Chronic Diseases Prevention Review 15 (2020) 25-31

Available at http:// www.cancercellresearch.org ISSN 2158-0820

Relationship between caffeine and alcohol intake and osteoporosis

Genquan Jin, Jingjing Wang, Xiubo Jiang*

School of Public Health, Qingdao University, Qingdao 266071, China

Abstract: Osteoporosis is a common bone metabolic disorder that can make people weak. It is characterized by reduced bone density and mass, and is often associated with damaged trabecular bone structures, leading to an increased risk of fracture. The pathogenesis of osteoporosis is complex, and the influencing factors include genetic factors, environmental factors, dietary conditions, poor living habits, etc. Moreover, the risk of osteoporosis also varies among different ages, genders and races. At present, there are few studies on the relationship between caffeine and alcohol intake and osteoporosis at home and abroad, and the conclusions of relevant studies are still controversial. Therefore, this study intends to use the large data set of the National Health and Nutrition Examination Survey to investigate the relationship between caffeine and alcohol intake and osteoporosis, and the results of this study can provide scientific basis for the prevention of osteoporosis in adults.

Keywords: Osteoporosis; caffeine; alcohol

Received 8 July 2020, Revised 13 August 2020, Accepted 15 August 2020

*Corresponding Author: Xiubo Jiang, jiangxiubo2005@126.com

1. Introduction

Osteoporosis is a degenerative metabolic bone disease caused by a variety of causes. It is mainly characterized by decreased bone density and bone mass, accompanied by microstructure destruction of bone tissue, resulting in increased brittle bone and prone fracture [1]. Fractures are the most common complication of osteoporosis, including fractures of the hip, spine, wrist, and other sites. Among them, hip (femoral neck) fracture is the most serious, which is more common in middle-aged and elderly people and usually occurs after a fall or squeeze[2]. It is estimated that by 2050, the number of hip fractures caused by osteoporosis will increase to 6.26 million[3].

Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that the incidence of femoral neck osteoporosis in white women, Hispanic women and African Women accounted for about 20%, 10% and 5%, respectively [4]. With the rapid development of people's living standards and lifestyle, the aging of the global population is becoming more and more serious, and osteoporosis is becoming a major public health problem that must be given priority attention. For elderly patients, once fracture occurs, it is usually accompanied by chronic pain, long-term bedridden, disability and even death, which to a large extent brings huge economic burden to the country and individuals [5].

Osteoporosis can be prevented and treated, but since the symptoms of this disease are not obvious at the early stage of the disease and there is no warning before the fracture occurs, the chronic bone loss is difficult to detect, which leads to the failure of timely diagnosis and effective treatment in the early stage of the disease in many middle-aged and elderly people [6]. Existing studies have shown that osteoporosis is the result of a combination of multiple factors, including genetic factors, demographic variables, anthropometric variables, adverse lifestyle and living environment factors, etc., and its pathogenesis has not been fully elucidated. Therefore, it is extremely important to explore controllable risk factors and protective factors related to osteoporosis.

A large number of domestic and foreign studies have been conducted on the relationship between osteoporosis and various influencing factors, but relatively few studies have been conducted on the relationship between caffeine and alcohol intake and the risk of osteoporosis, and the conclusions of each study are still controversial. Therefore, this paper summarizes the relationship between caffeine and alcohol intake and osteoporosis, providing scientific and effective directions and ideas for the further development of primary prevention of osteoporosis.

2. Osteoporosis

2.1 Definition of osteoporosis

Osteoporosis is a chronic disease classified as a degenerative bone disease characterized by reduced bone mass and destruction of bone tissue microstructure, resulting in increased fragility and susceptibility to fractures.

