence and relapse of peptic ulcers [10,57,59]. Many countries have formulated vacation policies based on their own 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 or family gatherings and activities during these two separate periods, leading to the relief of stress. Tom et al. found that the seasonal variation of peptic ulcers in Honolulu is primarily

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impacted not by climate, but by holidays [34]. Palmas discovered that from 1979 to 1981, the observed fluctuations of duodenal ulcer relapse in Turin, Italy were not influenced by climatic factors, but by stress relief due to the summer vacation [10]. Both studies suggest that vacation significantly reduces the incidence of peptic ulcers. Southard found that the vacation policies of the United States and European countries are strikingly different: while the United States does not require employers to pay employees for holidays, most European countries provide a certain number of paid holidays [60]. Due to the psychological impact of vacationing for the release of stress, vacation policies can determine and significantly affect the seasonal patterns of peptic ulcers.

There might be many other environmental and social factors not listed here, but they are influenced by the seasonal changes on the earth, resulting in psychological stress in a proportion of individuals in the population and eventually, an incidence of peptic ulcers. Notably, these factors varied temporally, regionally, culturally, and religiously.

2. Periodic fluctuation of incidences caused by a single factor

In *Theory of Nodes*, peptic ulcers are a psychosomatic disease triggered by psychological stress. There are always a proportion of individuals in the population 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 their stomach or have had a negative life view in their mind. Thus, they are ready-to-ulcerate individuals and may become ulcer patients if psychological stress is induced for any reason [26], such as climate or work. Notably, while climate or work cause a monthly incidence, vacations reduce the monthly incidence (Figure 1A), suggesting that each of the single factors causes a fluctuation curve independently (Figure 1B). To highlight the periodic fluctuations, herein the Monthly Incidence (MI) by a single factor is calculated and presented by MI = Cases of the month ÷ Monthly Average Cases of a year x100%.

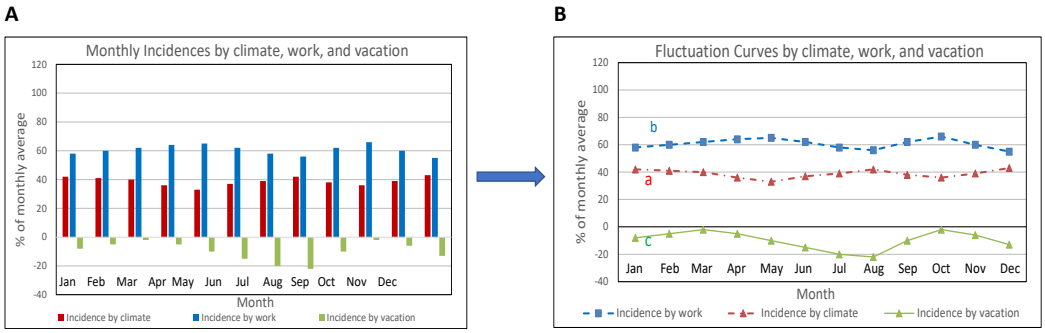

Figure 1. Climate, work, and vocation cause their own monthly incidences independently. The data in the graphs is representative of a hypothetical scenario over a year, where the total monthly incidence is caused by climate, work, and vacation. **A:** Each of climate, work, and vacation causes its own monthly incidences independently. **B:** The monthly incidences by climate, work, and vocation were horizontally superposed to gain their respective fluctuation curves. **a)** Coldness or heat in winter or summer causes a little bit higher monthly incidences than in spring or autumn. **b)** Seasonal work schedules make the monthly incidences in spring and autumn a little bit higher than in winter and summer. **c)** Opposite to climate and work, vacations reduce the monthly incidences, especially during summer vacation and Christmas holidays.

