THE COMPREHENSIVE LITERATURE REVIEW OF STUDIES ON THE RELATIONSHIP BETWEEN CARBONATION (CO_2) IN SOFT DRINKS AND HUMAN HEALTH

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Research Question

- Does consumption of carbonated soft drinks (CSD) impact on human health?

→ To study the impact of carbonation (CO_2) in CSD on human health

Methodology

- Using the PRISMA methodology (Preferred Reporting Items for Systematic Reviews & Meta Analyses)

- Step 1: Literature review of published studies → Identify 3 groups of health issues: (1) Tooth enamel and bone density; (2) digestive system; (3) urinary system

- Step 2: Classify studies into identified groups of impacts and select qualified studies for analysis

- Review 489 related studies available on academic research date → 48 studies qualified for this comprehensive review

Impact on tooth enamel

- Have negative impact on tooth enamel due to the acidity of H2CO3 in CSD.
- Empirical studies show: De-carbonation in the water reduces 27% of mineral solubility of tooth enamel. However, the absolute reduction is insignificant.
- Acidity in CSD is stronger due to the added acid substances (citric, phosphoric etc.) → alter the pH and acid-base titration

Impact on tooth enamel

- Compare with the impact of non-sugar added CSD on tooth enamel

- Impact of sugar added CSD is higher (Coke, Redbull)
- Impact of calcium and fluoride supplemented CSD is lower

Impact on bone density

- Direct research on the population: comparison between the CSD consuming and water consuming groups show no difference in bone turnover maker.
- Research on postmenopausal women: reduced femoral bone density in the group drinking Cola, not the other who drinks other kinds of carbonated beverages.

Impact on bone density

- Study on adolescents: reduce bone density of heel in the group consuming diet coke.
- Also, the group consuming CSD tends to diet, calcium intake from foods is low → impact of calcium/phosphate ratio.

Impact on digestive system

- Gastro esophageal reflux:

- All the CSD alter the temporary pH in the esophagus, reduce the lower esophageal sphincter pressure, cause heartburn due to stomach distension, decrease gastric motility in short time (2-3 minutes)

- However, no studies indicate such phenomenon stops when no more consumption of CSD.

Impact on digestive system

- Empirical research shows that sugar increases the risk of reflux 2 hours after eating, no relation between the CO_2 content with function of digestive system.

- Cause short-term satiation through increased sympathetic nerve activities

- Increase secretion of acid HCL → positively impact digestion, relieve constipation, and increase gastric secretion syndrome

Impact on digestive system

- Esophageal lesions
- Acidity can cause damage to esophageal mucosa, but there is no evidence of the damage.
- Studies indicate no relation between CSD consumption with esophageal cancer.
- There was no relation between the lesions in intestine, colon, pancreas, liver and gallbladder with CSD consumption

Impact on the kidneys

- Urinary stones.

- The risk of recurrence of urinary stones reduce when stopping consumption of CSD with high phosphoric acid. There is no difference in the risk of recurrence regardless of stopping or not stopping consuming other kinds of carbonated beverage.

- Studies provide contradict evidence of the impact on the urinary biochemical changes towards creating a favorable environment for kidney stone formation.

Impact on the kidneys

- Studies indicate no relation between urinary tract cancer and CSD consumption.
- In people with chronic kidney disease, the group who drink cola (with phosphoric acid), their renal function is declined, no similar impact is observed in the group who drink other kinds of carbonated beverage (citric acid).

CONCLUSIONS

- Consistent evidence of the impact of CSD on the tooth enamel, but the impact is insignificant.
- The evidences in the studies cannot indicate the impacts of CO2 in CSD on any specific health status.
- No conclusions on the additives although some indirect evidences indicate their impacts (phosphoric acid, caffeine). There is no study on the impacts of other additives.
- It is necessary to conduct separate studies on the impacts of additives in CSD.

Systematic review system on the relationship between sugar-free carbonated beverages and health

The research team independently conducts this study. The members of the group do not have any conflicting views about the topic. The group was responsible for the conclusions in the report. The results to be cited in this report should be consulted with the research group to avoid misunderstanding and misuse of the results.

This study is implemented in accordance with the contract with American Commercial Chamber. The research team does not bear any influence from the donor during the process of conducting a literature review as well as conclusions. Methods of collecting and analyzing materials are generally prescribed according to the systematic review protocol.

The review implementation period is from 19 March 2014 until 29 April 2014.

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SUMMARY

Introduction

Carbonated water was invented in the 18th century and widely used in recent decades. Over the time, many other ingredients were added to carbonated water to make flavor, color and particular characteristics followed the manufacturer's desires, which now has been known by a common name called carbonated beverages. The increasing consumption of carbonated beverage and carbonated water all over the world and in Vietnam market, as well as the growing diversity of carbonated beverages, show the importance of evaluating the overall impact of carbonated beverage to consumers' health. This study reviews the effects of carbonated beverages on health through analyzing and synthesizing peer-reviewed papers and reports published at Vietnamese and English resources.

Methods

This study applies PRISMA approach (Preferred Reporting Items for Systematic Reviews and Meta - Analyzes) and the review process is conducted in two steps as follows:

• Step 1: reviewing all published and unpublished studies that focus on identifying all possible effects of carbonated beverages on the health. In this step, we identified three main groups which affected are: (1) Tooth enamel and bone; (2) the digestive system; and (3) urinary system.

• Step 2: conducting parallel reviews and each of them focuses on a group identified in step 1. At this stage, we only reviewed officially published studies on the academic peer-review journal written in English or Vietnamese. The scope of the study focused on assessing the impact of beverage carbonation on three groups of health effects. Data was managed in Endnote software and processed in Excel, using the criteria of the PRISMA analysis.

Results

1. Impact on tooth and bone

127 published studies were screened, of which 16 studies that meet the review selection criteria were selected for the final review. Related to tooth enamel impact, carbonation increase the beverage acidity, however the impact on tooth wear is low. In fact, the level of tooth wear depends on carbonated beverages due to their different additives, for instance other organic acids, added to the beverages.

Carbonation of drinks is not associated with the loss of bone mineral density. Some contents of carbonated beverages such as caffeine and phosphoric acid, following physicochemical mechanisms, are believed to have negative effects on bone. However, the dose that could cause the affect is still unclear. Besides, studies also illustrates that the use of carbonated drinks is not the only associated factor to the decrease of bone mineral density. Other factors such as nutrition and diet, especially the amount of calcium intake through food sources among study participants also play an important role to the bone density. It is necessary to have more evidence on the

impact of separate contents of carbonated beverages on bone density as well as their interactive terms.

2. Impact on digestive system

We found 253 related published studies, of which 22 studies that meet the review inclusion criteria were analyzed. The possible impacts of carbonated beverages on digestive system include gastroesophageal reflux, esophageal cancer, change in gastric motility, secretion of gastric acid, and other impacts on pancreas, liver and gallbladder. Study results show that carbonated drinks can cause the feeling of fullness in the short-term, pressure reduction of the lower esophageal sphincter, the change of pH level of esophageal in the short time and the increase of gastric acid secretion. The studies however do not indicate a consistent relationship between the amount of CO_2 in carbonated beverages and any specific disease of digestive system.

3. Impact on urinary system

Among 109 related published studies, 10 studies met the review criteria and were included in the analysis. Reviewed impacts on urinary system can be divided into 2 groups: related to kidney stone formation, and effects on renal function. In general, studies do not show any association between beverage carbonation and kidney stone formation or renal function. Some studies specifically indicated that the impacts on kidney and renal function were due to beverage additives such as phosphoric acid.

The impacts of beverage additives including caffeine and phosphoric acid on human health have been discussed in reviewed studies. However, the studies do not measure and provide direct evidence about these impacts. In stead the researchers only used results of other studies on the impacts of those additives to explain the differences in the results of their research. To have concrete evidence of additives of carbonated beverages on health, it is necessary to conduct separate reviews of each additive to human health or empirical studies applied appropriate methods.

Conclusion

Three groups of carbonated beverage impacts on health were reviewed including (1) tooth enamel and bone; (2) digestive system; and (3) urinary system. Except the low impact on tooth wear, reviewed studies have not shown any specific disease caused by CO_2 dissolved in carbonated beverages. It is necessary to have longitudinal clinical trial to assess separately the impact of CO_2 of carbonated beverages on health for more concrete conclusion. This review does not give any conclusion on impact of additives used in carbonated beverages on health.

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1. INTRODUCTION

Carbonated drink is a beverage that has carbon dioxide (CO_2) dissolved into it under the low temperature and high pressure when sealing bottle/container. This process is known as carbonation. The dissolved gas escapes as bubbles when the bottle/container is opened and pressure relieved suddenly. Carbonated drink was invented in the 18th century and has become one of most popular drinks.

Many of packed drinks in the market now a day are carbonated beverages. They are added with many other ingredients to make flavor, color and particular characteristics followed the manufacturer's desires. Consumption of carbonated beverages has been increasing especially in developing countries including Vietnam. This poses the need to evaluate the overall impact of carbonated beverage to consumers' health. Currently published studies and health messages on Internet websites hold different perspectives on health impact caused by carbonated beverages.

In order to have more understanding of the issue we conduct a systematic review of academic literature to answer the question - *whether the use of carbonated beverages would cause any impact on health?*

The impact of carbonated beverages on health depends on the beverage contents including the amount of dissolved CO_2, amount of sugar or artificial sweeteners, and other additives by manufacturers. The diversity of contents in different carbonated beverages is probably one of reasons to explain the inconsistency of study results. Given this concern, in this review we focus on the impact of carbonation only or the effect of dissolved CO_2 on human health. The impact of sugar or sweeteners is thus excluded from the review.

2. OBJECTIVES

The objectives of the review are as follows:

- Collecting and screening published studies on health impact of carbonated beverages from Vietnamese and English academic databases.
- Assessing collected study methods, data analyses and results to explore the main effects of carbonated beverages on health.
- Synthesizing study results to conclude the possible effect size of carbonated beverages.

3. METHODS

3.1. Inclusion criteria

Studies that are selected to the review are those that meet the following four groups of criteria (Table1)

Table 1 – Inclusion criteria

Criteria	Details	Yes/No
Study type	Clinical trial (including randomized control trial)	
	Case-control	
	Cohort study (prospective and retrospective)	
	Cross sectional survey	
Study participant	Human	
Study result	Study on carbonated beverage combined with searching terms (MeSH terms, key words) of health effects (refer below)	
Publication	Study published in peer review journals	
	Study results based on experiment data	
	Study presented in full text	

The study quality is assessed based on two criteria, i.e, study design and study sample. In the regard with study design, intervention holds stronger effect in assessing the causal relationship compared with observational study.

Intervention studies includes:

- Randomized Controlled Trial (RCT): This is study where eligibile participants are randomized to groups and the groups are compared with respect to outcome interest.
- Quasi-experimental controlled study: Study outcomes before and after the introduction of an intervention are compared among groups of participants.
- Before-and-after study: Comparison of study outcomes is before and after the introduction of an intervention on the same sample of participants.

Observational studies include:
- Cohort stud
- Case control study
- Cross sectional study

3.2. Review approach

This study applied PRISMA approach (Preferred Reporting Items for Systematic Reviews and Meta - Analyzes) and the review process was conducted in two steps as follows:

Step 1: Identify the main effects of carbonated beverages on health

Research team reviewed all published and unpublished studies that focus on identifying of all possible effects of carbonated beverages on the health. In this step, we searched all academic and grey literatures.

Academic bibliographic databases:

- PubMed
- Database of Abstracts of Reviews of Effects (DARE) for quality-assessed systematic reviews of interventions;
- Cochrane Database of Systematic Reviews;
- NHS Health Technology Assessment (HTA) programme reports;
- Centre for Reviews and Dissemination (CRD) HTA database;
- National Institute for Health and Clinical Excellence (NICE) guidelines (for systematic reviews performed to support guideline recommendations).
- Google scholar

Other sources:
Internet website such as www.google.com, www.yahoo.com

Two sets of terms were used for electronic article search strategy. First, terms to search for beverages include "carbonated drinks, carbonated water, carbonated beverages, soft drinks, soda pop". Second, terms to search for health condition are "adverse health effects/adverse impacts/negative effects or health effects, health impacts". The sets of terms were then joined together with the "AND" operator to limit the retrieved articles of the interest. Key words to search relevant studies published in Vietnamese websites are: nước giải khát có ga/tác động sức khỏe".

With the above searching strategy, we accessed articles of all types of carbonated beverages. Therefore we had to screen all article abstracts and excluded studies on health impacts that do not caused by beverage carbonation. Specifically we exclude the studies of sugar and/or sweetened carbonated beverages and of health impacts related to sugar or sweetener of the beverages.