Generally speaking, osteoporosis can be divided into three categories according to the cause of the disease, namely primary, secondary and idiopathic osteoporosis. Among them, the primary cause of secondary osteoporosis is clear, mostly related to some diseases

affecting bone metabolism (such as secretory disease, digestive system disease, blood disease, etc.) or drugs (such as glucocorticoid, heparin, etc.). Idiopathic osteoporosis, on the other hand, is caused by any cause not currently known, including idiopathic adolescent osteoporosis (which is rare) and idiopathic adult osteoporosis, whose etiology and pathogenesis are quite different. As the most common and main type, primary osteoporosis is divided into two types according to its pathogenesis, namely type I and type II. Type I primary osteoporosis is postmenopausal osteoporosis in postmenopausal women. It is mainly due to the lack of postmenopausal estrogen, which leads to enhanced osteoclast activity, accelerated bone loss, and enlarged bone space. Type II primary osteoporosis, known as senile osteoporosis, occurs in the elderly. Due to the gradual decrease of sex hormone secretion accompanied by aging, osteoblasts were inhibited and osteoclasts enhanced in function, resulting in nutritional dysfunction and organ failure.

Osteoporosis is clinically manifested as fracture, bone pain and spinal deformity (such as hunched back, shortened height). Fractures occur in the proximal femur (hip), vertebrae (spine), and distal forearm (wrist), and in other parts (ribs, humerus, clavicle, etc.). While spinal compression fractures are more common in PMOP patients, hip fractures are more common in patients with senile osteoporosis, often due to falls or compression. It is important to note that osteoporosis is called "a silent epidemic" because most osteoporosis patients are generally asymptomatic in the early stages of the disease, leaving chronic bone loss undetected.

Measurement methods of osteoporosis

Bone Mineral Density (BMD) measurement is the main and quantitative method for the diagnosis of osteoporosis. BMD measurement methods are relatively large. At present, the methods of measurement are mainly adopted by dual-energy X-ray Absorptiometry (DXA) and Quantitative Ultrasound (QUS). DXA is the BMD measurement method recommended by the World Health Organization. Its results can be used as the "gold standard" for the diagnosis of osteoporosis and can also predict the risk of fracture in patients with osteoporosis. The main measurement sites are the axial bone (including the lumbar spine and proximal femur). QUS is mainly used to measure the calcaneal position. The measuring device is fast and portable, low cost and free of ionizing radiation.

2.2 Diagnostic criteria for osteoporosis

The diagnostic criteria for osteoporosis vary according to the specific population. In the United States, for postmenopausal women and elderly men with osteoporosis, the results of the axial bone (lumbar, femoral neck, or hip) BMD measured by DXA is T<-2.5 as its diagnostic criteria. Based on T score (T<-2.5), the diagnosis of osteoporosis is an important method to identify individuals at risk of fracture [7].

In The Guidelines for the Diagnosis and Treatment of Primary Osteoporosis 2017, China points out that there are two diagnostic methods, in addition to the diagnosis based on BMD measurement, there is also a diagnosis based on fragile fracture. A brittle fracture, also known as a nontraumatic fractures or osteoporotic fracture, especially one resulting from a fall from a standing or lower height. Participants were diagnosed with the disease if they met one of three conditions: (1) brittle fractures of the hip or vertebral body;(2) T<-2.5 at the axial or distal 1/3 of the radius; (measured by DXA); (3) BMD measurements showed a low bone mass (-2.5 < T < -1.0) and brittle fractures of the proximal humerus, pelvis, or distal forearm.

In addition, the National Bone Health Alliance (NBHA)[8] still recommends the use of T score as the diagnostic criteria for osteoporosis, and recommends the FRAX score or the presence of an osteoporosis fracture as the diagnostic criteria for osteoporosis.

2.3 Factors influencing osteoporosis

Osteoporosis is a systemic metabolic bone disease, and its occurrence and development are inevitably affected by a variety of factors. Currently, the widely recognized influencing factors of osteoporosis include genetic demographics and anthropometry variables, such as poor lifestyle and living environment.

Studies have shown that different vitamin D receptor gene polymorphisms have different effects on postmenopausal osteoporosis and BMD in postmenopausal women[9]. A case control study conducted by Cai et al.[10] showed that the genetic susceptibility to PMOP in han postmenopausal women was related to the reduced thioquinone gene. In addition, a meta-analysis of Chinese postmenopausal women concluded that there was a significant correlation between the risk of postmenopausal osteoporosis and rs35767 gene polymorphism[11]. Therefore, genetic factors are closely related to the risk of osteoporosis.

