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Scientometrics as a Powerful Tool in Integrating Isolated Medical Specialties: A Case Study of the Rediscovery of the Luigi Cornaro Diet

Ligen Yu, Boxuan Yu and Bowei Yu

Abstract

Modern medicine is divided into different specialties. While well-trained experts can serve the patients better, each medical specialty is isolated to itself. For example, it is a norm for gastroenterology that fasting can lead to gastrointestinal tract (GIT) mucosa atrophy, and make the patient prone to bacterial translocation and sepsis. Yet, physiologists still think that fasting might be a feasible solution for obesity and related illnesses, as it can trigger autophagy which has multiple physiological functions benefiting the body. In this chapter, using the rediscovery of the Luigi Cornaro diet as an example, we demonstrate that scientometrics methods can be a powerful tool to integrate the isolated medical specialties. The Luigi Cornaro diet is able to maintain the homeostasis of GIT mucosa while keeping a serum starvation to fit for a rare physiological condition of fully developed sustained upregulated autophagy (SUA) in the body. Although fully developed SUA is relatively rare, low-grade upregulated autophagy (UA) is quite common, reflected by the prevalence of obesity in population. UA is the main component of our self-healing capacity, and the connector between infection and obesity. Such discovery of scientometrics could be the next generation medical practice.

Keywords: Bibliometrics analysis, medical specialties, isolation, integration, Luigi Cornaro diet, upregulated autophagy, sustained upregulated autophagy, self-healing

1. Introduction

Just as the division of labor in every single field of activity is an emblematic feature of modern society, medical specialization is now a self-evident necessity in medical science and medical practice [1]. Nowadays we are not expecting any general practitioner to address life-threatening diseases of specific organs in the body, as highly specialized medical specialists are more professional and productive, as they make better diagnoses, fewer mistakes than general internists and general practitioners do [2]. Medical science research follows the same trend, and the importance of specialization in medical science should not be slighted.

While Hippocrates (and basically every one after him) described disease as occurring when there is an imbalance between the four ‘humors’ (phlegm, black bile, yellow bile and blood) [3], today’s medical specialists know any of the human organ and any disease in more detail than the physicians in the time of Hippocrates did.

Yet, the specialization of medical research creates a vast amount of medical knowledge, which is also expanding exponentially in such a way that no medical specialist can grasp this medical knowledge in all [4–10]. As a result, specialists are more or less focused on their own specialties, and isolated from other specialties. For example, it is a norm for gastroenterology that fasting can lead to gastrointestinal tract (GIT) mucosa atrophy, causing the patient to be prone to bacterial translocation and sepsis [11–13]. Yet, physiologists still think that fasting might be a feasible solution for obesity and related illness, as it can trigger autophagy which has multiple physiological functions benefiting to the body [14, 15].

This problem might not be solved by the specialists themselves, simply because it takes a lot of time for them to become specialists, and they may not have the time to spare on other specialties. Here comes the scientometrics, we are not specialists on any medical division, so we may not have detailed knowledge on any of the medical divisions. Yet, we specialize in literature analysis. By analyzing the connections among the literatures from various specialties of medical researches, we may break the isolation, find the close relations among them, and integrate them.

Here we give the rediscovery of Luigi Cornaro diet as a case study.

Luigi Cornaro (1464–1566) was a Venetian noble man. He lived freely when he was young before 35 or 40. After a severe illness at the age around 40, he began to reduce his diet under medical advice. At the age of 70–80, he restricted himself to a daily allowance of 12 ounces of solid food and 14 ounces of new wine. Later in his life, he found that he could support his life and strength with no more food than the yolk of an egg with a few spoonful milk with bread in the 24 hours. He was so habituated to this simple diet that when he was about 70 years of age the addition of 2 ounces a day had proved fatal. His diet was so effective in keeping him in good health that his strength and all his senses were kept in very good condition throughout his lifetime. His book, *The Art of Living Long* [16], is one of the most successful diet books, which is still in print over 460 years after it was first published in Padua in 1558. It was an instant success, went through many editions, and was translated into many languages.

Despite the success of Luigi Cornaro’s own practice and his books, common people find that his diet is very difficult to follow. This even happened at the time of Luigi Cornaro. In his discourses [16], he had repeatedly mentioned that it was extremely hard for ordinary people to follow his diet. For example, he said: “Now, I am often at a loss to understand why men of fine parts and understanding, who have attained middle age, do not, when they find themselves attacked by disorders and sickness, betake themselves to a regular life, and that constantly.”; “One of the younger of them said that I appeared to enjoy the special grace of being able to relinquish, with ease, one kind of life, and embrace another, a thing which he knew from theory to be feasible, but in practice to be difficult, for it had proved as hard to him, as easy to me.”; “There are some sensualists, my Lord, who say that I have thrown away my time and trouble, in writing a treatise upon temperance, and other discourses on the same subject; alleging, that it is impossible to conform to it.”

In the nineteenth century, German philosopher Friedrich Nietzsche read Luigi Cornaro’s book, tried the diet and commented that Luigi Cornaro was “mistaking the consequence for the cause” [17]. Nietzsche said: “The worthy Italian saw in his diet the cause of his long life: while the prerequisite of long life, an extraordinarily slow metabolism, a small consumption, was the cause of his meagre diet. He was not free to eat much or little as he chose, his frugality was not an act of ‘free will’: he became ill when he ate more.”