After this step, we identify three main groups of impact on health when using carbonated beverages as follows:

- Impact on tooth and bone
- Impact on digestive system
- Impact on urinary system

Step 2: Conduct the separate review on each identified health impact

In this step, research team searched literature of each health impact identified in step 1. Articles that meet the inclusion criteria mentioned in Table1 were selected for the review.
In step 2, we only searched articles that have been published in academic peer-review bibliographies including:

- PubMed
- Database of Abstracts of Reviews of Effects (DARE) for quality-assessed systematic reviews of interventions;
- Cochrane Database of Systematic Reviews;
- NHS Health Technology Assessment (HTA) programme reports;

- Centre for Reviews and Dissemination (CRD) HTA database;
- National Institute for Health and Clinical Excellence (NICE) guidelines (for systematic reviews performed to support guideline recommendations).
- Google scholar
- Vietnames peer-review journals

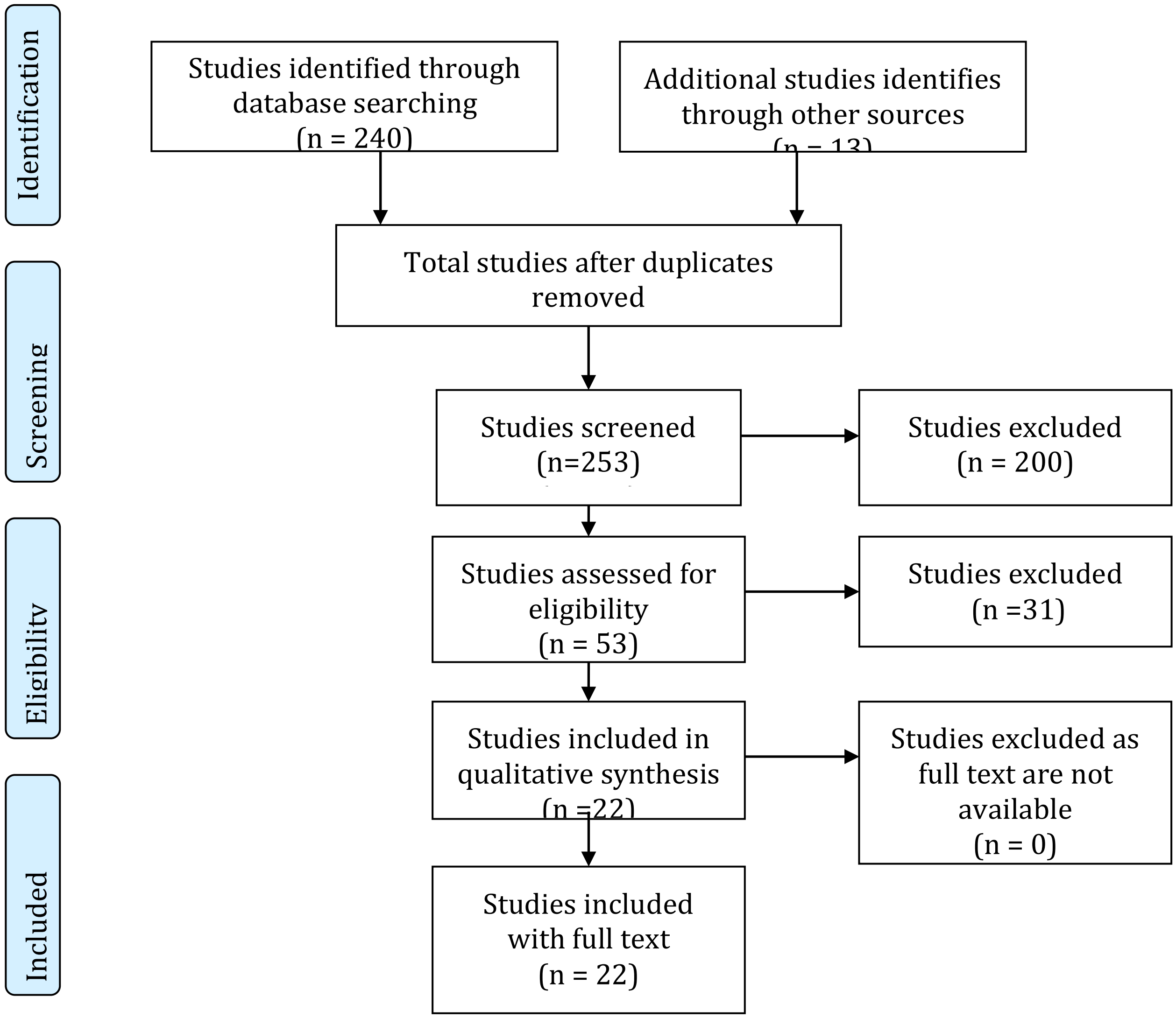
3.3 Sample frame and review sample

There are a number of articles that present more than one of health impact groups. For instance some articles mention the effects of carbonated beverages on both esophagus and tooth. Therefore they were included in both reviews on tooth and on digestive system. However, we did not duplicate the counting in total sample of articles for the overall review.

3.3.1. Sample frame and sample size of the review on the digestive system impact

Searching terms: Carbonated drinks/Carbonated beverages/Carbonated water and one of following terms:

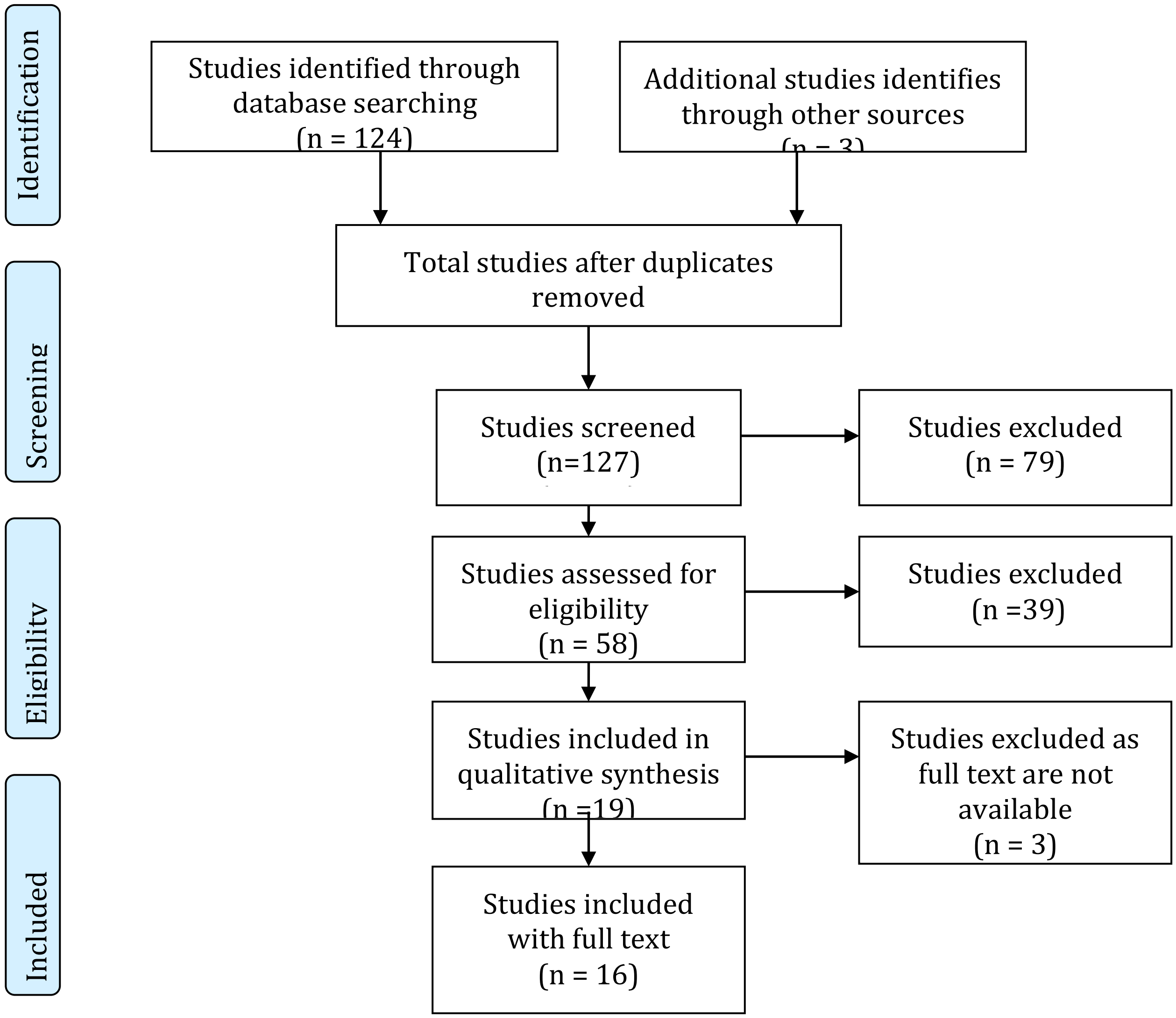
Esophagus
Gastric, Stomach
Liver
Pancreas
Gallbladder
Gastrointestinal system
Lower digestive tract, colon, megacolon



3.3.2. Sample frame and sample size of the review on the digestive system impact

Searching terms: Carbonated drinks/Carbonated beverages/Carbonated water and one of the following terms:

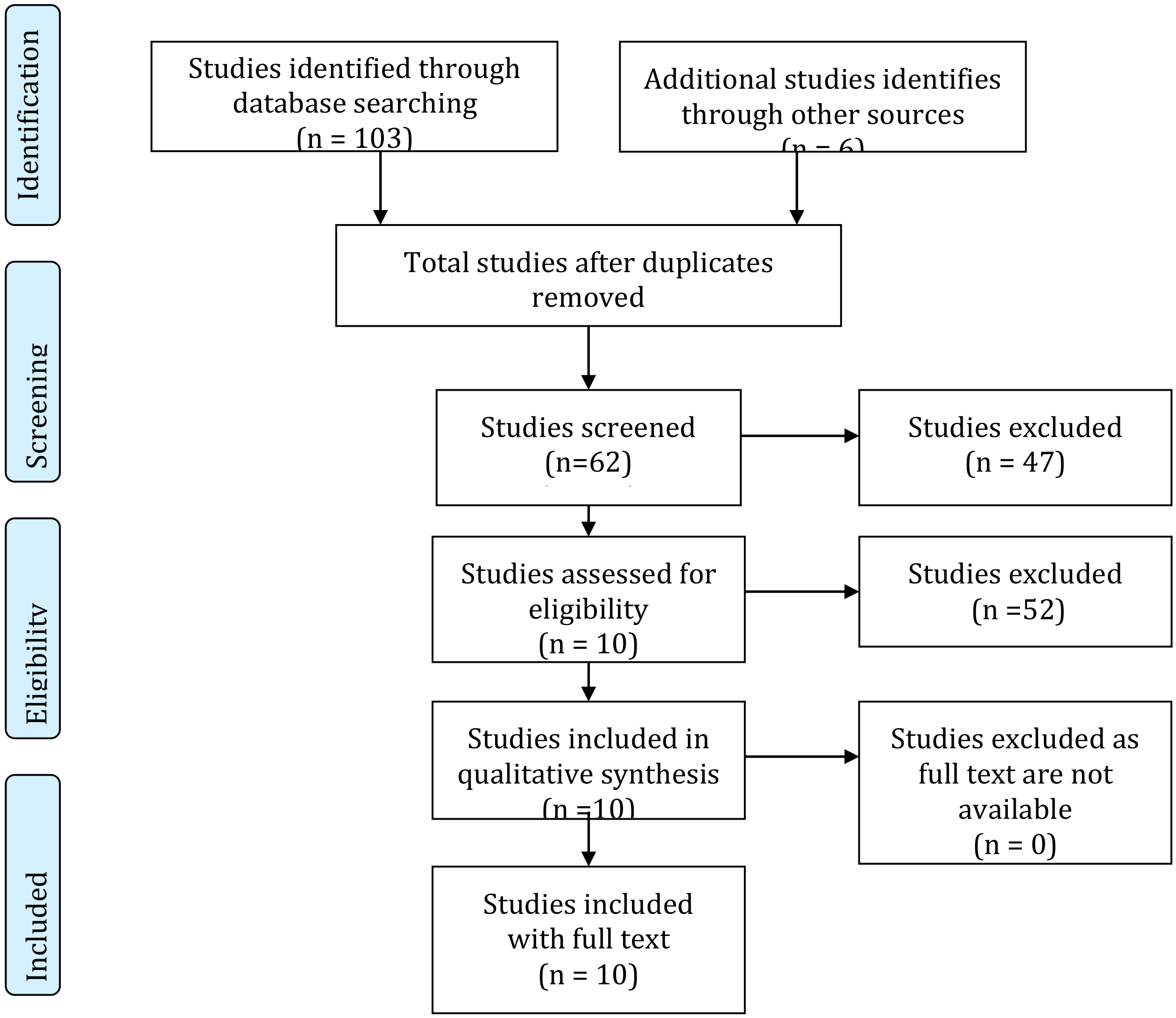
enamel erosion/tooth erosion
bone density



3.3.3. Sample frame and sample size of the review on the urinary system impact

Searching terms: Carbonated drinks/Carbonated beverages/Carbonated water and one of the following terms:

lithogenicity/nephrolithiasis/urinary stone/nephritis
carcinoma/kidney cancer



3.4. Analysis method

Included articles were managed by Endnote software. The software helped to store retrieved article information as well as to exclude duplication. Full text articles were also downloaded to Endnote. The software also helped to guarantee each included studies was counted once with specific code in the overall review.