Demographic and anthropometric variables also play an important role in osteoporosis. First of all, the prevalence of osteoporosis also varies among people of different ages, genders and RACES [12]. Considering that bone mineral content and BMD decrease with age, androgen deficiency is also involved in the formation of senile osteoporosis. Secondly, BMD decreases faster in women than in men after menopause. In addition to the age factor, reduced estrogen secretion in postmenopausal women leads to enhanced osteoclast function and accelerated bone loss, which is the main influencing factor of postmenopausal osteoporosis. In addition, studies have shown that postmenopausal women who are underweight or obese are more likely to suffer from postmenopausal osteoporosis [13].

The influence of adverse lifestyle and living environment factors on osteoporosis should not be ignored. Howe et al.[14] conducted a randomized controlled trial, pointing out that exercise is very important for the prevention of postmenopausal osteoporosis patients. At the same time, moderate to high intensity physical exercise can be used to effectively prevent postmenopausal osteoporosis[15]. A meta-analysis conducted by Moradi et al.[16] on the relationship between sleep duration and osteoporosis showed that middle-aged and elderly women with long-term sleep (i.e., sleep duration over 8 hours) may have a higher risk of osteoporosis. Another study[17] concluded that there was a U-shaped relationship between sleep time and osteoporosis in middle-aged and elderly people, and sleep time of more than or less than 8 hours may increase the risk of osteoporosis. In addition, existing evidence suggests that smoking and alcohol abuse may also contribute to the development of osteoporosis, but the specific mechanism needs further study[18].

A large number of studies have shown that dietary factors are closely related to osteoporosis. Intake of fruits[19] and fish and shellfish[20] is now known to be associated with a reduced risk of osteoporosis. A meta-analysis of observational studies conducted by Hu et al.[19] showed that fruit intake may play a role in preventing postmenopausal women from developing postmenopausal osteoporosis. Choi et al.[20] conducted a cross-sectional study in which the subjects were postmenopausal women and men aged 50 and over from the Nutrition and Health survey in the United States and South Korea. The results showed that moderate consumption of fish and shellfish also reduced the risk of osteoporosis in South Koreans. Secondly, moderate drinking of coffee or hot tea in leisure time[21] can also reduce the risk of osteoporosis by improving BMD. However, the association between caffeine intake (a major component of coffee) and the risk of osteoporosis needs to be further explored. In addition, increasing the intake of nutrients such as vitamin C[22] and calcium and vitamin D[23] is also an effective way to prevent the occurrence of osteoporosis.

3. Caffeine

3.1 Sources of caffeine

Caffeine is a plant alkaloid found mainly in coffee beans, tea leaves, cocoa beans and kola nuts. It is often added to some foods and beverages, among which important dietary sources include coffee, tea, yerba mate, soft drinks and energy drinks, etc.[24]. Coffee is the main source of caffeine, and the amount of caffeine depends on the type of bean (i.e. the raw material) and how it is prepared. The average cup of coffee contains 40 to 100 milligrams of caffeine. Tea is another important source of caffeine and contains about half the amount per cup of coffee. Different types of tea also contain different amounts of caffeine, with fermentable teas (e.g., black tea) generally containing more caffeine than non-fermentable teas (e.g., green tea). Soft drinks, such as Cola, contain caffeine, typically 10 to 50 milligrams per bottle. That compares with about 50 milligrams per energy drink.

3.2 Caffeine and disease

Caffeine, a stimulant, has been added to the list of causes of cancer by the World Health Organization's International Agency for Cancer. According to relevant studies, considering its special neuroexcitability and toxicity, it is believed that healthy adults who consume up to 400 mg of caffeine per day generally will not have obvious adverse reactions[25]. For healthy pregnant women and children, the recommended daily intake should not exceed 300 mg. Now, there is a growing interest in the link between caffeinated beverages and disease. A large number of epidemiological studies have suggested that moderate intake of coffee, tea or caffeine may have potential benefits for some chronic diseases, including type 2 diabetes[26], cardiovascular disease[27], Parkinson's disease[28], depression[29] and some cancers[30].