3. Reproducing the fluctuation curve of a weak seasonal variation

The total monthly incidence of peptic ulcers is the sum of the monthly incidences caused by all the single factors and therefore, it is calculated by vertical superposition of the monthly incidences by all the single factors. Similarly, the fluctuation curve of the total monthly incidence is obtained by horizontal superposition of the total monthly incidences. Notably, in regions or countries without traditions of summer vacation and/or Christmas holidays, only climate and work are considered for the data analyses. After vertical superposition (Figure 2A), the higher monthly incidences by climate

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in winter and summer are offset by the lower monthly incidences caused by work in the same season, and vice versa in spring and autumn (Figure 2B). As a result, the differences between any two total monthly incidences are too small (not statistically significant) to demonstrate a seasonal variation. This explains the 'weak seasonal variations' as observed in many studies, and addresses the controversy on the seasonal pattern of peptic ulcers [1,38].

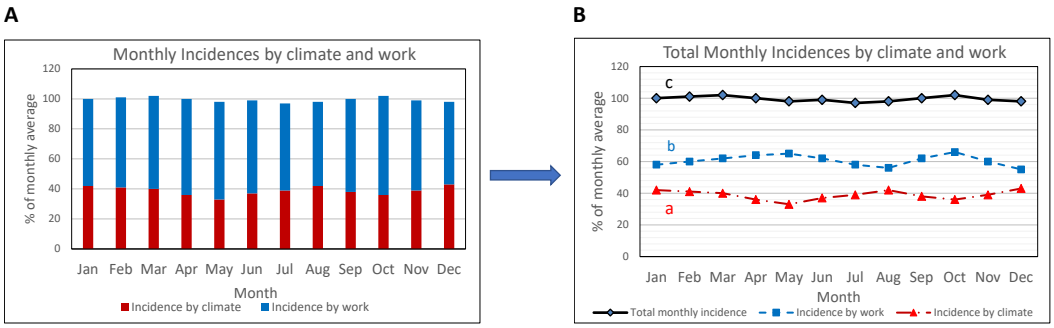

Figure 2. Reproducing the fluctuation curve of a weak seasonal variation. The data in the graphs is representative of a hypothetical scenario, in which the total monthly incidence is caused by climate and work. **A:** The total monthly incidence is obtained by vertical superposition of the monthly incidences by climate and work and calculated by formula $MI = I_{Climate} + I_{Work}$. **B:** The total monthly incidences are horizontally superposed to obtain 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 total monthly incidences caused by climate and work, which is obtained by the superpositions of curves a and b.

4. Reproducing the fluctuation curve of the seasonal variation in the United States

Vacationing is an important part of America's culture since the mid-1800s [61]. 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 vacationing. The Christmas break, starting from December 23 until New Year's Day (January 1st), is also a season that brings family and friends together. Noticeably, unlike climate and work, which induce psychological stress, taking vacation effectively relieves stress [57–59]. Therefore, vacations significantly reduce the monthly incidences of peptic ulcers in the United States in both seasons (Figure 3A). Although there is no obvious fluctuation after superposition of the monthly incidences by climate and work (Figure 2B), the involvement of vacation makes the fluctuation of total monthly incidences statistically significant (Figure 3B), suggesting that the seasonal variation in the United States is primarily caused by vacations. This reproduces the fluctuation curve of a 'typical seasonal variation' reported by Sonnenberg et al. in 1992.

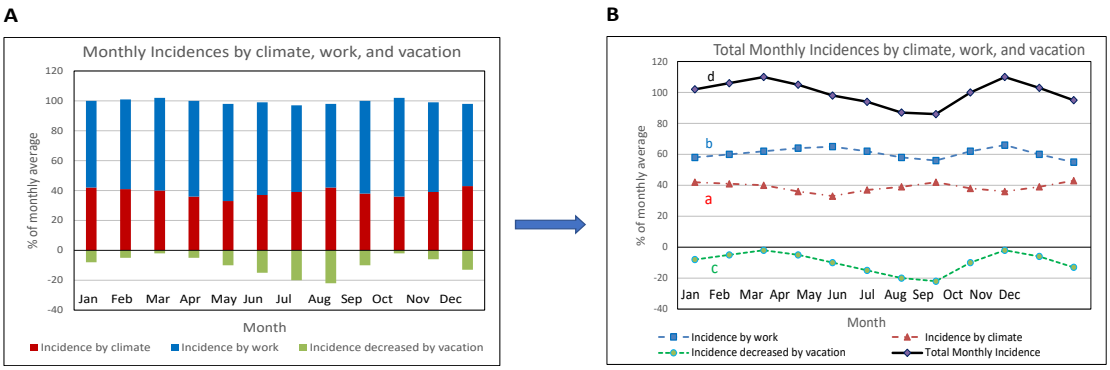

Figure 3. Reproducing the fluctuation curve of a typical seasonal variation. The data in the graphs is representative of a hypothetical scenario in the United States from 1986 to 1989. **A:** while climate