After selecting articles for the review according to the inclusion criteria (Table 1), research team analyzed the article information following the PRISMA 27 item checklist on Microsoft Excel program.

Table 2. Summary information of included studies

Information	Explanation
Author	
Title	
Key words	Key words of included studies. MeSH term if any
Date of study and its publication	
Study place	
Study design	Belong to any of the following design? Cross sectional Case control Clinical trial Randomized controlled trial etc
Study sample	Sample size On healthy people or people with diseases
Health condition	Listing the health impact and condition studied
Result	Relationship measure (OR, RR?) Confidence interval P value
Factors influencing the quality of study	Study validity and credibility Relevance of study method Study bias
Additional information from study references	Any relevant published studies that are not retrieved by the review searching strategy?

We planed to apply meta-analysis to identify the effect size of health outcomes associated with the use of carbonated beverages. However we decided not to use the method due to the following reasons:

- The health outcomes are various including many diseases and conditions of digestive system and urinary system.
- Studies of the same health outcomes (for instance esophagus) applied different study designs, leading to the differences in study quality and measures.
- If we stratify studies according to their health outcomes and study designs, the number of studies to be reviewed of each stratum will be very small and become inapplicable for meta-analysis.
- Meta-analyses on a certain of health outcomes have been published. Since then there has no new study to be updated into the analyses.

3.5. Review limitation

This review depends on the publication of international and internal peer-review journals. Thus it would face some common limits:

- Languages of the articles to be reviewed: most of articles are in English. We found very few publications in Vietnamese due to the limitation of study documentation and dissemination in Vietnam.
- There may have studies relevant to the review but are not accepted for publication. However when reviewing the relationship between the use of carbonated beverages and health impact we observe that publications include both significant and insignificant relationships. This means that publication bias might not be a problem.
- In this review we focus only on the effects of CO2 dissolved in the beverages on health, but the effects of sugar and sweeteners. However it is very difficult to review separately the effects of CO2 and other additives because many studies measure the relationship among people who consume carbonated beverages in general, including non-sweetened and sugar sweetened ones.

4. RESULTS

On the human body, CO_2 plays an important role as a hormone because it is produced from organs and impacts on almost organs in 3 major mechanisms: (1) the main factor of acid-base balance in the blood (2) the main factor of control of respiration process and (3) effects on the heart and peripheral circulation.

Carbonated beverages are drinks that include carbon dioxide (CO_2) dissolved in water under certain pressure and temperature in closed bottles or cans. Carbon dioxide, after being dissolved in water, combines partly with water to create carbonic acid (H_2CO_3), which explains to the amount of acid in carbonated drinks is higher than normal drinks. The level of acid in carbonated drinks is equal to orange juices or apple juices but it is much less than the level of acid in stomach. In normal condition, human body always has pH adjustment mechanism in equilibrium state (acid-base homeostasis).

In an alkaline environment, CO_2 is converted to carbonate (CO_3^-) and bicarbonate (HCO_3-), which can be seen in the gastrointestinal tract. However, once a bottle or can of a carbonated drink is opened, the carbon dioxide will begin to escape, thus most CO_2 hardly reach stomach. In addition, when CO_2 comes to esophagus and stomach, it can combines swallowed air to cause belching, and only small amount of CO_2 is absorbed through the intestinal wall.

Although it is valued that 1 ml (2 mg) of CO_2 could be dissolved in 1 ml of liquid medium (pH = 7) in standard pressure and temperature condition, it still difficulty estimates the amount of CO_2 absorbed into body through carbonated beverages. Besides, different kind of carbonated drinks, in fact, have different pressure and temperature. In general, during process manufacturing, the amount of CO_2 is usually taken 3-4 times higher than the amount of water. Therefore, approximately 0.5l -1.5l of CO_2 is absorbed into body, after excluding the amount released because of sudden fall in pressure of 1000ml of carbonated drink.

Table 3. pH level of some regular carbonated drinks [1]

Drinks	**pH level**
Coke	2,47 – 2,65
Diet Coke	2,94 – 3,19
Pepsi	2,5 – 2,51
Diet Pepsi	3,0 – 3,06
Sprite	3,24 – 3,3
Diet Sprite	3,35
7-Up	3,2
Dite 7- Up	3,7
Nước khoáng có ga	5,05 – 6,30

[1]Source: (Kesel, 1965; Parry, Shaw, Arnaud, & Smith, 2001)

4.1. Impact of carbonated beverages on dental health

4.1.1. Reviewed articles on carbonated beverages and dental health

Some studies have shown that acidic food and beverages can cause dental erosion due to direct exposure in the oral cavity. Erosion is defined as the removal of mineral from the tooth structure. In other words, erosion is typically process of the wearing away of tooth surface (ie, enamel or root surface) (Imfeld, 1996). The chemical reaction of oral cavity between ion H^+ of acid and hydroxyapatite of tooth causes the loss of mineral ions (Ca^{2+}, OH^-, PO_4^{3-})(Bartlett, 2005). Dental erosion could happen as a result of exogenous factors such as food and drinks brought to the oral caviry or endogenous factors such as the gastroesophageal system- especially with the case of gastroesophageal reflux disease. (Scheutzel, 1996).

The fact has shown that when pH below 5.5, the amount of minerals of both enamel and dentine tooth will loss, so acid food is considered as a factor of destroying enamel (Moynihan & Petersen, 2004). Erosive levels are associated with pH, titratable acidity, and pKa. (Benjakul & Chuenarrom, 2011). Erosive levels are also related to salivary flow, buffering capacity (Bartlett, Coward, Nikkah, & Wilson, 1998; Thorbjorg Jensdottir, 2005), food and drink adhesion (to the surface of the tooth), calcium and phospho mobilization, and enamel demineralization(Grobler, Senekal, & Laubscher, 1990; Lussi, et al., 2004.)

Table 4. Comparation between juices and carbonated drinks

Drinks	**PH level**	**Titratable acidity[1]**

[1]Titratable acid is amoung of ml 1mmol/L OH^- required to neutralize the acidic components of a given solution, or bring pH of the solution up to 7.

100% apple juices	3,0	102
Orange juices	3,64	136
Orange drinks	3,74	124
Coca-cola	2,60	34
Sport drinks	2,84	
Energy drinks	2,76	

Dental caries is the acid destruction of tooth surface associated with bacterial fermentation of sugars in the oral cavity and dental plaque (Moynihan & Petersen, 2004). Therefore, we exclude studies analysing the relationship between dental caries and carbonated drinks due to the fact that dental caries is related sugar levels in the drinks instead of the impact acid of beverages.

4.1.2. Comment on study designs

Through own research on studies of carbonated beverages and dental erosion, we recognize that cross sectional studies could not separate the relationship between dental erosion and what contents of bevarages. Therefore, we will review the effect of pH and titratable acidity on enamel erosion, followed by the interpretation to seek evidence on relationship of CO_2, H_2CO_3 of carbonated beverages.

In general, there are 2 evaluation methods in dental erosion studies:

1) The analysis of the relationship between carbonated beverage and enamel erosion based on large population often comes from national surveys in the US or UK, including NHANES, INS…. A sample could be all or part of participants of cohort studies.
Tool assessment for dental erosion is an adjusted Smith and Knight Index. The evaluation of tooth wear erosion is often independent of questionnaire survey. To specify, doctors who evaluate dental erosion do not know the information of food and beverage used by subjects. The typical questionare normaly derives from UK National Diet and Nutrition Survey. Therefore, it is suggested that results coming from different studies can be compared because of the same tool accessment. However, as a result of different technical statistic (i.e odds ratio, mean difference…), meta- analysis methods are inapplicable in seeking size effect among studies.

2) In vitro studies often use tooth sample put into mouth or exposed directly on liquid test, before using profilometer to measure the change of tooth surface, which determines the following degree of enamel tooth wear. In vitro studies, like cross-sectional ones, frequently measure the average of erosion exposed carbonated drinks and water testing. However, because studies are applied different time and way exposed, meta-analysis could also not be taken.
Experimental studies often demonstrate results on the relationship between carbonated beverages and enamel tooth wear being more accurate than cross- sectional ones. It is plausible that the relationship, in cross- sectional studies, is almost associated with the recall answer of participants through survey. In addition, dietary and nutrition are also frequently changed in various types. It should be noted that results of in vitro studies are likely serious than reality as consequences of taking sample out of mouth to advoid the impact of food and drink ouside scope of research on dental erosion. As mentioned above, the biological mechanism in mouth can

protect teeth from erosion, for example, the formation of remineralization process. (Thorbjorg Jensdottir, 2005). Thus, when sample was taken out of mouth, it is certainly difficult to measure the impact of bevarages through swallowing movement, saliva buffering capacity, etc.

4.1.3. Results of research on the relationship between carbonated drinks and dental erosion.

Studies have directly shown the relationship between carbonated drinks and dental erosion

There is only in -vitro experimental study that compares the impact of erosive levels between carbonated mineral drinks and non- carbonated mineral drink. It is valuable evidence of carbonation effects.

It is authorized by Parry, et al and published in 2011 (Parry, et al., 2001). The dissolution mineral levels and erosive levels were measured by exposing 4 different groups of drinks: 1) still mineral water; 2) carbonated mineral water; 3) Distilled water is generated in the laboratory; 4) orange juice and drinks Cola (Coca Cola, Pepsi, Diet Coke, Diet Pepsi).

Table 5. Dissolution phosphor levels of enamel caused by bevarages

Drinks	Dissolution mineral levels of enamel (μg)
Still mineral drinks (7 types)	0,003 – 0,017
Carbonated/sparkling mineral drinks (7 types)	0,029 – 0,082
Distilled water (control laboratory water)	0,023
Orange juice	2,5
Cola drinks (4 types)	2,754 – 6,352

Results showed that the dissolution of dental anamel by still mineral water and distilled water was very low. The dissolution is slightly higher by carbonated mineral water. Meanwhile, that of orange juice and Cola drinks was 30 - 219 times higer (Table 5). In 3 drink groups with low levels of dissolution dental anamel, synthetic hydroxyapatite was used to measure the dissolution of minerals. Table 6 showed results of pH and solubity of hydroxyapatite caused by 7 types of carbonated drinks, which was almost equal to 5 types of distilled water in the laboratory.

Table 6. pH level and hydroxyapatite dissolution.

Drinks	pH levels	The dissolution of hydroxyapatite (μg)
Still mineral drinks (7 types)	7,12 – 8,10	7,3
Carbonated mineral drinks (7 types)	5,05 – 6,30	23,6
Distilled water (5 types)	5,25 – 6,16	22,8

The interaction between minerals of mineral water and dissolution hydroxyapatite was found in this study. Specifically, the de-gassing of mineral water (Quezac) reduced 61 % of dissolution level of hydroxyapatite, which was accompanied by an increase in pH of 0.8. Meanwhile, the degassed water was adjusted in the pH to that prior to de-gassing, only 27 % reduction in dissolution hydroxyapatite was observed. The absolute reduction in the value of both two cases was significantly low. Therefore, carbonation of drinks or the process of dissolving carbon dioxide in water leads to the increase of drink acidity, but may not be an important factor in terms of their erosive potential per se.

Another study among children at14- year-old in the United Kingdom (Milosevic, Bardsley, & Taylor, 2004) showed that group with the frequency of intake carbonated beverages in general (there is no separation between sugar and non-sugar) over 2 times per day have 1.32 times higher at risk of dental erosion than group with that of below. Meanwhile, the similar risk was not observed in the group drinking carbonated mineral water. Apparently the above comparation does not provide clear evidence of the relationship between carbonation and erosion because minerals of the carbonated mineral water might also incease dental remineralization.

Other studies

All studies of this section could not show the component of carbonated drinks resulting in enamel tooth wear. As mentioned in the introduction, carbonated soft drinks have various components. By dint of appearing other acid such as citric acid, phosphoric acid, etc., beside a-carbonic acid, the acidity of carbonated beverages is higher than regular sparkling water. Therefore, the results of this study could only be references to dental erosion levels caused by carbonated beverages.

<u>Cross sectional studies</u>

A cross-sectional study which was conducted among 1314 children aged 13-19 years in 2011 in the USA (Okunseri, Okunseri, Gonzalez, Visotcky, & Szabo, 2011) reported that only apple juice was associated with enamel tooth wear.