4. Alcohol

4.1 Sources and classification of alcohol

Drinks that contain more than 0.5% alcohol are often called alcoholic beverages, also known as beverage alcohol. In addition to the main component of alcohol (ethanol), beverage alcohol also contains many other components (such as water, sugars, aldehydes, acids and a small amount of vitamins and minerals, etc. There are many kinds of drinks and different classification methods. Fruit and grain as the two main raw materials of beverage wine, so according to the different production of raw materials, will be divided into fruit wine (such as wine) and grain wine (such as yellow rice wine, liquor). Next according to brewing method classification, can be divided into brewing wine (fermented wine, such as beer), distilled wine (such as liquor) and prepared wine. In addition, still can undertake classification according to alcohol content, cent is low degree wine and high degree wine two kinds.

4.2 Alcohol consumption and disease

As one of the most popular drinks at present, alcohol (ethanol) is the main ingredient, which can be converted into alcohol in many ways. The World Health Organization has classified alcohol as a carcinogen, which is related to the amount of alcohol consumed[31].At present, a large number of epidemiological studies have reported the potential preventive effect of moderate alcohol intake on some diseases, including cardiovascular diseases[32], type 2 diabetes[33], cholelithiasis[34] and Parkinson's

disease[35].However, excessive alcohol consumption is associated with an increased risk of certain diseases, including cirrhosis[36], gout and periodontitis[37].

5. Caffeine and alcohol intake are associated with osteoporosis

5.1 Research status of caffeine intake and osteoporosis

Research on the relationship between caffeine intake and osteoporosis risk has focused on coffee drinks, and the results are still controversial, according to a national and international database search. First, Choi, etc.[38] from South Korea is the fourth and fifth national health and nutrition survey (2011-2008) KNHANES data of 4066 cases of postmenopausal women conducted a cross-sectional study, the results showed that after adjusting for age, BMI, and behavioral factors (including diet), social factors (including household income and education level) and hormonal factors, after drinking two cups of coffee a day and don't drink coffee, compared to a significantly lower risk of osteoporosis (OR, 0.64;95% CI: 0.43, 0.95).Shanghai, China, has conducted a study on the relationship between coffee intake and osteoporosis in postmenopausal women and men, and reached a consistent conclusion that coffee intake has a protective effect on postmenopausal women[39] and men[40] with osteoporosis.

Haiqing Wang, however, such as of a matching (differ according to age and menopausal status within 4 years old) of a case-control study, points out that in 110 pairs of elderly women osteoporosis patients and 220 control for 1:2 after the match, found that coffee intake can increase the prevalence of osteoporosis, can be used as older women a potential risk factors for osteoporosis. Similarly, a Swedish cohort study[41] showed a significant positive association between coffee and caffeine intake and osteoporotic fractures in women.

In addition, another cohort study conducted by Hollstrom et al.[42] in Sweden showed that there was no statistically significant association between coffee intake and the risk of osteoporosis. They concluded that long-term consumption of caffeinated beverages such as coffee had little effect on osteoporosis. Fei Qi et al. investigated the influencing factors of osteoporosis in elderly male patients over 70 years old in Fangzhuang community of Beijing, and found that coffee consumption had no significant correlation with the risk of osteoporosis in elderly male patients.

5.2 Research status of alcohol intake and osteoporosis

There have been relatively few studies on the relationship between alcohol consumption and the risk of osteoporosis. To date, several studies have reported an association between alcohol consumption and the risk of osteoporosis, but the results remain controversial. Therefore, Cheraghi etc.[18] in view of the relationship between drinking and osteoporosis, to conform to the inclusion criteria of six research conducted a systematic review and meta-analysis, the results show that compared with non-drinkers, drinking 1 to 2 glasses of wine a day can significantly increase the risk of osteoporosis, drink two cups a day and above also will increase the risk of osteoporosis.

Alcohol consumption has been shown to be a potential risk factor for osteoporosis in several studies [43, 44]. Hansen et al.[45] conducted a cohort study in the United States showing that alcohol consumption, especially beer and liquor, was associated with an increased risk of osteoporotic fracture in postmenopausal women. Similarly, a prospective cohort study of middle-aged women in the United States showed that alcohol consumption also significantly increased the risk of osteoporotic fractures[46]. However, no significant association between alcohol consumption and osteoporosis was found in other studies[47].