Although the Luigi Cornaro diet is very hard to follow by ordinary people, it is not impossible. There are people who are actually following this diet without their self-awareness. In our contemporary days, Prime Minister of Malaysia Tun Dr. Mahathir bin Mohamad is an example. According to a report of The Strait Times [18], Dr. Mahathir has a slice of bread for breakfast, has whatever the cook at home prepares for lunch, and has two spoonful of rice at night. This food amount may actually be less than the 12 ounces of solid food a day of Luigi Cornaro. Dr. Mahathir's diet may explain why at his current age of 93, he is still vigorous, and all his senses are as good as middle-aged persons, which is exactly the situation described by Luigi Cornaro [16].

Because of the practical importance of the Luigi Cornaro diet, we are interested in the biological process behind the diet. This biological process should be able to answer the following two questions:

1. How is the balance of energy and nutrition maintained in the body with such a low food intake in this diet?
2. How can this biological process effectively defend against common diseases like infection and the degeneration of body cells so that one's strength and senses are not as affected while one is aging?

In this chapter we will describe how we apply the Bibliometrics analysis method to the publications on topics relating to the Luigi Cornaro diet, and find that a rare physiological condition of fully developed sustained upregulated autophagy (SUA) is the answer to the above two questions [19]. This finding also explains why the Luigi Cornaro diet is not fit for ordinary people who can eat normally.

2. Literature survey on Luigi Cornaro diet and interpretation

Luigi Cornaro and his diet are mentioned in most of the dieting books. Nevertheless, modern medicine has very scarce literature on Luigi Cornaro. When we search "Luigi Cornaro" as keyword in Web of Science, only four papers can be found. Three of them were published in 1901 in Lancet, and one paper published in 2018 by Journal of The History of Medicine and Allied Sciences. These papers are not able to provide any useful medical explanations to the Luigi Cornaro diet.

In the discourses of Luigi Cornaro, he wrote [16]: "When men are taken ill they discontinue, or nearly so, their food. ... by reducing themselves to a small quantity, they recover from the jaws of death." What Cornaro described here is illness induced anorexia (IIA), and he employed IIA to justify his diet. So we turn to publications on anorexia (loss of appetite as a physiological symptom), especially search for publications on illness (infection, sickness) induced anorexia (IIA) as the start of our analysis.

2.1 Illness induced anorexia (IIA) accompanying upregulated autophagy (UA)

Decreased food consumption (anorexia) is the most common sign of infection and severe injury [20]. It is believed that IIA is an active host defense strategy for pathogen elimination and enhancing healing of injury [21–23]. Unlike the starvation-invoked regulatory mechanisms aim at conservation of protein mass in healthy subjects, patients with illness induced anorexia have increased energy expenditure and protein catabolism, associated with profound neuroendocrine alterations [23].

In Web of Science, we can find 53 papers on illness induced anorexia. **Figure 1** shows the mapping of terms used in the titles and abstracts in these 53 papers using

the VOSViewer Bibliometrics analysis software, which is developed by CWTS of Leiden University. Two papers relating illness induced anorexia to upregulation of autophagy catch our attention [24, 25], as highlighted in **Figure 1**.

Autophagy is the degradation of intracellular components in lysosomes to remove altered or dysfunctional proteins and organelles [26, 27]. It is a highly regulated process in eukaryotes to maintain homeostasis and manage stress responses. It has multiple physiological functions including cellular quality control, energetic

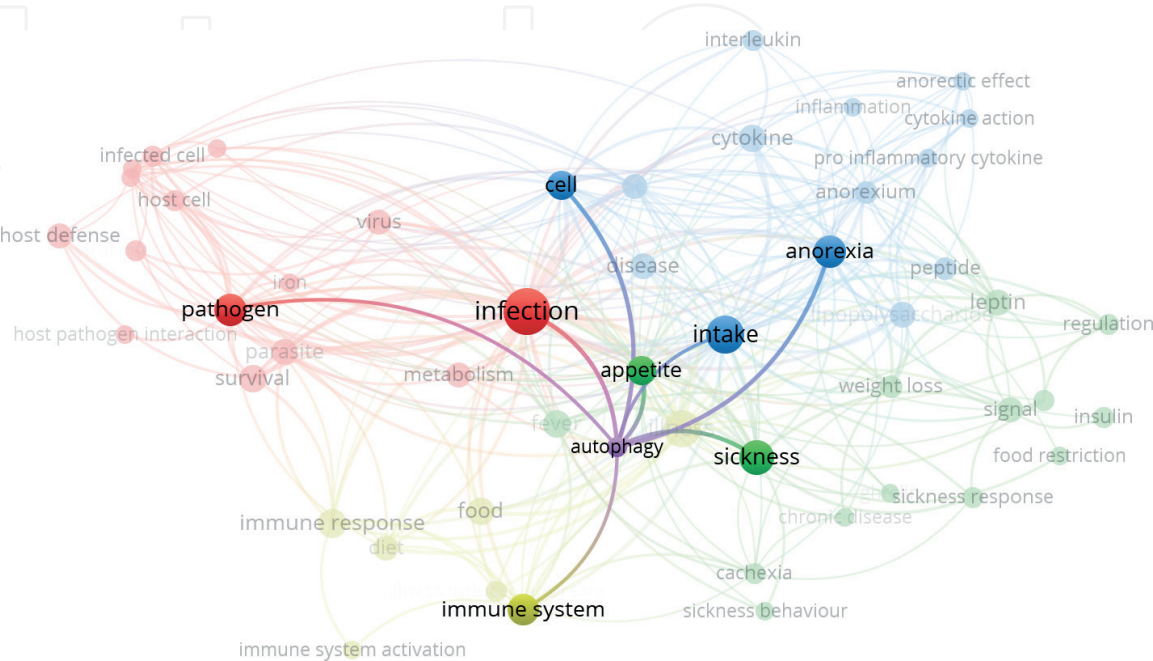


Figure 1.
Illness-induced anorexia is related to autophagy.