Similarly, the result of other study using convenience sample at King's College London among 1010 students 18-30 years indicated that there was no relationship between dental erosion and carbonated drinks. Meanwhile, apple juice showed strongly association with both enamel and dentine erosion (OR =7 and 3.7 respectively). Orange juice, also, caused a risk factor of erosion for occlusal tooth wear (Bartlett et al., 2011).

Results of some studies have indirectly shown the potential role of the removal of mineral by citric acid (component of orange and apple juice). Citric acid is usually added as flavor in several carbonated drinks. Other studies also demonstrated that citric acid in juices and carbonated drinks as the main factor have relationship with dental erosion (Attin, Meyer, Hellwig, Buchalla, & Lennon, 2003b; Lussi, Schaffner, Hotz, & Suter, 1991; Sardana et al., 2012; West et al., 1998). Citric acid is defined as chelator binding calcium of enamel or dentine tooth, which increases the levels of undersaturation and the favors more demineralization. However, other studies argured phosphoric acid (a component of Pepsi) was higher than citric, malic and lactic acid in the erosive potential (Rugg-Gunn, Maguire, Gordon, McCabe, & Stephenson, 1998; West, Hughes, & Addy, 2000).

Edward et al measured the pH and titratable acidity or buffering capacity of the beverages and fruit juices (Edwards, Creanor, Foye, & Gilmour, 1999) and results were classified following the descending order of buffering capacity:

- Fruit juice
- Fruit flavored drinks, including fruit flavored mineral water
- Carbonated soft drinks (Coca-Cola)
- Carbonated mineral water/ sparkling mineral water
- Non-carbonated mineral water

This result suggests an important role of the acid (citric acid, malic acid) in determining the buffering capacity of the beverage. The initial pH of the beverage could not reflect titratable acidity or buffering capacity of the beverages, so it is not the only indicator to show the risk of tooth enamel loss.

In relation to the impact of juices on enamel tooth, a cross- sectional study among students at 14-year-old in England contradictorily pointed that consumers of juices have no risk of enamel erosion (Milosevic, et al., 2004).

Unlike results provided by Okunseri and Barlett, other studies on children community showed a positive correlation between the level of carbonated drinks used and dental erosion, specifically:

- A study conducted among 458 Brazil students at 13-14 years old showed that those who had a daily consumption caused 1.7 times higher risk of erosion, and the relationship between erosion, juices and non-carbonated drinks was no statistical significance (Waterhouse, Auad, Nunn, Steen, & Moynihan, 2008). Results of this study also indicated the interaction between the amount of sugar or acid in soft drinks and enamel. When sugar in beverage forms dental plaque and bacterial fermentation, it will produce acids. These acids then combinate with exogenous acids of the beverages and can result in the increase of erosive level (Denehy, 2003, Zero & Lussi, 2005).
- In the study of 14-year-old students in London, results also pointed that the risk of enamel wear when drinking carbonated beverages (in both sugar and non- sugar) over 2 times per day was 1.3 (Milosevic, et al., 2004). Similarly, Millward et al demonstrated the relationship between carbonated drinks and erosive levels among 101 young patients in hospital (Millward, Shaw, Smith, Rippin, & Harrington, 1994). Specifically, those having ‘no/mild’, ‘moderate’ and ‘severe’ levels of enamel wear consumed carbonated drinks at 3.9, 5.8 and 13.6 times per week, respectively. This difference was statistically significant. Furthermore, not only the frequency but also the way of drinking carbonated beverages was associated with tooth erosion in children. For example, children aged 5-6 years who frequently drink at least one carbonated beverages at night were at high risk of erosion of palatal surfaces of maxillary incisors, following a study in 2002 (Al-Majed, Maguire, & Murray, 2002)

Results of the association between carbonated soft drinks and dental erosion through cross-sectional studies on population are not consistent. It is because the consumption of carbonated beverage is various in diffirent markets. The experiment study also showed that pH level, titratable acidity, component (including acids and minerals) of carbonated soft drinks are very different, followed by diverse impacts on dental erosion. In addition, some studies have limitation when it could not eliminate the interaction of other foods and drinks consumed by participants.

Expermential studies:

Ehlen and colleagues (Ehlen, Marshall, Qian, Wefel, & Warren, 2008) compared lesion depths in enamel and root surfaces following beverage exposure, namely carbonated soft drinks (Diet Coke, Coke), energy drinks (Redbull), sports drinks (Gatorade) and 100% apple juice. The results showed that all beverages were acidic. While the lesion depths in enamel and root surface of Diet Coke and 100% apple juice showed almost equal number, that of Coke and Red Bull were significant greater than other drinks. There was no relationship between dental erosion and pH, suggesting that neither pH nor titratable acidity can be used to predict erosive potential.

Jensdottir and colleagues, on the other hand, reported positive correlation between the two indicators, i.e pH and titratable acidity, and the weight loss of tooth (T. Jensdottir et al., 2004). Moreover, Benjakul and Chuenarrom et al illustrated the equation formulated from the pH and titratable acidity, which was used to estimate dental erosion levels caused by carbonated drinks in several other studies (i.e Trang et al in Viet Nam, 2003). However, this prediction equation are still considered since Ehlen et al pointed that the soft drinks are different in composition and nutrients/non-nutrient in soft drinks, in fact, has the potential impact on erosive tooth wear. Many other studies have indicated that the possibility of adding calcium, phosphate and fluoride will reduce the formation of lesions depth in enamel. (Attin, Meyer, Hellwig, Buchalla, & Lennon, 2003a; T. Jensdottir, Bardow, & Holbrook, 2005; Lussi, et al., 2004).

Table 7. Research on effects of carbonated drinks on erosive tooth following years

Author	Article title	Publication Year	Study design
Okunseri, C. et al.	Erosive tooth wear and consumption of beverages among children in the United States.	2011	Cross-sectional study based on students comunity
Barlett et al.	The association of tooth wear, diet and dietary habits in adults aged 18-30 years old	2011	Cross-sectional study on students comunity
Ehlen A. et al.	Acidic beverages increase the risk of in invitro tooth erosion	2008	In vitro experimental study
Waterhouse,J et al.	Diet and dental erosion in young people in south-east Brazil	2008	Cross-sectional study based on comunity
Milosevic et al.	Epidemiological studies of tooth wear and dental erosion in 14-year old children in North West England. Part 2: The association of diet and habits	2004	Cross-sectional study based on comunity
Jensdottir et al.	Relationship between dental erosion, soft drink consumption, and	2004	Prospective study

	gastroesophageal reflux among Icelanders		
Majed et al.	Risk factors for dental erosion in 5–6 year old and 12–14 year old boys in Saudi Arabia	2002	Cross-sectional study based on comunity
Parry et al.	Investigation of mineral waters and soft drinks in relation to dental erosion	2001	Experimental study
Millward et al.	The distribution and severity of tooth wear and the relationship between erosion and dietary constituents in a group of children	1994	Cross-sectional study at hospital

Table 8. Research on effects of carbonated drinks on erosive tooth following study design

Publication Year	Study design	Condition evaluation	Sample size	Result
2011	Cross-sectional study based on comunity	Erosive tooth wear	Of 1.314 children from 13 to 19, 523 were diagnosed with erosive tooth wear in different level.	- There was no relationship between carbonated beverage, juices (except apple) and erosive tooth wear. - The odds ratio for apple juice consumed was 1.24 (1.08-1.43)
2011	Cross-sectional study based on comunity	Erosive tooth wear	Of 1.010 students from 19 to 30, all were diagnosed with erosive tooth wear in different level.	- There was no relationship between carbonated beverage and erosion. - The odds ratio for apple juice consumed was 7 and 3.7; orange juice consumed was 1.7.
2008	Cross-sectional study based on comunity	Erosive tooth wear	458 students aged 13 to 14 years.	- The odds ratio for carbonated beverage consumed was 1.75 (1.11-2.75)
2004	Cross-sectional study based on comunity	Erosive tooth wear	2385 students at 14 years old.	- Odds ratio of carbonated beverage consumed was 1.32 (10.8-1.62) - The odds ratio for lemon tea consumed was 3.97 (1.26-13.89 and sport drinks consumed was 1.58 (1.1-1.75)
2004	Prospective study at	Erosion in both the	Of 57 adolescents from Nutritional	- There was positive association between frequency

	comunity	incisors and molars	Council Survey of Schoolchildren (INS) were selected at radom, 31 were diagnosed with erosion in both the incisors and molars	of carbonated beverage consumed in Iceland- especially with Coca-cola (drink above 1l Coca-cola/week or 3 times/ week) and erosion.
2002	Cross-sectional study based on comunity	Erosive tooth wear	Of 268 children 5-6 aged, 43 were diagnosed with erosion in deciduous maxillary incisors.	- There was positive association between the consumption of carbonated soft drinks at least once or above and erosion in deciduous maxillary incisors.
1994	Cross-sectional study at hospita	Enamel erosion	101 children at dental hospital; 21 in “mild “group, 45 in “moderate “group; 35 in “severe” group.	- There were highly significant differences between carbonated drinks consumed and erosion; the mean number of carbonated drinks consumed per week in the 'mild', 'moderate' and 'severe' erosion groups was 3.9, 5.8 and 13.9, respectively.
2008	Invitro experimental study	Erosive level in both enamel and root surface of deciduous teeth and adult teeth.	Tooth sample	- The erosive level in both enamel and root surface because of apple juice (57-77µm) and Diet Coke (61-66 µm) was equal - Coke (92-101 µm) and Diet Coke (100-131 µm) caused more erosion.
2001	Experimental study	Dissolution mineral levels	Tooth sample	- Sparkling mineral waters showed equal dissolution to still waters - De-gassing of a sparkling mineral water reduced its dissolution but the impact on erosion was very low.
1999	Experimental study using tooth enamel sample	Erosive tooth wear levels of sample.	9 samples applied on 11 pepple for each testing liquid.	- Erosive tooth wear levels exposed diet cola with phosphoric acid were 14,3 µm, significant higher than the distilled water (5,0 µm), orange juice with citric acid (6,1 µm), and orange juice with citric acid and calcium

				citrat malate (6,1 μm) .

4.2. Impact of carbonated water to bone density

4.2.1. Comment on method of research on carbonated soft drinks to bone density

Studies on relation between carbonated drink consumption and bone density are all either cross-sectional or double-blind case-control. Bone density is measured by Dual X-ray Absorptiomery (DXA) or by Quantitive Ultrasound (QUS). These are two measuring methods without interfere. Please refer to an analysis on comparing these methods by Diessel and colleagues (Diessel et al., 2000).

Due to the differences in drinks, measures, measured places of the bone among studies as well as the limited number of studies, we do not apply meta-analysis for calculating the size effect of the relation between carbonated drink consumption and bone density.

4.2.2. Results of carbonated soft drinks to bone density research

Study on carbonation impact of drinks on bone density

There was only one study that measured almost directly the impact of carbonation– this is comparing the relations of bone density of using carbonated soft drinks and regular drinks in postmenopausal women in Spain (Schoppen, Perez-Granados, Carbajal, de la Piedra, & Pilar Vaquero, 2005). 18 healthy postmenopausal women, not obese, not using vitamins or hormones, with average age of 53, have joined this study with 8 weeks of drinking control mineral water and then 8 weeks of drinking carbonated mineral water (1 liter per day), along with a controlled diet. The study variables include diet, exercise and sport, sun exposure, height, weight, blood pressure, biochemical determinations of blood and urine, T_{30} bone mineral density for the lumbar spine and femoral neck – calculated using the formula: (bone mineral density minus mean bone population bone mineral density at age 30) / standard deviation (SD).

The results showed that the pH of urine after drinking carbonated water was higher than after drinking control water, however 24-hour urine excretion did not differ between the two periods. The excretion of calcium through urine after drinking carbonated mineral water was lower than control water, while the amount of phosphorus excreted more. There was no difference in the amount of other urine electrolytes and values of bone turnover biomarkers.

Carbonated mineral water is said to be a combination of both contents that have positive and negative effects on bone. Related to bone density, mineral carbonated water is basically different from control water in the Na+, HCO3-, Cl-. High concentrations of Na+ is said to be a negative impact to bone density because it will increase the urine calcium excretion through mechanism of coupled transport Na+ and calcium in the kidney nephron. Because the amount of sodium excreted through urine after drinking control water and carbonated water had no difference, it suggested that the amount of Na+ taken into the body through the mineral water is not much. In the experiment, the amount of calcium excreted through urine after drinking carbonated water was lower than control water, which is consistent with other research demonstrated the positive effects of HCO_3^- (Kessler & Hesse, 2000). A liter of carbonated water will supply approximately 34mmol of HCO_3^-. This amount of anion tends to reduce the negative impact of NaCl on calcium excretion, increase renal calcium reabsorption in the distal tubules of the kidney and improve the calcium balance. Research of Schoppen and colleagues found that drinking 1 liter of carbonated mineral water daily did not cause bone remodelling.