6. Mechanism

6.1 Mechanisms of caffeine and osteoporosis

The biological mechanism between caffeine intake and osteoporosis is still under debate. We speculate on several possible potential mechanisms as follows. First, caffeine itself has an inhibitory effect on intestinal calcium absorption, but not a significant one[48]. A previous review reported that caffeine intake was associated with an increased risk of osteoporosis, but not the majority[48]. For young adult women with adequate calcium intake, moderate caffeine intake may have little harmful effects on bones, according to a comparison of available epidemiological data with animal and human studies. Other studies[49] indicated that low and medium doses of caffeine have a potential protective effect on adipocytes and bone marrow stromal cells, which can promote the differentiation of osteoblasts. However, this effect, mediated by activation of runt-related transcription factor 2, was significantly inhibited at high doses of caffeine. Secondly, caffeine intake can inhibit the longitudinal growth of bone by blocking the body components related to bone growth[50]. Meanwhile, caffeine exposure can directly inhibit the synthetic activity and orderly expression of chondrocyte related genes, thus interfering with cartilage induction[51]. Finally, studies have shown that exposure to caffeine in fast-growing mice can lead to the destruction of osteoblasts and the delay of bone development[51].

On the other hand, there have been many studies on the effects of caffeinated beverages on osteoporosis. The effects of soft drinks, such as coffee, tea, and energy drinks on osteoporosis are mostly beneficial

and may have little to do with the caffeine content. It is well known that in addition to containing caffeine, these caffeinated beverages contain many biologically active substances that can more or less influence the outcome.

6.2 Mechanisms of alcohol consumption and osteoporosis

Alcoholism may be a risk factor for bone diseases such as osteoporosis. The possible mechanisms we can think of are as follows: Firstly, alcohol can regulate the number and activity of osteoblasts and osteoclasts, accelerate the apoptosis of osteocytes, thus reducing bone formation and increasing bone resorption [52-54]. Secondly, chronic alcohol intake can inhibit bone formation by stimulating oxidative stress and blocking the Wnt signaling pathway. The Wnt signaling pathway plays an important role in the proliferation and differentiation of bone cells[55, 56]. Thirdly, long-term consumption of high dose of alcohol will damage the differentiation process of mouse bone marrow mesenchymal stem cells[57], resulting in bone loss and osteoporosis. Finally, alcohol intake can indirectly have a negative effect on bones through insufficient caloric intake and changes in body composition[58].

On the other hand, some studies suggest that moderate drinking may have a protective effect on osteoporosis, and the possible mechanism is as follows. Firstly, existing studies have shown that moderate drinking can significantly inhibit acute bone resorption[59]. Secondly, a small amount of alcohol intake can increase calcitonin production to inhibit bone resorption, which may have a beneficial effect on BMD, especially in older women[60, 61]. Finally, light to moderate alcohol consumption may slow age-related bone loss by reducing bone remodeling rates, which may be associated with elevated estrogen levels in postmenopausal women[62-64].

7. Conclusion

In summary, the relationship between caffeine and alcohol intake and osteoporosis risk remains controversial, so more prospective cohort studies and experimental studies are needed to further explore the relationship between caffeine and alcohol intake and osteoporosis. Through reasonable dietary habits and lifestyle changes, provide scientific and effective guidance and help for the prevention of osteoporosis, as far as possible to reduce the incidence of osteoporosis and its fracture, can effectively reduce the morbidity and mortality of patients, so as to improve the quality of life of patients.