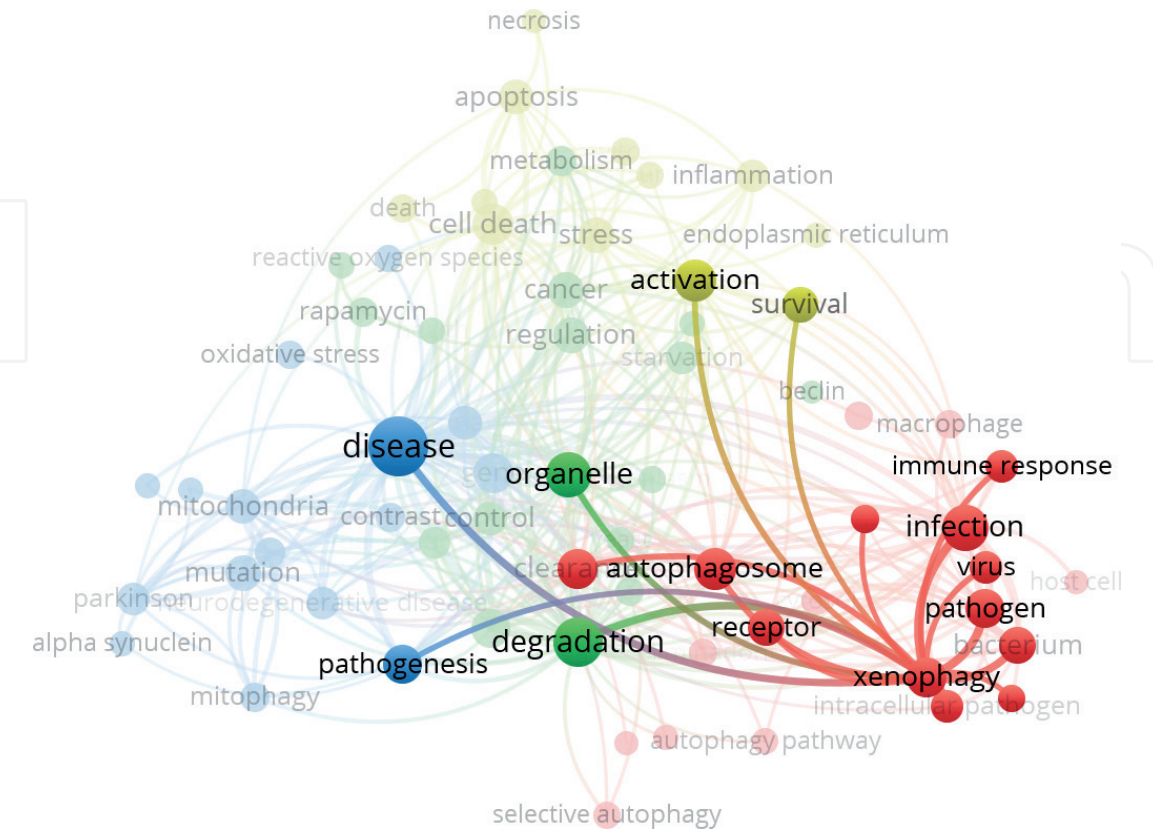


Figure 2.
Autophagy (xenophagy) is closely related to infection (pathogen) elimination.

balance maintenance, and pathogen cleaning [28]. In normal physiological conditions, a low level of basal or constitutive autophagy occurs to maintain cellular homeostasis by controlling the turnover of damaged proteins and organelles [29]. In pathological conditions (like infection or injury), autophagy as an adaptive cellular mechanism will be upregulated to eliminate pathogens and recycle and reutilize damaged macromolecules and organelles [26, 27]. During an infection, upregulated autophagy has a specific role in the capture and degradation of intracellular bacteria and viruses to reinstall health, a process termed as xenophagy [30–32].

In Web of Science, we can find more than 19,000 publications relating illness (infection, sickness, and disease) to autophagy, showing the close relation of autophagy to infectious pathogen elimination. The term analysis of the top 700 highly cited papers of these 19,000 papers is shown in **Figure 2**, with the keyword “xenophagy” highlighted.

Xenophagy as a catabolic process is able to recycle and reutilize the degraded pathogen components for energy or protein synthesis, it provides the host with plenty of energy and nutrients during the process. So our interpretation of IIA is that, in order to avoid over-nutrition, our body intentionally induced anorexia (loss of appetite) as a counter measure against upregulated autophagy.

2.2 Upregulated autophagy (UA) as the connector between infection and obesity

It has been noticed that infection can enhance one's proneness to develop obesity, and the term infectobesity was coined by Dr. Nikhil V. Dhurandhar in 2001 [33]. Yet the connection between infection and obesity is unclear. Given the close relation of autophagy to infection elimination, we searched publications on infection induced obesity together with autophagy, and 238 publications are found in Web of Science. **Figure 3** shows the terms used in titles and abstracts of these publications, and autophagy is an obvious connector for infection and obesity.