Studies on carbonated soft drinks in general

Studies about the relationship between bone density and the use of carbonated soft drinks in general which were reviewed were mainly conducted in the United States. There are two populations of study concern due to their vulnerability to bone density: those are postmenopausal women and adolescents. Postmenopausal women have high risk of osteoporosis. Meanwhile adulthood is also a complete bone structure phase and mostly decides bone status in old age.

Studies on postmenopausal women

Kim and colleagues published the results of a cohort study of over 1,000 women aged from 44 to 98 involved in an osteoporosis research from 1988 to 1992 (Kim, Morton, & Barrett-Connor, 1997). After adjusting factors such as low consumption of calcium, estrogen use, phosphoric and caffeine levels in soft drinks, the results indicated no association between bone density and the use of carbonated soft drinks in general. However, a point worth noting is the amount of carbonated soft drinks consumed during this time was not much, at the time of the study, only 65% of women drank 1 can/day (12 oz/day ~ 355ml/day) and women who have used over 10 years is 90 people in total of 1,000 women.

Cross-sectional study on 438 American Indian women in postmenopausal period did not provide evidence of an association between bone density and the use of carbonated soft drinks. The questionnaire collected information about the frequency and volume of 4 carbonated drink groups with caffeine, without caffeine, with sugar and without caffeine, without sugar and without caffeine. In both linear and regression model (converted to bone density level which is considered osteoporosis by WHO), the consumption of carbonated soft drinks have no statistically significant association with bone mineral density or the osteoporosis status. Despite not presenting tables, the authors stated that there was no correlation observed when separating drink consumption by caffeine content. However, the method of collecting data might also influence partly on the result of consumption of carbonated soft drinks, for example, respondents choose to drink units/day (equivalent to 12 oz/day ~ 355ml/day) and selected units. In some questionnaires, the total amount of drinks in 1 day was up to 8.5 liters (Supplee et al., 2011).

In round 7 of the Framingham cohort study, Tucker and colleagues evaluated the association between the consumption of carbonated beverages and bone density of 1,413 men and 1,125 women in the period from 1996 - 2001 (Tucker et al., 2006). After controlling confounding factors such as BMI, height, smoking status, alcohol use, age, activity level, energy consumption, calcium, vitamin D, caffeine in food groups which is not carbonated soft drinks, mineral ratio, fruit juices, etc., Tucker and colleagues found no association between the use of carbonated beverages (except for Cola) with bone density in both male and female. Meanwhile, Cola drinks have different effects on two sexes. In men, the researchers found no relationship between bone density and the use of Cola. In contrast, in women, drinking Cola was related to bone mineral density of total hips, femoral neck, Ward's area and trochanter. But there was no relation to spinal bone density. (Because 2 studies by Kim and Supplee did not divide the data to the Cola drinking group so it is unable to conduct meta-analysis to see the size effect in the 3 studied populations).

Tucker has focused on testing the relationship between bone density and some ingredients in cola but little or no in other carbonated soft drinks, i.e. caffeine and phosphoric acid. After controlling confounding factor, which is caffeine from other sources and adjusting caffeine from cola, bone density results showed no significant differences. The ratio of calcium/phosphorus in cola drinking group was lower in non-cola drinking group. However, when the ratio was adjusted between two groups, also no significant difference was found in bone density results.

In theory, high phosphorus and low calcium diet will lead to creation of complexes which reduces serum calcium, stimulating parathyroid hormone, followed by bone resorption in order to return serum calcium to homeostatic value. The impact of cola reducing serum calcium has been demonstrated in mice (Amato et al., 1998; Ogur et al., 2007). However, studies on animal do not control the level of nutrients, including calcium intaken. That what level of phosphoric acid in cola cause the above situation in human is still a matter of debate, for example, the amount of phosphoric acid in cola and orange juice are equivalent (approximately 5mg/oz ~ 0.17 mg/ml) (Fitzpatrick & Heaney, 2003).

Caffeine when taken into the body will cause a loss of calcium through urine immediately. However, the renal will later adjust to reduce calcium clearance. Caffeine also limits calcium absorption in small degree, but if the amount of calcium was taken adequately into the body through diet, it will not cause any impact to the bone. Double-blind case-control study on 16 postmenopausal healthy women showed that if an amount of 400mg/day of caffeine (approximately 7.3 to 10.2 mg/kg body weight) was taken into the body, and calcium intake through daily diet was 15mmol/day, it would not cause any impact to the calcium balance of the body (Barger-Lux, Heaney, & Stegman, 1990).

In addition to identifying the ingredients in cola related to bone density, Tucker found there was no relation between the amount of milk and cola consumption by women. But total calcium, fruit juice intake was lower than in cola user group. However, when adjusting to the amount of fruits and vegetables intake, the results also showed no significant difference between the two groups (This is acknowledged by the authors, no data were given in the article).

<u>Research on adolescent group</u>

2,017 adolescents aged 12-15 years in Northern Ireland joined Young Heart epidemiological investigation by filling the questionnaire about social demographic characteristics, diet, exercise mode, were measured forearm bone density, heels and were checked pubertal status (McGartland et al., 2003). The results showed that there is a negative correlation between the dominant heel bone density in female groups with the use of carbonated soft drinks in general. After adjusting factors such as height, weight, pubertal status, alcohol use, smoking, socioeconomic status, physical activity, drinking milk and calcium intake from other food sources, the correlation was observed only among women using diet carbonated beverage type (diet - use artificial sweeteners). The study also showed no relationship between bone density and the use of carbonated soft drinks containing sugar, including cola. The results differed from findings of Tucker and colleagues who pointed out that only female drinking cola group reduced bone density (femoral neck). However, in the study on adolescent group, there was significantly reduced in the amount of milk consumed in the group drank more carbonated soft drinks. Especially in the diet group (use sweetened beverages) calcium intake through food and drink were much lesser. A similar study on 9 and 10 grade girls in Boston, USA (Wyshak, 2000) showed the relationship between fracture status and the use of carbonated beverages (including cola and no cola). However, this study did not collect information related to nutrition, especially calcium.

Gender factors in the relationship between the use of carbonated beverages and bone density

Studies on populations about the impact of carbonated beverage on calcium density showed gender (male/female) is one of related factors. The level of sports exercise and calcium intake in men group is always higher than in women group, and they are considered to be a factor which explains gender differences in bone density when used carbonated beverages (McGartland et al., 2003, Tucker et al., 2006). However, in research on adolescent groups, a point needed to be considered is that males and females have different stages of puberty, females are often on diet, and vitamin deficiency risk is higher than men. It may also be the factors explaining gender differences in research (Fitzpatrick & Heaney, 2003).

Table 10. Reviewed articles on the effects of carbonated water to bone density by time

Author name	Article name	Publish year	Type of study
Supplee et al	Soda intake and osteoporosis risk in postmenopausal American-Indian women	2011	Cross-sectional survey
Tucker et al	Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study	2006	Cross-sectional survey on the Framingham cohort sample
Schoppen et al	Bone remodelling is not affected by consumption of a sodium-rich carbonated mineral water in healthy postmenopausal women	2005	Empirical research
McGartland et al	Carbonated Soft Drink Consumption and Bone Mineral Density in Adolescence: The Northern Ireland Young Hearts Project	2003	Cross-sectional survey
Wyshak	Teenage girls, carbonated beverage	2000	Cross-sectional

	consumption and bone fractures		survey
Kim et al	Carbonated Beverage Consumption and Bone Mineral Density among Older Women: The Rancho Bernardo Study	1997	5-year cohort study

Table 11. Reviewed articles on the effects of carbonated water to bone density by study design

Publish year	Type of study	Assessed status	Study sample	Main results
2011	Cross-sectional survey	Bone density	438 American Indian postmenopausal women, aged of 55 on average	- There was no relationship between bone density and the use of carbonated beverages
2003	Cross-sectional survey	Bone density	591 men and 744 women aged of 12-15	- There was an association between reducing heel bone density and drinking much non-sugar carbonated beverages in women group
2000	Cross-sectional survey	Fracture status	460 women from 9 and 10 grade of high school	- There was an association between the use of carbonated beverages and bone fractures (OR 3.14, 95% CI:1.45-6.78). It can be seen clearly in the female group had more physical activity (OR 4.94, 95% CI: 1.79-13.62)
2006	Cross-sectional survey from the cohort sample	Bone density	1125 American females and 1413 American males	- There was an association between reducing bone mineral density at some measured places of the femur and drinking cola. - There was no relationship between bone density measured at some places and drinking noncola beverages
1997	Cohort study	Bone density	1.000 women aged of 44-98 in California, USA	- There was no relationship between bone density and carbonated beverages use in general

4.3. Effects of carbonated drinks on oesophagus

Regarding to effects of carbonated drinks on esophagus, there are 4 main factors considered, including: the amount of CO_2 dissolved (2) the amount of sugar or sweetener added to water (3) The effect of other substances used by industries for their preparation used in manufactory (3) the amount of acid as some types of carbonated drinks containing high level of acid, such as soda, cola or beer (the acidity of soda comes from the chemical reaction of Co_2 and H_20 to HCO_3^- and H^+ ion as well as the accumulation of additive supplement ,i.e citric acid or phosphoric acid)

In the scope of this issue, studies mainly focus on effects of CO_2 and the acidity in carbonated drinks. However, it is difficult to control for combined effects of factors, particularly combined effects of sugar, sweeteners and CO_2. Theoretically, in alkaline conditions, CO_2 will be converted to bicarbonate carbonate CO_3^- and HCO_3^-, and CO_2 absorbed is likely to appear in the digestive tract. However, Most of the CO_2 in a carbonated beverage does not actually reach the stomach. Much is loss in the fizz when the can or bottle is opened and some combines with swallowed air to cause belching. Therefore, most of the CO_2 present in a beverage does not reach the digestive tract and the small amount that is readily and rapidly absorbed through the wall of the gastrointestinal system

4.3.1. Effects on gastroesophageal reflux

Most effects of carbonated waters on esophagus is to cause gastroesophageal reflux disease. The main symptoms of gastro-esophageal reflux epigastric is heartburn

A prospective cohort study with very large sample sizes authorized by Fass and colleagues have shown the relationship between the risk of heartburn leading to wake up and carbonated drinks. This result reaches statistical significance (OR = 1:24; CI: 1:07 to 1:45) (Fass, Quan, O'Connor, Ervin, & Iber, 2005)

Feldman and Barnett studied the effect of 11 different types of carbonated drinks as well as milk, yogurt drinks, alcoholic beverages on the symptoms of heartburn Findings have shown that the frequency of having heartburn different following types of water, in which 10% -19.8% of people who drink various carbonated beverages suffer heartburn burning pain and gastroesophageal reflux and there are not difference between the group of diet carbonated drinks (diet) and the group of normal ones. However, in this study, authors do not identify effects of carbonated waters containing sugar or other kinds of acid, thus it could not have sufficient evidence to determine whether or not the amount of carbonate in carbonated waters is the main factor causing reflux symptoms and heartburn (Feldman & Barnett, 1995).

The relationship between carbonated water and gastroesophageal reflux disease can be explained through the following mechanisms:
Most carbonated water are at high acidic level (pH from 2.4 to 4.0) so after drinking carbonated water, PH level of intra-esophagus changes together with the appearance of heartburn which similars to gastroesophageal reflux disease. However, some studies have shown that the impact of changing pH level of esophagus occurs in the short-term. A research authorized by Shoenuthas demonstrated that although pH level of esophagus changes, effects of carbonated water are really temporary, for instance, the amount of time of pH level staying at number 4 is

about 7.7 minutes if taking Cola drinks, and 3.3 minutes if taking beer.(Shoenut, Duerksen, & Yaffe, 1998). Besides, Argawal and colleagues compared the impact of various beverages on changing pH level of esophagus, such as fruit juices, coffee, tea, wine and carbonated water, and the results showed that the pH level reaches the lowest number when drinking water carbonated, but this situation only lasted within 90 seconds in average (Agrawal, Tutuian, Hila, Freeman, & Castell, 2005).

The impact of carbonated water on the lower esophageal sphincter tone: Activities of the lower esophageal sphincter is a key factor of gastroesophageal reflux disease. It has an important role in protecting the esophageal mucosa from HCL acid of the stomatch. Normally, the lower esophageal sphincter only open when swallowing, then constantly closed to prevent stomach acid fluid to flux into (Kuribayashi et al., 2009). A study with a small sample size (9 healthy people) evaluated effects of carbonated water on the esophageal sphincter have shown that all beverages can reduce pressure of esophageal sphincter from 30% to 50% for at least 20 minutes, compared with normal water. The author also explains that this phenomenon happened due to the distension of the stomach containing gas. However, this study could not show the direct evidence of increased acid in the esophagus as a result of drinking carbonated waters (Hamoui et al., 2006). Shukla and colleagues in India researched about the effects of carbonated water on pressure and relax time of the esophageal sphincter among 18 healthy volunteers. The study illustrated that drinking 200ml of carbonated water reduce pressure of the lower esophageal sphincter and also increase the relax time of these sphincter, compared with drinking 200ml of cold water. While the latter finding reaches statistical significance, the former ones show the opposite results.(Shukla et al., 2012).