References

[1] Ensrud KE, Crandall CJ. Osteoporosis [J]. Ann Intern Med, 2017, 167(3): Itc17-itc32.
[2] Peeters CM, Visser E, Van De Ree CL, et al. Quality of life after hip fracture in the elderly: A systematic literature review [J]. Injury, 2016, 47(7): 1369-82.
[3] Melton LJ, 3rd. Hip fractures: a worldwide problem today and tomorrow [J]. Bone, 1993, 14 Suppl 1(S1-8.
[4] Looker AC, Orwoll ES, Johnston CC, Jr., et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III [J]. J Bone Miner Res, 1997, 12(11): 1761-8.
[5] Cosman F, De Beur SJ, Leboff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis [J]. Osteoporos Int, 2014, 25(10): 2359-81.
[6] Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis [J]. Am J Obstet Gynecol, 2006, 194(2 Suppl): S3-11.
[7] Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis [J]. J Steroid Biochem Mol Biol, 2014, 142(155-70.
[8] Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group [J]. Osteoporos Int, 2014, 25(5): 1439-43.
[9] Zhang L, Yin X, Wang J, et al. Associations between VDR Gene Polymorphisms and Osteoporosis Risk and Bone Mineral Density in Postmenopausal Women: A systematic review and Meta-Analysis [J]. Sci Rep, 2018, 8(1): 981.
[10] Cai X, Yi X, Zhang Y, et al. Genetic susceptibility of postmenopausal osteoporosis on sulfide quinone reductase-like gene [J]. Osteoporos Int, 2018, 29(9): 2041-7.
[11] Gao ST, Lv ZT, Zhou CK, et al. Association between IGF-1 polymorphisms and risk of osteoporosis in Chinese population: a meta-analysis [J]. BMC Musculoskelet Disord, 2018, 19(1): 141.
[12] Melton LJ, 3rd. The prevalence of osteoporosis: gender and racial comparison [J]. Calcif Tissue Int, 2001, 69(4): 179-81.
[13] Głogowska-Szeląg J. [Assessment of the relationship between bmd and body mass index bmi in women with postmenopausal osteoporosis] [J]. Wiad Lek, 2018, 71(9): 1714-8.
[14] Bonaiuti D, Shea B, Iovine R, et al. Exercise for preventing and treating osteoporosis in postmenopausal women [J]. Cochrane Database Syst Rev, 2002, 3): Cd000333.
[15] Moreira LD, Oliveira ML, Lirani-Galvão AP, et al. Physical exercise and osteoporosis: effects of different types of exercises on bone and physical function of postmenopausal women [J]. Arq Bras Endocrinol Metabol, 2014, 58(5):