Based on **Figure 3**, we suspect that, chronic low-grade inflammation triggered low-grade upregulated autophagy (UA), yet the inflammation degree is so low that the inflammation is not accompanied by fever and illness-induced anorexia. This low-grade upregulated autophagy provides certain amount of recycled energy and nutrients to the body of the host. Over nutrition and excessive energy will occur if one still eats normally. These energy and nutrients accumulate inside the body over the years, and lead to obesity. Therefore, obesity is a good indicator of low grade UA. As the degree of obesity is related to the degree of UA, and UA is generally protective, it should not be alerted if a person is slightly overweight or obese without accompanying with metabolic diseases like high blood pressure, diabetes, cardiovascular disease. Also, as the degree of UA grows with aging, older people can generally be healthier than young people, if old people can lower their food intake according to the degree of their UA when they are growing older.

2.3 Sustained upregulated autophagy (SUA) and the Luigi Cornaro diet

The biological process of triggering upregulated autophagy with or without the accompanying illness induce anorexia by infection/inflammation cannot explain the Luigi Cornaro diet, as Luigi Cornaro never fell ill after he adopted his simple diet. So we take a step further to hypothesize that Luigi Cornaro had a rare condition of fully developed sustained upregulated autophagy (SUA) without anorexia (loss of appetite) [19]. And we have provided the possible cause and the feature of SUA in our paper [19]. As SUA is able to provide plenty of recycled energy and nutrients to the body from each cell in the body, regular restrictive eating is now compulsory. The small amount of food is mainly used to maintain the homeostasis of the GIT mucosa [19]. Thus, we answer the question set out by Dr. Ernest Van

Somerén in 1901 [34]: “Did he (Luigi Cornaro) make use of a physiological process unknown to us, of the value of which he was not cognisant?” This also explain why the Luigi Cornaro diet cannot be adopted by ordinary people.

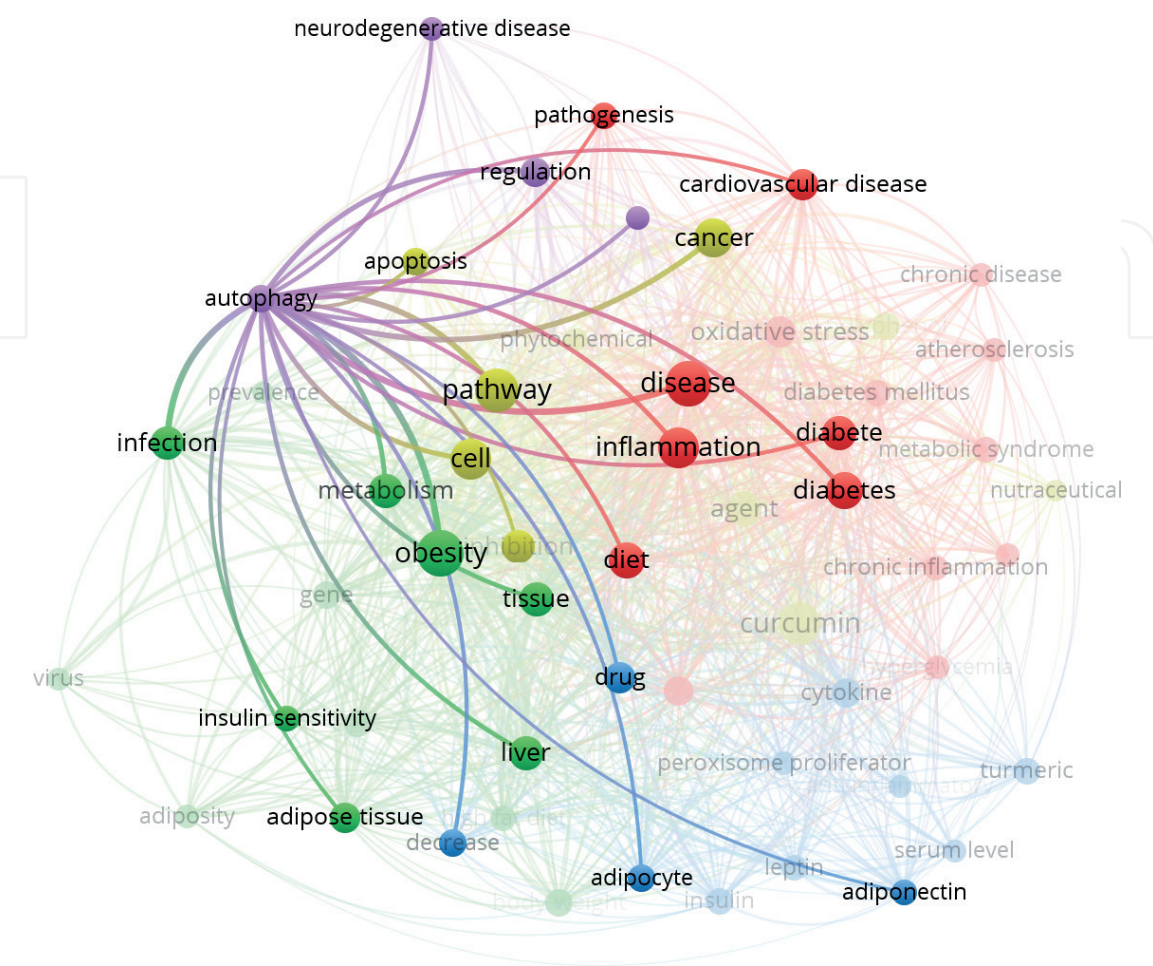


Figure 3.
The close relations among infection, autophagy and obesity.