The effects of carbonated water on esophagus and stomach motility: We have not found any published studies that show the effect of carbonated water on the motion of the esophagus. There are a number of studies assessing the impact on the motion and function of the stomach and most of these studies are unable to show statistical evidence about the relationship between carbonated water and motion/ function of the stomach or the process of gastric emptying. Zach Wieja and colleagues conducted an experiment among 8 men with 4 different types of water, namely: sweetened carbonated water, non- sweetened carbonated water, non- sweetened non-carbonated water, non-carbonated sweetened water within 120 minutes ofcycling. After each cycling races, the content of each cyclist's stomach was aspirated and there was no difference in the retained volume fater each of the beverage (Zachwieja, Costill, Widrick, Anderson, &McConell, 1991). Similarly, Cuomo and his colleagues conducted study with a sample size of 13 healthy subjects, and showed that there is no statistically significant difference between effects of sweetened carbonated water, non- sweetened carbonated water, and sweetened non-carbonated on the process of gastric emptying (Cuomo et al., 2008). Other study of Cuomo was performed on 22 patients suffering symptoms of functional indigestion and constipation. Subjects were asked to consume carbonated water or tap water for almost 15 days. Water without carbonation demonstrated a shorter gastric emptying duration but it did not reach statistical significance. In a study in 1997, 8 healthy volunteers were required to eat radio labeled meal and consumed either distilled or carbonated water. Although this study does not indicate differences in time of the process of gastric emptying between using water and carbonated water, including the duration of the lag phase between the two drinks. However, there was a greater retention of food (both solids and liquids) in the proximal stomach with carbonated water as compared with distilled water.

There was retention of the meal within the proximal stomach, which ended with the lag phase and was likely related to proximal gastric distention. The authors stated that gastric distention by liberated C02 from carbonation was not associated with alteration in overall gastric emptying but more with modification of intragastric distribution of a meal (Pouderoux, Friedman, Shirazi, Ringelstein, & Keshavarzian, 1997).

In general, though studies have suggested different mechanisms and interpretations about the relationship between carbonated drinks and reflux syndrome but there is still lack of specific evidences on this issue(Johnson, Gerson, Hershcovici, Stave, & Fass, 2010).
Most important, a study in 2006 which reviewed on the impact of changes in risk behavior of ongastroesophageal reflux disease could not find scientific evidences to prove that stop drinking carbonated water would reduces Gastroesophageal reflux disease. (Kaltenbach, Crockett, & Gerson, 2006) Therefore, we need to conduct more prospective clinical trial study with sample sizes being large enough in order to provide convincing evidence about the relationship between drinking carbonated water and gastroesophageal reflux disease.

4.3.2. Oesophageal damage

It has been suggested that frequent ingestion of carbonated beverages might cause oesophageal mucosal damage due to the high acidity of beverage

There was a study designed among 16 healthy students with the aim of investigating the risks of lesions of esophageal mucosal if drinking carbonated water compared with salt water. Results have shown that students who drink Cola have a higher regenerative index by flow cytometry than those drinked saline, which may show some irritating effect of Cola drink to esophageal mucosal (Kapicioglu et al., 1998). Up to now, no studies clearly demonstrating an increased risk for oesophageal mucosal injury in the form of oesophagitics, oesophageal ulceration or even oesophageal stricture, partly because oesophageal mucosa was shown to have unique capacity to withstand acid even in very high concentration.(Johnson, et al., 2010).

With regard to the association between two variables: carbonated drinks and esophageal cancer, evidences do not reach statistical significance. Mayne and colleagues conducted a case-control study in 2006 in U.S. community with a sample of 687 controls and 282 cases of adeno carcinoma, 255 cases of gastric carcinoma, and 206 cases of squamous cell carcinoma. Results have shown that carbonated drinks (especially with one containing only little sugar) reduce the risk of esophageal adeno carcinoma but no relationship with gastric carcinoma or squamous cell carcinoma (Mayne et al., 2006). There is a similar results investigated by a case-control study from Switzerland in 2006 which proves that there is no association between esophageal carcinoma and the consumption of carbonated water (including cases when drink over 6 times per week).The sample size of this study consists of 189 patients with carcinoma, 262 patients with gastric carcinoma and 820 people in control group, and with retrospective data collected in the period from 1995 to 1997 (Lagergren, Viklund, & Jansson, 2006). Another case-control study with large sample sizes in Australia in 2008 showed that the daily consumption of canrbonated water at high levels has no relationship with the risk of esophageal carcinoma (adjusted OR = 0.94, 95% CI 0.53-1.66), but related to inversely proportional to the risk of squamous cell carcinoma (adjusted OR = 0.4, 95% CI 0.35-0.81) (Ibiebele, Hughes, O'Rourke, Webb, & Whiteman, 2008).

Among studies conducted in Asia and Africa's population, there are no results that could illustrate the relationship between carbonated water and esophageal cancer. Studies conducted in the Americas and Europe, Australia areas, in other hand, have larger sample sizes. However, all studies have applied case-control design, so there may be bias such as recall bias of the amount or time of using carbonated water.

Table 12. Reviewed articles on the effects of carbonated water to the esophagus by time

Author name	Article name	Publication year	Study design
Zachwieja, J.J.,	Effects of drink carbonation on the gastric emptying characteristics of water and flavored water.	1991	Clinical trials
Pouderoux, P.,	Effect of carbonated water on gastric emptying and intragastric meal distribution.	1997	Clinical trials
Shoenut, J.P.,	Impact of ingested liquids on 24-hour ambulatory pH tests.	1998	Prospective study
Cuomo, R.,	Effects of carbonated water on functional dyspepsia and constipation.	2002	Clinical trials with random sample size
Fass, R.,	Predictors of heartburn during sleep in a large prospective cohort study.	2005	Cohort study
Hamoui, N.,	Response of the lower esophageal sphincter to gastric distention by carbonated beverages.	2006	Clinical trials
Mayne, S.T.,	Carbonated soft drink consumption and risk of esophageal adenocarcinoma.	2006	Case-control study on community
Lagergren, J., P.	Carbonated soft drinks and risk of esophageal adenocarcinoma: a population-based case-control study.	2006	Case-control study on community
Cuomo, R.,	Sweetened carbonated drinks do not alter upper digestive tract physiology in healthy subjects.	2008	Clinical trials
Ibiebele, T.I.	Cancers of the esophagus and carbonated beverage consumption: a population-based case-control study.	2008	Case-control study on community

Johnson, T.,	Systematic review: the effects of carbonated beverages on gastro-oesophageal reflux disease.	2010	SystematicReview
Shukla, A.,	Ingestion of a carbonated beverage decreases lower esophageal sphincter pressure and increases frequency of transient lower esophageal sphincter relaxation in normal subjects.	2012	Clinical trials

Table 13. Reviewed articles on the effects of carbonated water to the esophagus by study design

Publication Year	Study Design	Health status	Sample size	Main results
2006	Case-control study on community	Esophageal cancer	687 controls, 282 cases of esophageal carcinoma, 255 cases of gastric epithelial cancer and 206 cases of esophageal squamous cell	Carbonated water reduced the risk of esophageal carcinoma and no association with gastric carcinoma or squamous cell carcinoma
2006	Case-control study on community	Esophageal cancer	189 cases ofcarcinoma, 262 cases of gastric carcinoma and 820 controls	There was no association between esophageal carcinoma and carbonated water used.
2008	Case-control study on community	Esophageal cancer	1484 controls, 294 cases of esophageal carcinoma, 325 case of gastroesophageal junction carcinoma, 238 squamous cell carcinoma	Drinking the large amount of carbonated water daily was not associated with esophageal carcinoma but had inversely proportional to the risk of squamous cell carcinoma
2005	Cohort study	Epigastric pain during sleep (manifestations of gastroesophageal reflux)	15,314 people	There was an association between carbonated water and epigastric pain during sleep
1998	Prospective study	Nồngđộ PH củathựcquản pH level of esophagus	82 patients	There was no diffirenence of pH level of esophagus when drinking diffrerent type of water such as tea,

				coffee, juices
2010	Systermatic review	Gastroesophageal reflux disease	29 article	Carbonated water changed pH level of esophageal in the short time, reduced pressure of the lower esophageal sphincter. There was inadequate evidence to conclude that carbonated water is a factor leading to gastroesophageal reflux disease
1991	Clinical trials	Time of gastric emptying	15 healthy people	The amount of Co2 in carbonated water was not related to the process of gastric emptying
1997	Clinical trials	Time of gastric emptyingand distribution of food in the stomach after eating	8 healthy people	Carbonated water did not change the time of gastric emptying but have an impact on the distribution of food in the stomach, also could cause increased pressure on the upper part of stomach
2006	Clinical trials	Pressure of the lower esophageal sphincter, status of gastric distension	9 healthy people	Carbonated water reduced pressure ofthe lower esophageal sphincter
2008	Clinical trials	Gastroesophageal reflux disease, process of gastric emptying, gallbladder contractions and feeling after eating.	30 healthy people	Drinking carbonated with increasing the amount of CO2 gradually had no impact on the upper gastrointestinal tract
2012	Clinical trials	Pressure and relax time ofthe lower esophageal sphincter	18 healthy people	Carbonated water reduced pressure and relax time of the lower esophageal sphincter.

2002	Clinical trials	Symptoms of dyspepsia, abdominal distension and constipation	21 patients with dyspepsia and constipation	Carbonated water reduced the risk ofabdominal distension and constipation.

4.4. Effects on the stomach

CO_2 in carbonated water ca have effect on stomach through two mechanisms: 1) Mechanics: Changing gastric motility and slowing gastric emptying process and2) Chemistry: The acidity of carbonated beverages, as well as its chemical effects of CO_2 on the formation of HCL acid and gastric parietal cells secretion.

4.4.1 Effects of carbonated water on gastric motility

Once in the body, the metabolism of CO_2 in carbonated water depends on the condition of the stomach at the time of drinking. If the stomach is empty, the water will quickly go into the duodenum. In this alkaline environment, CO_2 is transformed into to bicarbonate. The carbon dioxide dissolved is rapidly realsed in gaseous form as the fluid is warmed. The free carbon dioxide may be belched if the expanding gas increases the pressure and stimulates the gastric fundus triggering the belching mechanism. Distention of the gastric fundus can actually increase transient lower esophageal sphincter relaxation. (Straathof, van Veen, &Masclee, 2002). If drinks carbonated water when eating or after eating, it will tend to accumulate in the upper stomach and can create a feeling of fullness or full stomach. Some observations showed that when gastric distended suddenly by pump or CO_2 gas, the stomach would stop working within 2-5 minutes after belching. Specifically, it was observed that ingestion about 150-200 ml of soda could inhibit all peristalsis for 2-3 minutes. These observations indicated that stomach stretching was related to motility (Cuomo, Sarnelli, Savarese, &Buyckx, 2009).

In a healthy person, with the normal amount of carbonated drinks, recent studies indicated no association between carbonated drinks and gastric emptying time or gastric function. For instance, Pourderoux's research has shown that no difference in gastric emptying or in feeling of fullness between 300ml of carbonated and still water drunk with a meal of 700 calories but an increased need to belch after drinking carbonated water was recorded (Cuomo, et al., 2009; Pouderoux, et al., 1997). Study of Ploutz-Snyder Loris used the magnetic resonance imaging method to compare the effects of drinking 800ml of water, light carbonated water, non-sugar soft drinks and Cola on empty stomachs, and it showed that only after drinking Cola, stomach activity reduced and the gastric emptying was slower, there is no difference between drinking light carbonated water and regular water (Ploutz-Snyder et al., 1999). The study on 30 healthy subjects of Cuomo et al, the study subjects drank 300ml of soft drinks with increasing CO_2 concentration and the assessment on gastroesophageal reflux and gastric emptying by ultrasonography showed that sugar components rather than CO_2 in water increases the risk of reflux after eating 2 hours and the increasing of CO_2 concentrations in carbonated water in the experiments is not related to the movement or function of the upper gastrointestinal as well as the gastric emptying process (Cuomo, et al., 2008).

4.4.2. Effects of carbonated water to the feeling of fullness

In 2012, Wakisaka did a randomized clinical trial on 19 healthy women in order to assess the impact of carbonated water to the fullness feeling. The study participants were assessed in 3 days on stomach mobility with times drinking250ml of water or carbonated water. Results showed a higher fullness index with statistical significance in the group drinking carbonated drinks compared to regular water, which means that carbonated water can cause short-term fullness feeling by increasing sympathetic nerve activity (Wakisakaetal, 2012).