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and work cause monthly incidences of peptic ulcers, vacation decreases the monthly incidences during summer break (July and August) and Christmas holidays. Therefore, all the values of monthly incidences by vacation are negative. **B:** The total monthly incidences are calculated by formula MI = $I_{Climate} + I_{Work} + I_{Vacation}$, which are horizontally superposed to gain 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 by the superpositions of curves a, b, and c. Note: curves a and b are the same as the curves a and b in Figure 2B and Figure 1B; curve c is the same as the curve c in Figure 1B.

5. Reproducing the fluctuation curve of the seasonal variation in Turin, Italy

In Italy, 'during the month of August, more than half of the population leave the city to go on vacation'[62], suggesting that, while Italians attach a lot of importance to the vacation in August, they care less about Christmas Day. As a result, the summer vacations in August significantly lower the monthly incidences of peptic ulcers, whereas the Christmas breaks only slightly reduce the monthly incidence (Figure 4A). It is very likely that in Turin, to get ready for the August vacation, July is busier than most other months, causing more psychological stress and a small peak (Figure 4B). This reproduces the fluctuation curve of the seasonal variation in Turin, Italy reported by Palmas et al. in 1984 [10].

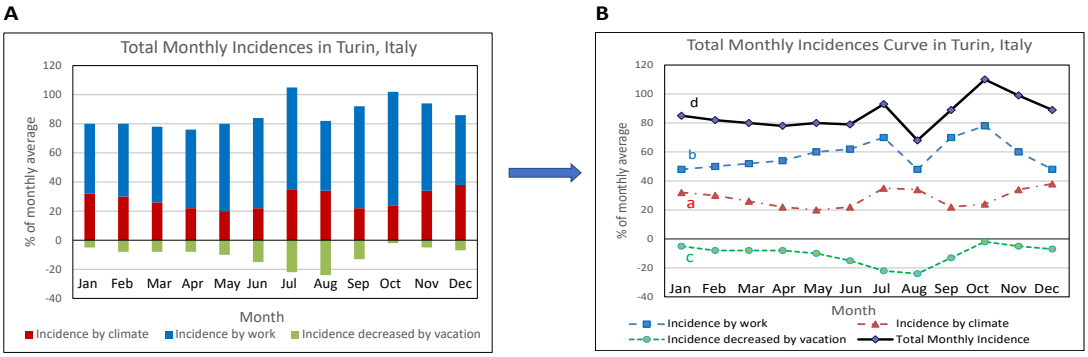

Figure 4. Reproducing the fluctuation curve of seasonal variation in Turin, Italy. The data in the graphs is representative of a hypothetical scenario in Turin, Italy from 1979-1981. **A:** The vertical superposition of the monthly incidences due to work, climate, and vacation. The total monthly incidences were calculated by MI = $I_{Climate} + I_{Work} + I_{Vacation}$. **B:** The total monthly incidences were 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 is higher than most of the other months of the year. **c)** The fluctuation curve of monthly incidences caused solely by vacations, where Christmas breaks only slightly reduce the monthly incidence. **d)** The fluctuation curve of total monthly incidences caused by climate, work, and vacation is the vertical superposition of the curves a, b, and c.

6. Comparison between the birth-cohort phenomenon and seasonal variation

The data analyses above suggest that if peptic ulcers are considered a psychosomatic disease triggered by psychological stress, according to the local actual situation, the fluctuation curves of seasonal variation of peptic ulcers can be reproduced. Notably, this etiology also elucidated another epidemiological pattern of peptic ulcers, the birth-cohort phenomenon. Interestingly, both epidemiological observations were elucidated by the iterations of *Superposition Mechanism*, although the two patterns examine the annual and monthly trends of the incidences of peptic ulcers, respectively. Table 1 lists the major similarities and differences between the two characteristic epidemiological patterns of peptic ulcers.