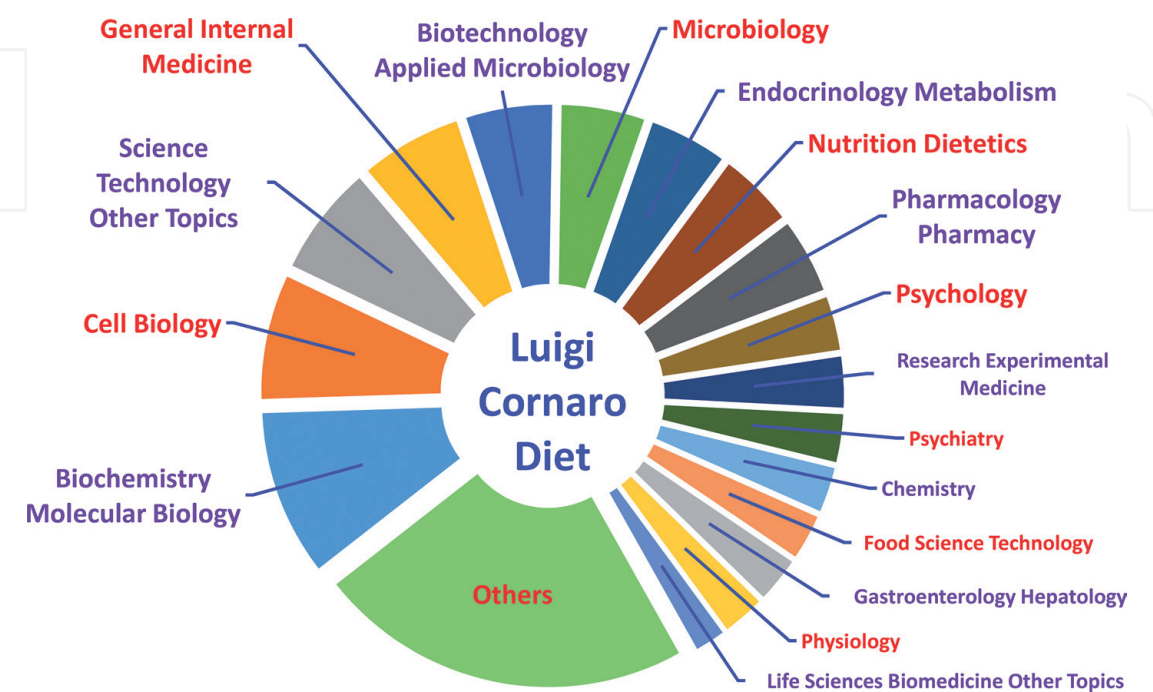


Figure 4.
Research areas of publications used to interpret Luigi Cornaro diet.

2.4 The interpretation of Luigi Cornaro diet requires knowledge from multiple medical disciplines

In the Bibliometrics analysis on Luigi Cornaro diet above, we have searched publications in different research areas of medical science, as shown in **Figure 4**. The extensive research on autophagy in the last 60 years helps us in understanding the biological process behind the simple Luigi Cornaro diet of Eat-but-Little. Autophagy itself is a multidisciplinary research topic. And the understanding of Luigi Cornaro diet also requires knowledge from gastroenterology, infectious diseases, food science and technology, psychology and so on.

3. The possible therapeutic application of the Luigi Cornaro diet

3.1 Research on the self-healing capacity of human being should be enhanced

The Luigi Cornaro diet clearly shows that our body has the self-healing capacity, with UA/SUA as its main component. We searched the term “self-healing” in Web of Science from 1990 to 2018, and 10,488 publications can be found. The Web of Science subject category analysis shows that most of the top 25 subject categories are in materials science and computer science, as shown in **Figure 5**. Only one subject category, dermatology, in the top 25 subject categories is related to medical science. Keyword analysis was carried out for these publications using VOSViewer, and 27,337 keywords are identified. Among these keywords, 2540 keywords have occurrences of five times and above, as shown in **Figure 6**. Using the clustering of keywords in the VOSViewer mapping in **Figure 6**, 11 topics are identified. **Table 1** gives the representative keywords in these 11 topics. It is very clear that, most of the keywords are on materials science and artificial intelligence of computer science. Furthermore, topic analysis on the keywords shows that the relative volume of self-healing research in medical science is shrinking in the last 29 years, from around 40% of the total publication in 1990 on self-healing to less than 10% in 2018, as shown in **Figure 7**. This is quite unusual, as “self-healing” is initially a medical term borrowed by materials science and computer science. So we suggest that the medical community should pay more attention to this self-healing capacity of the organs in our body, which can greatly lower the medical burden of every country in the world, and make our society more healthy.