4.4.2. Effects of carbonated water to acid secretion and the digestive process

Some studies have shown that CO2 plays a major role in the formation of HCl acid as well as secretion in the parietal cells of the gastric mucosa. Usually, CO2 is supplied to the cells from the blood and interstitial fluids but under some condition, also from the lumen of the stomach. The diffusion of CO2 into cell is due to the weakness of carbonic acid as well as its liposolubility. There is an inverse relationship between the amount of hydrochloric acid secrected by the stomach and the quantity of carbon dioxide disffused in the lumen when secretion was stimulated by histamine. After drinking carbonated beverages some of the carbon dioxide may be absorbed through the gastric wall, partly contributing together with the carbon dioxide from the interstitial fluid and plasma to the formation of hydrochloric acid (Kurtz &Clark).

Absortion of carbon dioxide is very high in the stomach. Equilibrium for CO2 is reached within 80-90 min through the wall of the stomach while it takes longer for other gases such as nitrogen, oxygen, or methane. Water, alcohol, soluble gases and especially CO2 can be absorbed efficiently from the stomach contrarily most foodstuffs are very little
With acidity of carbonated water as well as its ability to increase HCl secretion in the stomach, some studies showed the impact of drinking Coca-cola in dissolve phytobezoars in the stomach (created by the fiber, hair and other undigested material staying in stomach for a long time and cause blockage in the the stomach) (Matsushita, Fukui, Uchida, Nishio, & Okazaki, 2008). Most recently in 2013, Ladas and colleagues conducted a study by reviewing 24 articles published in the period 2002-2012 on the impact of Coca-cola in helping to dissolve phytobezoars material in the stomach and concluded that Coca-cola can help to dissolve long-time indigestible foreign material in the stomach, combination of Coca–cola and other measures such as endoscopic may be resolved 90% of the cases of phytobezoars (Ladas, Kamberoglou, Karamanolis, Vlachogiannakos, &Zouboulis- Vafiadis, 2013).

Cuomo and his colleagues conducted a randomized clinical trial study with on 21 patients with functional dyspepsia and constipation. The control group drank tap water for 15 days while the intervention group used carbonated water. Results showed that drinking carbonated water reduced the dyspeptic symptoms statistically significant. Symptoms of constipation also decreased in subjects using carbonated water, compared to tap water (Cuomo, etal., 2002).

Table 14. Reviewed reports on the effects of carbonated water on stomach by time

Author name	Article name	Publishcation year	Study design
Pouderoux, P.,	Effect of carbonated water on gastric emptying and intragastric meal distribution.	1997	Clinical trial
Cuomo, R.,	Effects of carbonated water on functional dyspepsia and constipation.	2002	Clinical with random distribution
Cuomo, R.,	Sweetened carbonated drinks do not alter upper digestive tract physiology in healthy subjects.	2008	Clinical trial
Cuomo, R.,	Carbonated beverages and gastrointestinal system: between myth and reality	2009	Review
Wakisaka, S.,	The effects of carbonated water upon gastric and cardiac activities and fullness in healthy young women.	2012	Clinical trial
Ladas, S.D.,	Systematic review: Coca-Cola can effectively dissolve gastric phytobezoars as a first-line treatment.	2013	Review

Table 15. Reviewed reports on the effects of carbonated water on stomach by study design

Study design	Health status	Study sample	Main results
Review	Gastro-oesophageal, stomach reflux, esophageal cancer, lower gastrointestinal tract	Did not mentioned clearly in the article	No clear evidence of the impact of carbonated water on the digestive system. Need clinical studies with larger sample and better design

Review	Undigested foreign bodies in the stomach	24 articles	Cocacola helps to dissolve the long-day foreign bodies in the stomach
Clinical trial	Gastric emptying time and distribution of food in the stomach after eating	8 healthy people	Carbonated water does not change gastric emptying time but have an impact on the distribution of food in the stomach, can increase pressure on the upper part of the stomach
Clinical trial	Gastroesophageal reflux, gastric emptying process, gallbladder contractions and feeling after eating	30 healthy people	Drinking carbonated water with increasing gas concentrations has no impact on the upper gastrointestinal tract
Clinical trial	Impact on operation of stomach, heart and fullness feeling	19 healthy people	Higher fullness index with statistical significance in the carbonated water drinking group compared to regular water
Clinical trial with random distribution	Symptoms of dyspepsia, abdominal distension and constipation	21patients with dyspepsia and constipation	Carbonated water reduces abdominal discomfort and relieve constipation in patients

4.4. Effects on intestine, colon, pancreas, liver and gallbladder

The accumulation of gas in intestines and colon, as a result of effects on bowel and colon, causes symptom of numerous diseases. However, hardly do studies show the impact of carbonated drinks and the demonstration of intestinal and colon due to 2 factors (1) Most CO_2 is absorbed before going to the lower gastrointestinal tract and (2) CO_2 diffuses rapidly across the gastrointestinal wall. If carbon dioxide is present in the intestine it will equilibrate with the amount already in the body fluids: therefore, if it is low it will diffuse from body fluids into the intestine and vice versa. (Cuomo, et al., 2009).

The study was designed as a case-control investigated, in which 490 pancreatic cancer patients and the corresponding number of control group were selected. The purpose of this study was to identify the association between drinking tea, soda, beer, wine and pancreatic cancer. However, results indicated that statistical significance is not found in the association. (Mack, Yu, Hanisch, & Henderson, 1986)

Besides, other study using ultrasound explored effects of carbonated water on the contraction of gallbladder. Results suggested that patients who suffer dyspepsia caused by carbonated drinks (drink 1.5l in 15 days) have higher frequency of gallbladder contractions than those who are not to drink. However, with scientific evidence being investigated by the same author in later period, it is valued that the relationship between the gallbladder contractions of healthy people using sugar-sweetened carbonated or not and the increase of CO_2 is not statistical significance. (Cuomo, et al., 2008)

4.5. Effects on the kidney

It can be classified into two groups: (1) related to urinary tract stones/kidney stones, and (2) renal function in general.

4.5.1. Related to urinary stone formation

Crystal formation and stones development is influenced by endogenous factors as well as diet. Urine volume and inhibitors (citrate, pyrophosphate, urinary glycoprotein) and the catalyst are important factors in urinary stone formation. Theoretically, drink is one of factors associated with urinary stone formation. First, the volume of water taken will increase the amount of urine and dilute the concentration of ions and salt creating stones (Borghi et al., 1996). Second, the composition of the beverages directly impacts the constituent components and creates urinal crystals (Hesse, Siener, Heynck, & Jahnen, 1993). In oxlate calcium stone preventive treatment, the oral solution should reduce calcium excretion, oxlate and urate, and increase magnesium excretion, citrate and increase the alkalinity of the urine. Citrate creates chelat with calcium, creates soluble Ca – citrate complex that reduces calcium concentration. Stones are created by uric acid, which can be dissolved when the urine pH reached 6.5 at minimum.

A cohort study conducted from 1986 to 1990 with the participation of 81,093 women aged of 40-65, with no history of kidney stones, examined the relationship between the risk of kidney stones and 17 drinks (Curhan, Willett, Speizer, & Stampfer, 1998). During 553,081 people-year, there were 719 cases of kidney stones reported. After adjusting BMI, consumption of calcium, potassium, sodium, sucrose and the amount of fluid intake, results showed that the relative risk reduced when using alcohol (RR = 0.4), coffee or caffeinated tea (RR = 0.9), but increased when drinking grape juice (RR = 1.4). The relative risk of using sugar and non-sugar carbonated soft drinks were not statistically significant. However, it should be noted that the amount of carbonated soft drinks consumed by women was very little, for example, the rate of drinking less than 1 can per day was 61%, while the rate of drinking 1 can per day accounted only 3%.

Shuster and colleagues conducted a randomized intervention study in 3 years (1985-1988) to monitor the impact of the use of carbonated beverages with recurrent kidney stones. 1,009 men diagnosed with kidney stones consumed at least 160ml of carbonated soft drinks per day. A randomized half of the participants stopped using carbonated beverages, the other half continued and played as the control group. The results showed that experimental group had 6.4 % higher rate of 3 -year stone recurrence free compared with the control group. The authors also observed that the group refraining from consumed carbonated beverages acidified by phosphoric acid had a 15% higher rate of 3-year stone recurrence free than the control group. Meanwhile, there is no statistically significant difference between the group stopping using carbonated beverages added citric acid and the control group (Shuster et al., 1992).

Empirical studies on drinking cola and analyzing urine composition and electrolytes were conducted. In 1992 (Weiss, Sluss, & Linke, 1992), the experiment took place on a small scale, with 4 males aged of 17 to 59 drank 2.8 liter of Pepsi-cola in 48 hours. Blood and 24- hour urine were analyzed before and after cola intake. Results showed that calcium oxalate excretion of 24h urine increased 8.3 mg, reduced magnesium excretion at the average of 2.6 mg, and reduced average citrate excreted of 122mg. However, the test sample is too small, in which the increase or decrease of measure indexes of a participant are completely opposite.

In 1999, a similar empirical study was conducted, but on a larger sample size: 14 healthy males and 31 healthy females, with no medical history related to urinary stones, aged of 20-26 (Rodgers, 1999). 24h urine samples were analyzed (scanning electron microscopy - SEM) before and after drinking 2 liters of cola in 24 hours. In both male and female groups, increase oxalate excretion was observed. However, in men, there are two indicators which indicates the risk decrease of urinary stone formation after drinking cola, those are the increase of 24 hours urinary volume and the decrease of relative supersaturation of brushite. Particularly, in female group, there were 4 more indexes of urinary stone risk, include: reducing magnesium excretion, increasing phosphate excretion, reducing pH, increasing the saturation state of uric acid. The change in the absolute value still lies in the threshold but is considered to be unbeneficial when the indexes incline toward favorable environment for stones formation. In addition, urine analysis by SEM showed that there was an increase in the number or the size of calcium oxalate dihydrate and trihydrate crystals after drinking cola. Sugar is considered to be the cause of change in urinary oxalate levels. Specifically, this level increased after using glucose, decreased after using fructose and stayed the same if using sucrose. Thus, the cause of increasing urine oxalate is considered to be sugar component in cola (Rodgers, 1999).

Following this research direction, in 2012, Herrel and colleagues published the results of a study on the risk of urinary stones and using cola (Herrel, Pattaras, Solomon, & Ogan, 2012). 13 healthy people and 3 people who have kidney stones in history involved in the prospective crossover study under 2 phases, each phase lasted 6 days. The analyzed results showed no differences in the urinary biochemical indices determined related to the risk of stone formation after drinking deionized water and cola. Passman and his colleagues also conducted a similar crossover experiment on 3 types of water including bottled water, Coke without caffeine, carbonated beverages with much citrate, with the participation of 6 people. Results also showed no differences in the urinary biochemical indices compared to control phase (Passman et al., 2009).

Whether citric acid component of carbonated soft drinks increases citric clearance through the urine and thus reduces the risk of urinary stone formation? Sumorok and his colleagues selected Diet Sunkist Orange carbonated drink to perform a cross empirical study on 9 healthy men and women aged of 26-54 with inversion testing phase in 2 randomized groups. Results indicated no statistically significant difference on citrate concentration, pH urine as well as other indicators (uric acid, oxalate, calcium, oversaturation of uric acid and oxalate calcium). The authors suggested that the results showed no difference due to insufficient amount of drinking. 1 liter per day in this study is equivalent to 10.5 mEq/liter of citrate in alkaline form, while other research indicated drinking sports drinks with 23.6 mEq / liter of citrate increases concentration of citrate (Sumorok, Asplin, Eisner, Stoller, & Goldfarb, 2012).

4.5.2. Related to renal function in general

In many carbonated beverages, phosphoric acid is an acidulant, often used in order to maintain carbonation. As mentioned in section 4.2, plasma phosphorus is maintained by both kidney and bone through parathyroid hormone. The kidney is the main organ regulate plasma phosphorus, so when renal function impairs, it will cause excess phosphorus in the body and the effects mainly on bone. Studies on the effects of excessive phosphorus taken into the body through consumption of processed foods and carbonated beverages all made recommendation about limiting the amount of phosphorus from the diet, especially in older people, to avoid putting pressure on the kidney when its performance gradually declines with age, and in people with diseases such as diabetes (Calvo, 2000).

Serum creatinine is used as laboratory index that measures kidney function in studies. Saldana and colleagues performed a retrospective case-control study to explore the relationship between the use of carbonated beverages with chronic kidney disease (Saldana, Basso, Darden, & Sandler, 2007). Case group consisted of 465 patients who were diagnosed with chronic kidney disease in 4 hospitals in North Carolina, USA in the 1980-1982 period, based on serum creatinine $\geq$ 130μmol/liter (in order to exclude another types of kidney disease) and control group consisted of 467 healthy people in the community. After adjusting variables like age, ethnicity, sex, BMI, income, education, analgesic use, proxy respondent status, regression model results showed that those who drank more than 2 glasses of cola per day were at risk for kidney disease 2 times greater compared to those with no drinking or drinking less than 1 glass per week. Meanwhile, no similar risk was seen on people drinking carbonated non-cola beverages. When considering history of diseas, the researchers found that although the interaction of diabetes status in history had no statistical significance, but the risk of chronic kidney disease in the group with a history of diabetes taking cola is higher than the control group. The results are consistent with other studies about the effects of phosphorus on kidney disease. Additive in non-cola soft drinks is citric acid, whereas in cola drinks is phosphoric acid.