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

	Birth-cohort Phenomenon	Seasonal Variation
Similar Features	1. Important epidemiological patterns caused by psychosocial factors.	
	2. Suggest the important causal roles of psychosomatic factors and psychological stress in peptic ulcers.	
	3. Caused by superposition mechanism: the repeated superposition of incidences caused by multiple psychosocial/environmental factors.	
	4. Without taking *H. pylori* infection into consideration.	
Different Features	1. Fluctuation curves were primarily due to CRUCIAL events, incidences by common events are included in the calculation, and it fluctuates within a wide range.	1. Fluctuation was caused by COMMON events; incidence by crucial events is not considered and incidence fluctuates within a narrow range.
	2. LESS DIVERSITY: the peak is maintained by sudden or unpredictable crucial events, decreasing trend after the crucial events, not a rhythmic phenomenon.	2. MORE DIVERSITY: the peak can be maintained by many periodic and predicable environmental factors, causing a rhythmic phenomenon.
	3.Crucial events may induce duodenal ulcers in those 'ready-to-ulcerate' individuals, and the secondary stressors induce hyperplasia and hypertrophy of gastrin and parietal cells and cause duodenal ulcer in 3-5 years.	3. Common events may induce duodenal ulcers in those 'ready-to-ulcerate' individuals with hyperplasia and hypertrophy of gastrin and parietal cells in the stomach.
	4. On the ANNUAL incidences of peptic ulcers, which increase and decrease sharply.	4. On the MONTHLY incidences of peptic ulcers, which increase and decrease slightly.
	5. Needs much more data covering MANY CONSECUTIVE YEARS and harder to study, resulting in relatively LESS REPORTS in the existing literature.	5. Data covering ≥ 3 RANDOM YEARS is sufficient and much easier to study, resulting in MANY REPORTS in the existing literature.

Discussion

Despite 13 etiological theories, including the most recent *Theory of H. pylori*, being proposed to explain the pathogenesis of peptic ulcers, the seasonal variation has remained an epidemiological mystery for more than 90 years. Starting from the etiology of peptic ulcers identified earlier [24], *Theory of Nodes* elucidated that the seasonal changes on the earth, which periodically alter multiple

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environmental/social factors, lead to psychological stress and eventually, peptic ulcers. It is the superposition of the monthly incidences caused by all the single environmental/social factors that incurs the seasonal variation of peptic ulcers. Based on the actual situation of local psychosocial/ environmental factors, *Theory of Nodes* reproduced 3 typical fluctuation curves reported in the literature, suggesting that the seasonal variation of peptic ulcers cannot be fully elucidated unless the disease is considered a psychosomatic disease triggered by psychological stress and the superposition mechanism is applied to data analyses.

Currently, peptic ulcers were widely believed to be an infectious disease caused by *H. pylori*, but this etiology cannot elucidate both the birth-cohort phenomenon and seasonal variations of the disease, as well as the 15 major characteristics and 81 observations/phenomena [20]. Interestingly, without taking *H. pylori* infection into consideration, *Theory of Nodes* explicitly elucidated both of the two epidemiological observations. In addition, when *H. pylori* infection was not considered a cause of peptic ulcers, *Theory of Nodes* explicitly elucidated 14 major characteristics and 72 observations/ phenomena of peptic ulcers in the first 4 articles of a series (Supplementary Table S2-S6). All these indicate that *H. pylori* infection may not be the cause of the disease. Moreover, existing studies also confirmed that the seasonal changes of *H. pylori* infection are not paralleled with the seasonal variation of peptic ulcers [21,22]. Not surprisingly, *Theory of H. pylori* cannot explain this phenomenon. In *Theory of Nodes*, *H. pylori* infection is not a cause of peptic ulcers, but a risk factor playing a secondary role in only the late phase of ulcerations. Thus, the infection proportionally increases the total monthly incidence of each month but won't affect the (rise and fall) trends over the year. Therefore, a full understanding of both the birth-cohort phenomenon and seasonal variation in *Theory of Nodes* confirms that *H. pylori* infection is not an etiological factor of peptic ulcers, and so are the other two concrete local factors in the stomach, gastric acid and NSAIDs.