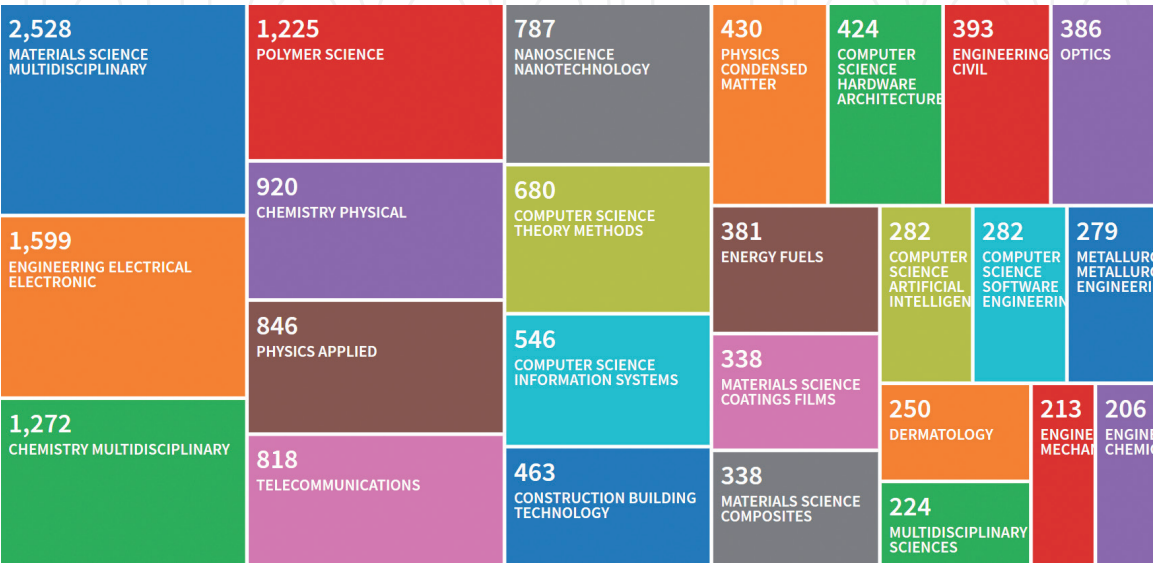


Figure 5.
 Top 25 Web of Science subject categories for publication on “self-healing” during 1990–2018.

3.2 More caution should be placed on the use of total parenteral nutrition (TPN)

Parenteral nutrition (PN) is the administering of specialist nutritional products to a person by way of a vein, bypassing the usual process of eating and digestion (referred as enteral nutrition). Total parenteral nutrition (TPN) was introduced by Dudrick et al. in clinical practice over 50 years ago [35]. The principal indication for TPN is a seriously ill patient where enteral feeding is not possible.

For critically ill patients, there is an ongoing debate on whether providing them with early enteral nutrition, or tolerating permissive underfeeding. Recently ESICM clinical practice guidelines [36] and the Surviving Sepsis Campaign [37] all suggest using early enteral nutrition (EEN), initiated at a low rate, in the majority of critically ill patients, and suggest delaying EN only in some special cases like in patients with uncontrolled shock, uncontrolled hypoxemia and acidosis, and other sever complications. These suggestions agrees well with our finding about the Luigi

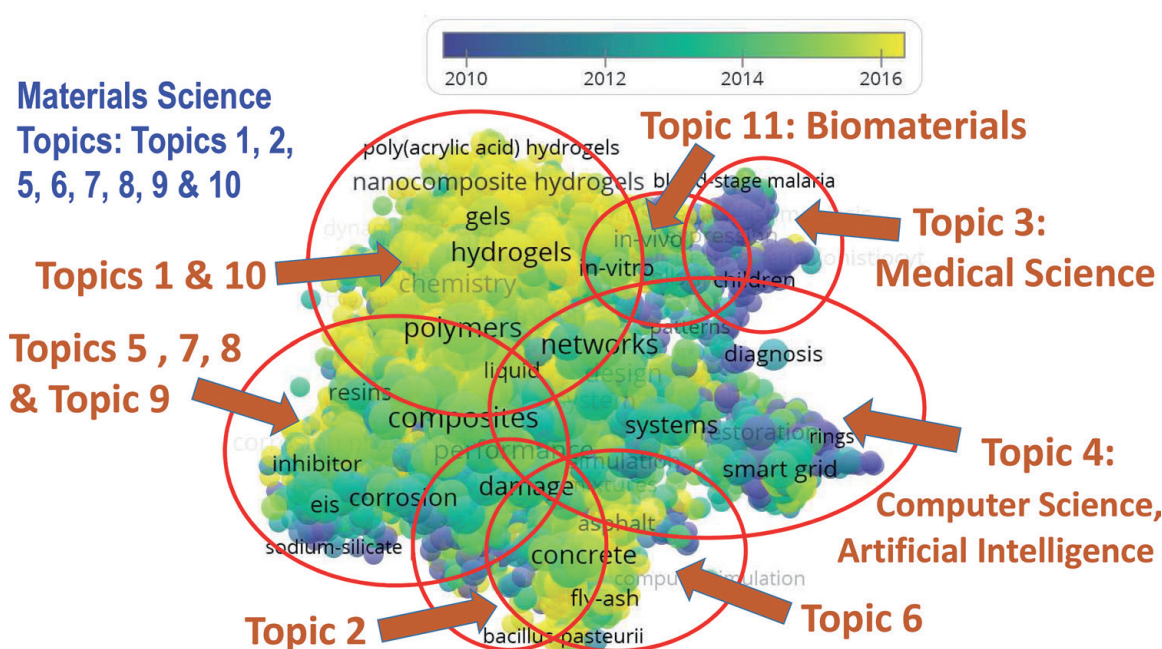


Figure 6. *Most of the publications on self-healing are in materials science and artificial intelligence.*