Mahmood (Mahmood Saleh, Al - Alawi, & Ahmed, 2008) conducted a cross-sectional study to find out the relationship between carbonated beverages and laboratory investigations related to kidney function. Retrospective data was collected on 275 students aged from 10-22 in the United Arab Emirates, about using carbonated beverages behavior and samples of blood, urine. More than half of students' carbonated beverages were coca-cola. Results showed no difference between using and not using carbonated beverages groups in the indexes of urea and creatinine in the blood. At the same time, the authors concluded that people using carbonated beverages may have higher risk of increasing urinary calcium and phosphoric excretion about 1.1 times higher than non-drinking group (related to urinary stone formation - see above). However, figures given by the authors did not support this conclusion (OR 1.1, 95 % CI: 0.38 to 3.3).

From 1993-1997, Hu and colleagues studied about the relationship between total fluid and specific beverage intake and the risk of renal cell carcinoma in 1,138 patients and in those without this disease (controls of 5,039 people) in Canada. Results showed no significant relationship between carbonated beverages and this disease (Hu et al., 2009). Systematic review on 13 prospective studies in communities from 1980 to 2000 by Lee et al also showed no relative risk of urinary tract cancer when using carbonated beverages (Lee et al., 2007)

Table 16. Reviewed articles on the effects of carbonated water to the urinary tract by time

Author name	Article name	Publication Year	Study design
Herrel et al	Urinary stone risk and cola consumption	2012	Cross empirical
Sumorok et al	Effect of diet orange soda on urinary lithogenicity	2012	Cross empirical
Hu et al	Total fluid and specific beverage intake and risk of renal cell carcinoma in Canada	2009	Cross-sectional case-control
Mahmood et al	Health effects of soda drinking in adolescent girls in the United Arab Emirates	2008	Cross-sectional with multi-stage random sample
Lee et al	Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies	2007	System rerview
Saldana et al	Carbonated Beverages and Chronic Kidney Disease	2007	Case-control
Rodgers	Effect of cola consumption on urinary biochemical and physicochemical risk factors associated with calcium oxalate urolithiasis	1999	Empirical
Curhan et al	Beverage use and risk for kidney stones in women	1998	Cohort
Shuster et al	Soft drink consumption and urinary stone recurrence: a randomized prevention trial	1992	Randomized intervention
Weisse et al	Changes in urinary magnesium, citrate, and oxalate levels due to cola consumption	1992	Empirical

Table 17. Reviewed articles on the effects of carbonated water to kidney by type of study

Publication Year	Study design	Assessed status	Sample size	Main results
2007	Systematic review	Urinary tract cancer	13 prospective studies from 1980-2000	- Relative risk had no statistically significance
1998	Cohort	Kidney stones	81 093 women aged 40-65, including 719 cases of kidney stones	- No relative risk of kidney stones when using carbonated drinks
1992	Randomized intervention	Recurrent stones	1,009 male with a history of kidney stones	- rate of of 3 year without the risk of stone recurrence when stopping using carbonated beverages group was 6.4% higher compared to the control group
2007	Case-control study	Chronic kidney disease	465 people with serum creatinine ≥ 130μmol/liter, and 467 healthy people	- The OR was 2.13 (1.23-3.70) for drinking 1-2 glasses of cola per day group - The OR was 2.82 (1.62-5.0) for more than 2 glasses of cola per day group - There was no risk relationship in drinking non-cola carbonated beverage
2012	Cross empirical study	Urinary electrolytes	16 people	- There was no association between the change of urinary electrolytes and drinking cola
2012	Cross empirical study	Increasing concentrations of citrate	9 male and female, aged of 26-54	- No increase in the citrate concentration when drinking carbonated water Diet Sunkist Orange
2009	Cross-sectional with controlled retrospective	Conclusion of disease	1.139 patients 5.039 people of control group	- There was no association between drinking carbonated water and renal cell cancer
2009	Cross empirical study	Urine electrolytes	6 people	- There was no association between urinary electrolytes and drinking cola
2008	Cross-sectional uncontrolled retrospective	Biochemical indices of blood and urine	257 people aged 10-22	- There was no association between the use of carbonated beverages and blood urea and creatinine, urinary calcium and phosphoric excretion
1999	Empirical	Urine biochemical indices	14 male and 31 female, aged of 20-26	- Women group rose 5 indexes related to favorable environment for stone

				formation
1992	Empirical	Urine biochemica l indices	4 male, aged of 17 to 59	- Increased 24 hours urine calcium oxalate excretion of 8.3 mg - Reduce average Mg excretion of 2.6 mg - Reduce average citrate excretion of 122mg.

5. Conclusion

Systematic review of the effects of the use of carbonated drinks on human health is the process of collecting, reviewing, analyzing and synthesizing research results published in both Vietnamese and English peer-review databases. The carbonated drinks on the market today are very diverse, yet the impact on human health is possibly derived from 4 main group factors (1) The amount of CO2 dissolved in water (2) The amount of sugar or sweetener added to water (3) The additive substance used in manufactory and (4) The amount of acid as a result of the combine between CO2 and water to form carbonic acid (H2C03). In addition, additive subtance in carbonated water are naturally acidic.

In the scope of this review, we focus on assessing the impact of CO2 dissolved in carbonated drinks on heath. There is not enough evidence to estimate the amount of CO2 being absorbed into the body through different kind of carbonated drinks, however, with the pressures used in beverages, the volume of CO2 will be 3-5 times the volume of the liquid, so 1 liter of liquid contain 3-5liters of CO2. Most of CO2 escapes when the bottle is opened because of the sudden drop of pressure so it is estimated that ingestion ranges between 0.5 to 1.5 liter of carbon dioxide at a time when drinking 1 liter of liquid.
The scope of this review does not include the impact of sugar or sweetener in carbonated beverage. Using PRISMA approach, study has showed main results of effects on human health as follows:

Effects of carbonated drinks used on tooth enamel.
The evidence suggests that the amount of CO2 dissolved into water increases the acidity of water, but the impact of CO2 on enamel tooth is very low.

However, beside carbonic acid, the presence of different acids in beverages has considerable impact on pH level and titratable acidity of the beverages. Therefore the level of enamel tooth wear is different following types of carbonated drinks. Equally, the effect of carbonated drinks is also associated with drinking behavior (for example using straws can reduce the direct impact on tooth), nutrition, particularly the amount of calcium intaken, the minerals added in beverages such as calcium, phosphorus, fluorine.

Effects of carbonated drinks used on bone mineral density

Carbonation of drinks is not associated with the loss of bone mineral density. In terms of physicochemical mechanism, bicarbonate (HCO_3^-) increases renal calcium reabsorption to remains calcium homeostatic.

In general, some contents of carbonated beverages such as caffeine and phosphoric acid, following physicochemical mechanisms, are believed to have negative effects on bone. However, the dose that could cause the affect is still unclear. Although population based studies have shown different results of the effects of carbonated drinks on bone density, there is no specific evidence of the effects on males. Some studies have pointed that a number of carbonated drinks may be associated with decreased bone density in postmenopausal women. Specifically, two studies investigated into adolescents have shown evidence of negative impacts of carbonated soft drinks on dominant heel bone density of young girls and on bone fracture in some active girls. Besides, studies also illustrates that the use of carbonated soft drinks is not the only associated factor to the decrease of bone mineral density. Other factors such as nutrition and diet (especially with the amount of calcium intake through food sources) among study participants also play an important role to the bone density. It is necessary to have more evidence on the separate impact of carbonated beverages on bone density as well as interactive terms. For example, statistics indicate that women in white group have a higher rate of osteoporosis than those in black group. Meanwhile the current studies were only investigeted into women of white group.

Effects of carbonated drinks on esophagus

The mechanism of carbonated drinks can impact on esophageal theoretically in following way: (1) changes of pH level of the esophagus caused by increased acid (because carbonated have high acidity) (2) damage of the esophageal mucosa as a result of constantly absorbing carbonated drinks (3) increase of relax time and reduction of the pressure of the lower esophageal sphincter, or (4) changes of the status of gastric distension and motion of gastro-esophageal. Due to these theoretical mechanisms, studies have explored the association between drinking carbonated water and 2 esophageal diseases, namely: (1) gastroesophageal reflux, and (2) esophageal cancer

Although there have been different results suggesting the relationship between carbonated drinks and gastroesophageal reflux disease, scientific evidence are not adequate to understand the relationship. In particular, no study can demonstrate that stop drinking carbonated water relieve gastroesophageal reflux.

Regarding the impact of carbonated water on esophageal cancer, there is no evidence on the relationship between using of carbonated beverages and esophageal cancer.

Effects of carbonated drinks used on stomach

The impact of CO_2 in carbonated drinks on stomatch can be through mechanical mechanisms such as changes in gastric motility and slow gastric emptying, or chemical mechanism such as the effect of CO_2 in the process of formation HCL and acid secretion in gastric parietal cells.

On the mechanical effects (such as changes of gastric motility), studies have shown that carbonated drinks can cause the feeling of fullness in the short-term through the process of stimulating sympathetic nervous system activity. However, different levels of CO_2 in different types of carbonated drinks was not shown to be not responsible for the movement or function of the digestive tract as well as the process of gastric emptying

On the chemical mechanism: when drinking carbonated water, some of CO_2 can be absorbed through the stomach wall, combined with CO_2 in intestinal fluid and plasma to form HCL acid. Besides, it is believed that carbonated drinks cause the increase of secretion of gastric acid. This effect actually is beneficial in some case, for instance, some patients suffering gastrointestinal dyspepsia can improve their health status if drinking carbonated water, or patients with foreign objects in the stomach (such as the block fiber) can be relieved by drinking Cola. However, with patients suffering the increased secretion syndrome, the use of carbonated beverages is not beneficial.

Effects of carbonated drinks used on kidney

There can be divided into 2 groups: (1) related to urinary tract/kidney stone formation, and (2) effects on renal function in general.

Studies have shown diverse evidences on the impact of cola drinks on kidney stone formation. Despite the various results, phosphoric acid in cola drinks is believed to be factors leading the change of urinary electrolytes that favours stone formation as well as the risk of recurrent kidney stone. It is evident that the amount of phosphoric acid and additives in cola drink affects negatively on renal function, especially in people who suffer chronic kidney disease or metabolic disease such as diabetes, high blood pressure. The use of cola drinks containg sugar can lead to weight gain, type II diabetes, metabolic syndrome which is demonstrated to be the risk factors associated with urinary tract stones in the long- term.(Herrel, et al., 2012; Obligado & Goldfarb, 2008; Shoham et al., 2008).

The association between kidney stones and carbonated drinks in general used is not statistical significance. However, at the time of the study, the amount of carbonated beverages is still consumed at low levels. Therefore, it is neccesary to find more evidence to conclude this issue. In general, there is no association between urinary tract cancer and carbonated beverages used.

There is now insufficient evidence to understand the impact of beverage carbonation on kidney.

6. Several notes when reviewing research results

The study results should be viewed with the following points:

Information about the amount of carbonated beverage consumption in many studies on populations based on the report of the study participants, so recall bias is unavoidable. In addition, consumers can use a variety of carbonated beverages in daily diet, so the data about each type of beverages could not be collected correctedly, they can only categorized into main groups such as cola and non-cola, normal group and diet group, etc, in the questionnaire.

Meanwhile, carbonated soft drinks on the market are diverse in composition formula (though the carbonated beverages sweetened group has been mentioned). This can also be a part of reasons to explain the differences in study results, especially when the impact on health is said to be influenced by additives.

Some additives in carbonated beverages such as caffeine, phosphoric acid have been proven to impact human health especially on bones, urinary system through physiology, biochemistry mechanism. However, many of the reviewed studies did not measure and provide direct evidence about this effect, the researchers only use the results of other studies on the impact of those additives to explain differences in the results of their research. To have concrete evidence of additives of carbonated beverages on health, it is necessary to conduct separate reviews of each additive to human health or empirical studies applied appropriate methods.

Some reports mentioned other contents in carbonated beverages including benzoate, sorbate, 4-methylimidazole, etc. However, with literature searching method of this review, we have not seen any studies that addressed these contents. Therefore, we cannot provide any conclusion about impact of the contetns.

As stated in the Methodology section, in this study, we did not review the impact of sweetened carbonated drinks. In the process of collecting and analyzing data, in initial steps, we have taken in a number of studies on the association between carbonated beverages and some types of cancer (pancreatic cancer, prostate cancers) and cardiovascular disease. However, when analyzing, we have excluded these studies because the relationship is due to the potential impact of sugar and some sweeteners like aspartame in beverages.

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