514-22.
[16] Moradi S, Shab-Bidar S, Alizadeh S, et al. Association between sleep duration and osteoporosis risk in middle-aged and elderly women: A systematic review and meta-analysis of observational studies [J]. Metabolism, 2017, 69(199-206.
[17] Wang D, Ruan W, Peng Y, et al. Sleep duration and the risk of osteoporosis among middle-aged and elderly adults: a dose-response meta-analysis [J]. Osteoporos Int, 2018, 29(8): 1689-95.
[18] Cheraghi Z, Doosti-Irani A, Almasi-Hashiani A, et al. The effect of alcohol on osteoporosis: A systematic review and meta-analysis [J]. Drug Alcohol Depend, 2019, 197(197-202.
[19] Hu D, Cheng L, Jiang W. Fruit and vegetable consumption and the risk of postmenopausal osteoporosis: a meta-analysis of observational studies [J]. Food Funct, 2018, 9(5): 2607-16.
[20] Choi E, Park Y. The Association between the Consumption of Fish/Shellfish and the Risk of Osteoporosis in Men and Postmenopausal Women Aged 50 Years or Older [J]. Nutrients, 2016, 8(3): 113.
[21] Guo M, Qu H, Xu L, et al. Tea consumption may decrease the risk of osteoporosis: an updated meta-analysis of observational studies [J]. Nutr Res, 2017, 42(1-10.
[22] Malmir H, Shab-Bidar S, Djafarian K. Vitamin C intake in relation to bone mineral density and risk of hip fracture and osteoporosis: a systematic review and meta-analysis of observational studies [J]. Br J Nutr, 2018, 119(8): 847-58.
[23] Harvey NC, Biver E, Kaufman JM, et al. The role of calcium supplementation in healthy musculoskeletal ageing : An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF) [J]. 2017, 28(2): 447-62.
[24] Reyes CM, Cornelis MC. Caffeine in the Diet: Country-Level Consumption and Guidelines [J]. Nutrients, 2018, 10(11): 101-105.
[25] Wikoff D, Welsh BT, Henderson R, et al. Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children [J]. Food Chem Toxicol, 2017, 109(Pt 1): 585-648.
[26] Jiang X, Zhang D, Jiang W. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies [J]. Eur J Nutr, 2014, 53(1): 25-38.
[27] Ding M, Bhupathiraju SN, Satija A, et al. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies [J]. Circulation, 2014, 129(6): 643-59.
[28] Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease [J]. Geriatr Gerontol Int, 2014, 14(2): 430-9.
[29] Grosso G, Micek A, Castellano S, et al. Coffee, tea, caffeine and risk of depression: A systematic review and dose-response meta-analysis of observational studies [J]. Mol Nutr Food Res, 2016, 60(1): 223-34.
[30] Caini S, Cattaruzza MS, Bendinelli B, et al. Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis [J]. Eur J Nutr, 2017, 56(1): 1-12.
[31] Carvalho AF, Heilig M, Perez A, et al. Alcohol use disorders [J]. Lancet, 2019, 394(10200): 781-92.
[32] Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis [J]. Bmj, 2011, 342(d671.
[33] Li XH, Yu FF, Zhou YH, et al. Association between alcohol consumption and the risk of incident type 2 diabetes: a systematic review and dose-response meta-analysis [J]. Am J Clin Nutr, 2016, 103(3): 818-29.
[34] Wang J, Duan X, Li B, et al. Alcohol consumption and risk of gallstone disease: a meta-analysis [J]. Eur J Gastroenterol Hepatol, 2017, 29(4): e19-e28.
[35] Zhang D, Jiang H, Xie J. Alcohol intake and risk of Parkinson's disease: a meta-analysis of observational studies [J]. Mov Disord, 2014, 29(6): 819-22.
[36] Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis [J]. Drug Alcohol Rev, 2010, 29(4): 437-45.
[37] Wang M, Jiang X, Wu W, et al. A meta-analysis of alcohol consumption and the risk of gout [J]. Clin Rheumatol, 2013, 32(11): 1641-8.
[38] Choi E, Choi KH, Park SM, et al. The Benefit of Bone Health by Drinking Coffee among Korean Postmenopausal Women: A Cross-Sectional Analysis of the Fourth & Fifth Korea National Health and Nutrition Examination Surveys [J]. PLoS One, 2016, 11(1): e0147762.
[39] Yang P, Zhang XZ, Zhang K, et al. Associations between frequency of coffee consumption and osteoporosis in Chinese postmenopausal women [J]. Int J Clin Exp