T1: Polymer	T2: Ceramic Coatings	T3: Medical Science	T4: Computer Science and AI	T5: Thin Films	T6: Concrete
polymers	behavior	degradation	design	films	concrete
networks	temperature	cells	systems	corrosion protection	strength
hydrogels	oxidation	skin	model	corrosion	permeability
mechanical-properties	surface	self-healing reticulo-histiocytosis	smart grid	resistance	cracks
chemistry	microstructure	tissue	self healing	release	bacteria
T7: Composites	T8: Nanocomposites	T9: Nanostructured membranes	T10: Dye-Doped Polymer	T11: Biomaterial	-
composites	performance	coatings	polymer	drug-delivery	-
microcapsules	nanocomposites	nanoparticles	photodegradation	hydrogel	-
damage	carbon nanotubes	water	dye	in-vitro	-
repair	graphene	fabrication	stabilization	delivery	-
composite	graphene oxide	surfaces	biopolymer	chitosan	-

Table 1.
Representative keywords for topics on self-healing.

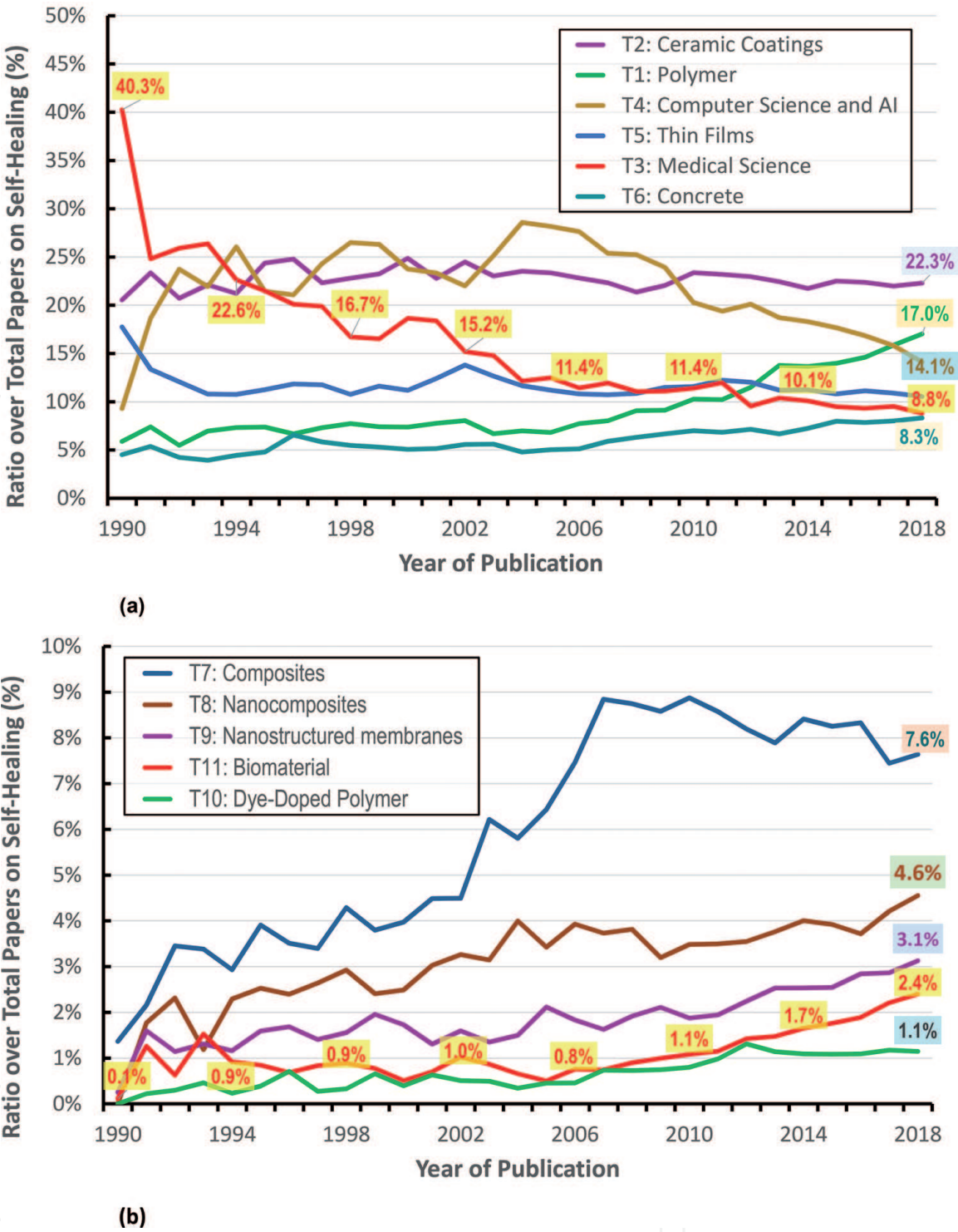


Figure 7.
 (a) Relative volume trends of publications on topic 1 to topic 6 of self-healing. (b) Relative volume trends of publications on topic 7 to topic 11 of self-healing.

Cornaro diet, since low rate early nutrition supports and protects the proper function of GIT mucosa, while the serum starvation ensures the full function of UA in the body, helping the patient in recovering from the illness by his own self-healing capacity.