Unequivocally, the seasonal variation of the disease cannot be fully elucidated unless peptic ulcers were considered a psychosomatic disease triggered by psychological stress. It is noteworthy to mention that while elucidating the seasonal variation of peptic ulcers, *Theory of Nodes* adopted a unified standard before replicating all 3 fluctuation curves. Uncomfortable climate (coldness and heat) and busy work schedule were assumed to induce psychological stress and thus, increase the monthly incidence of peptic ulcers, whereas vacation was assumed to relieve psychological stress, thereby decreasing the monthly incidence of peptic ulcers. The slight difference in vacation policies between Italy and the United States results in two different seasonal patterns of peptic ulcers. Notably, Manfredini et al. observed a seasonal pattern in the region of Emilia-Romagna, Italy in 2010, which is similar to the one in Turin, Italy reported by Palmas in 1984, but the July peak disappeared. *Theory of Nodes* hypothesizes that the different industries in the two adjacent regions account for this nuance. In July, while people in Turin were busy for construction, tourism and service industries [63], people in Emilia-Romagna were relatively relaxed due to its agricultural and manufacturing (automobile, motor and mechanics) industries [64]. Thus, to elucidate the underlying mechanism of the seasonal variations in a region, we should be aware of the local geographical environment, historical tradition, unique climate, industry categories, vacation and well-being policies, and all the other social and environmental factors that may induce psychological stress in the population. All these suggest that peptic ulcers are a typical psychosocial disease [65,66], highlighting the causal role of psychosomatic factors and psychological stress in the disease.

Apparently, both a definite etiology and effective analytical methods are essential for a full understanding of disease. It was the methodological concept, superposition mechanism, that directed *Theory of Nodes* to analyze the existing data and therefore, both the season variation and birth-cohort phenomenon of peptic ulcers can be elucidated. However, this concept has never come into being in modern medicine. Consequently, even though *Psychosomatic Theory* and *Stress Theory* recognized the real cause of peptic ulcers, both theories could not elucidate the two epidemiological patterns for many decades, but were deemed outdated soon after the discovery of *H. pylori* [67]. In *Theory of Nodes*, the Superposition Mechanism was iterated to elucidate many characteristics and observation/phenomenon of peptic ulcers. For example, in the first article, this concept directs *Theory of Nodes* to superpose the corrosive intensities of all the local aggressive factors into a total corrosive

intensity and thus, all the clinical, laboratory, and epidemiological observations associated with duodenal ulcers were elucidated. In the second article, the superposition of all what the individual experienced before formed a negative life-view and therefore, the pre-ulcer lesion in the gastric wall can be predicted and then the morphology, along with many other local characteristics, could be fully understood. In the third article, as well as this fifth one, the data analyses were centered on the *Superposition Mechanism*. All these indicate that *Superposition Mechanism* is an indispensable concept for a full understanding of any life phenomena and human diseases. The wide application of this mechanism to our daily research may allow us to gain unprecedented insights into many life phenomena and human diseases.

Conclusions

Seasonal variation is an important epidemiological feature of peptic ulcers with a great diversity. The seasonal changes on the earth periodically alter multiple environmental/ social factors, each of which induces psychological stress in a proportion of individuals, resulting in a monthly incidence independently. The repeated superposition of the monthly incidences caused by climate, work, and vacation reproduced 3 typical fluctuation curves of the seasonal variation, indicating peptic ulcers are not an infectious disease caused by *H. pylori*, but a psychosocial disease associated with psychological stress induced by multiple environmental/social factors. The validity showcased herein suggests that superposition is a universal mechanism, and the wide application of this mechanism may allow us to gain unprecedented insights into many life phenomena and human diseases.

Supplementary Materials: The online supplementary materials include 6 tables in a PDF document.

Institutional Review Board Statement: This study was conducted with integrity, fidelity, honesty, and did not involve any human or animal specimen.

Data Availability Statement: All the supporting data in this article are published papers or books, or in the online supporting information.

Conflicts of Interest: The author has no conflict of interest to declare.

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