Med, 2015, 8(9): 15958-66.
[40] Yu Q, Liu ZH, Lei T, et al. Subjective evaluation of the frequency of coffee intake and relationship to osteoporosis in Chinese men [J]. J Health Popul Nutr, 2016, 35(1): 24.
[41] Hallström H, Wolk A, Glynn A, et al. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women [J]. Osteoporos Int, 2006, 17(7): 1055-64.
[42] Hallström H, Byberg L, Glynn A, et al. Long-term coffee consumption in relation to fracture risk and bone mineral density in women [J]. Am J Epidemiol, 2013, 178(6): 898-909.
[43] Hannan MT, Felson DT, Dawson-Hughes B, et al. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study [J]. J Bone Miner Res, 2000, 15(4): 710-20.
[44] Kanis JA, Johansson H, Johnell O, et al. Alcohol intake as a risk factor for fracture [J]. Osteoporos Int, 2005, 16(7): 737-42.
[45] Hansen SA, Folsom AR, Kushi LH, et al. Association of fractures with caffeine and alcohol in postmenopausal women: the Iowa Women's Health Study [J]. Public Health Nutr, 2000, 3(3): 253-61.
[46] Hernandez-Avila M, Colditz GA, Stampfer MJ, et al. Caffeine, moderate alcohol intake, and risk of fractures of the hip and forearm in middle-aged women [J]. Am J Clin Nutr, 1991, 54(1): 157-63.
[47] Berg KM, Kunins HV, Jackson JL, et al. Association between alcohol consumption and both osteoporotic fracture and bone density [J]. Am J Med, 2008, 121(5): 406-18.
[48] Heaney RP. Effects of caffeine on bone and the calcium economy [J]. Food Chem Toxicol, 2002, 40(9): 1263-70.
[49] Su SJ, Chang KL, Su SH, et al. Caffeine regulates osteogenic differentiation and mineralization of primary adipose-derived stem cells and a bone marrow stromal cell line [J]. Int J Food Sci Nutr, 2013, 64(4): 429-36.
[50] Choi YY, Choi Y, Kim J, et al. Peripubertal Caffeine Exposure Impairs Longitudinal Bone Growth in Immature Male Rats in a Dose- and Time-Dependent Manner [J]. J Med Food, 2016, 19(1): 73-84.
[51] Choi H, Choi Y, Kim J, et al. Longitudinal bone growth is impaired by direct involvement of caffeine with chondrocyte differentiation in the growth plate [J]. J Anat, 2017, 230(1): 117-27.
[52] Malik P, Gasser RW, Kemmler G, et al. Low bone mineral density and impaired bone metabolism in young alcoholic patients without liver cirrhosis: a cross-sectional study [J]. Alcohol Clin Exp Res, 2009, 33(2): 375-81.
[53] Maurel DB, Jaffre C, Rochefort GY, et al. Low bone accrual is associated with osteocyte apoptosis in alcohol-induced osteopenia [J]. Bone, 2011, 49(3): 543-52.
[54] Sampson HW, Perks N, Champney TH, et al. Alcohol consumption inhibits bone growth and development in young actively growing rats [J]. Alcohol Clin Exp Res, 1996, 20(8): 1375-84.
[55] Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling [J]. Bone, 2008, 42(4): 606-15.
[56] Chen JR, Lazarenko OP, Shankar K, et al. A role for ethanol-induced oxidative stress in controlling lineage commitment of mesenchymal stromal cells through inhibition of Wnt/beta-catenin signaling [J]. J Bone Miner Res, 2010, 25(5): 1117-27.
[57] Liu Y, Kou X, Chen C, et al. Chronic High Dose Alcohol Induces Osteopenia via Activation of mTOR Signaling in Bone Marrow Mesenchymal Stem Cells [J]. Stem Cells, 2016, 34(8): 2157-68.
[58] González-Reimers E, García-Valdecasas-Campelo E, Santolaria-Fernández F, et al. Prognostic value of nutritional status in alcoholics, assessed by double-energy X-ray absorptiometry [J]. Alcohol Alcohol, 2008, 43(3): 314-9.
[59] Jugdaohsingh R, O'connell MA, Sripanyakorn S, et al. Moderate alcohol consumption and increased bone mineral density: potential ethanol and non-ethanol mechanisms [J]. Proc Nutr Soc, 2006, 65(3): 291-310.
[60] Ellerington MC, Hillard TC, Whitcroft SI, et al. Intranasal salmon calcitonin for the prevention and treatment of postmenopausal osteoporosis [J]. Calcif Tissue Int, 1996, 59(1): 6-11.
[61] Vantyghem MC, Danel T, Marcelli-Tourvieille S, et al. Calcitonin levels do not decrease with weaning in chronic alcoholism [J]. Thyroid, 2007, 17(3): 213-7.
[62] Gaddini GW, Turner RT, Grant KA, et al. Alcohol: A Simple Nutrient with Complex Actions on Bone in the Adult Skeleton [J]. Alcohol Clin Exp Res, 2016, 40(4): 657-71.
[63] Gavaler JS. Should we consider an acceptable drinking level specifically for postmenopausal women? Preliminary findings from the postmenopausal health disparities study [J]. Alcohol Alcohol, 2005, 40(5): 469-73.
[64] Onland-Moret NC, Peeters PH, Van Der Schouw YT, et al. Alcohol and endogenous sex steroid levels in postmenopausal women: a cross-sectional study [J]. J Clin Endocrinol Metab, 2005, 90(3): 1414-9.