While Luigi Cornaro diet introduce small amount of food in the GIT and keep a serum starvation to meet the requirement of SUA, TPN just does the opposite. It introduces nutrition to the blood to interfere the proper functioning of UA, depriving the body of a key cell survival mechanism. Furthermore, TPN starves the GIT, which may result in GIT mucosa atrophy and dysfunction. Research shows that it is critical to have small amount food in the GIT to maintain a full functioning GIT mucosa,

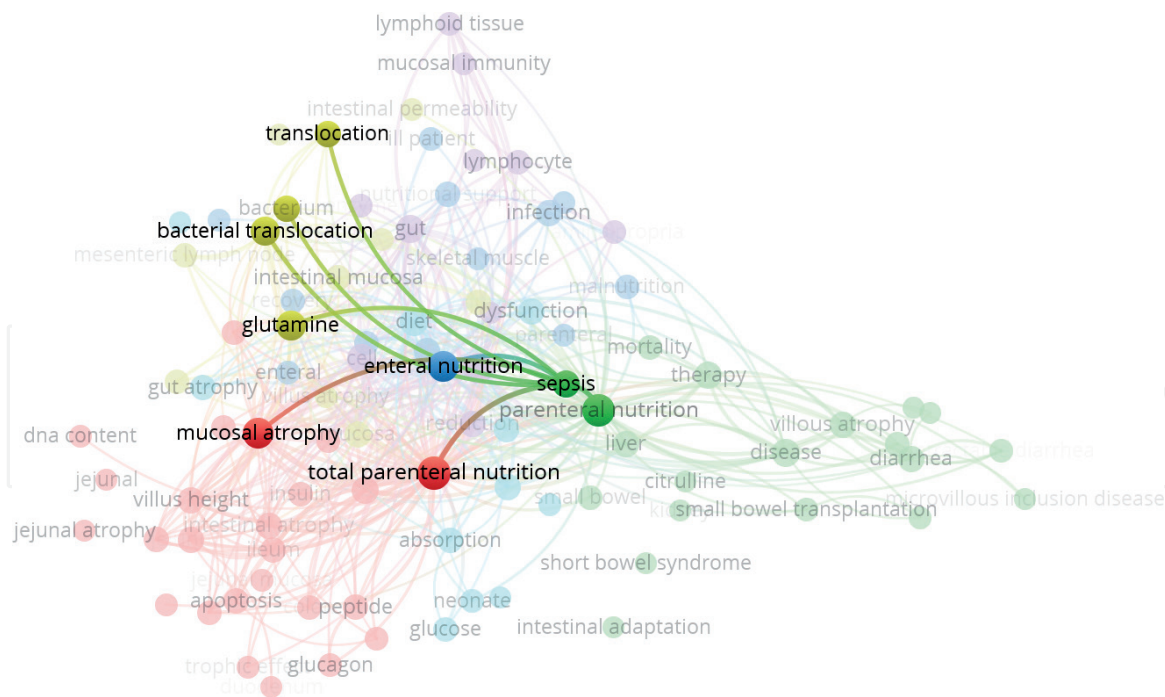


Figure 8.
Keywords analysis for publications on TPN shows the close relation of TPN to bacterial translocation and sepsis.

preventing it from atrophy, avoiding its proneness for bacterial translocation and sepsis [13]. **Figure 8** shows the keywords mapping of publications on TPN, with the term “sepsis” highlighted. We can clearly see the close relation of TPN to sepsis.

Based on the above discussion, we suggest that great caution should be placed on the use of TPN in treating sickness. TPN should only be conducted for seriously ill patients who are too emaciated to have proper running of SUA activity in their body, and enteral feeding is truly not possible.

4. Summary

Specialization is an established part of the medical landscape nowadays, and the importance of specialization in medical research and practice should not be disdained. Yet, specialists are more or less focused on their own specialties, and isolated from other specialties. Here we use the rediscovery of the Luigi Cornaro diet as an example to show that, scientometrics can be a powerful tool in integrating various isolated medical specialties. After its publication in 1558, the simple diet of Luigi Cornaro, “Eat but Little,” puzzled people for over 460 years. By analyzing the keywords in the titles and abstracts of publications on topics related to the Luigi Cornaro diet, we find that the fully developed sustained upregulated autophagy (SUA) without anorexia is a pre-requisite for the Luigi Cornaro diet. The fully developed SUA performed a multifaceted role in helping Luigi Cornaro maintaining the energy and nutrition balance; and effectively defending the common diseases like infection and the degeneration of body cells. This was why he could keep health until the end of his days, and his strength and senses were not affected while he was aging. Considering the connections among infection, illness-induced anorexia, upregulated autophagy (UA) and obesity, and sustained upregulated autophagy (SUA) and the Luigi Cornaro diet uncovered by scientometric analysis coupled with a long history of anecdotal evidence, a carefully designed study should be undertaken to confirm the causal link and define the conditions under which a Cornaro diet should be medically advised.

5. Disclaimer

This chapter is based on the authors' limited personal experience and literature Surveys. The authors are not medical doctors and do not want to make medical recommendations. Instead, this chapter should be regarded as a thought-provoking impulse for future research. Neither the authors, the publisher, nor any other party who has been involved in the preparation or publication of this chapter guarantees that the information contained herein is in every respect accurate or complete. Therefore, this chapter is intended as reference only, and does not serve as a medical advice. The information in this publication is only to help you make informed decisions about your health. It is not intended as a substitute for any treatment that may have been prescribed by your doctor, who is familiar with your specific needs. If you suspect that you have a medical problem, we urge you to seek competent medical care.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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