

Review Article

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/



A Review on Excessive Daytime Sleepiness in Patients with Obstructive Sleep Apnoea

Sushil Kumar Sah^{a*}, Anil Kumar Shah^b, Sarita Shah Kanu^c

^a Department of Otorhinolaryngology, Hubei University of Medicine, Hubei, China, ^b Department of Business Research, Excelsia College, Sydney, Australia, ^c Department of Aged Care, Aged Care of Estia Health Bendigo, Victoria, Australia

ARTICLEINFO

Accepted 19 April 2021

Keywords: daytime sleepiness, obesity, obstructive sleep apnoea, motor vehicle crash

SUMMARY

Excessive daytime sleepiness (EDS) is one of the major clinical presentations of obstructive sleep apnoea (OSA) affecting 18% of the world population. There are multiple factors that stimulate daytime sleepiness. EDS is one of the least understood symptoms and the majority of people remain undiagnosed in society. EDS increases in the geriatric population due to multiple factors such as obesity, various medical conditions as well as mental and emotional stress. People have EDS even more in developed countries due to the increased elderly population in the past few decades. EDS is one of the leading causes of impaired quality of life and motor vehicle crashes. The United States alone accounts for 2.4 to 3.9 million commercial drivers who are likely to have OSA and most remain undiagnosed. According to multiple independent studies, the risk of motor vehicle accidents was increased among those with untreated OSA. To reduce long-term complications and improve the quality of life, factors influencing EDS need to be identified. Multiple methods are available for screening and identifying the cause of EDS in an individual with OSA. One of the most effective tools for diagnosing OSA is a good questionnaire; and a polysomnography test. The main purpose of this study is to gain a clear understanding of factors influencing EDS, thus enabling clinicians to treat individuals in a timely manner.

Copyright $\ensuremath{\mathbb{C}}$ 2022, Taiwan Society of Geriatric Emergency & Critical Care Medicine.

1. Introduction

Daytime sleepiness and obesity are growing concerns in today's world. There are multiple factors that influence daytime sleepiness in individuals with obstructive sleep apnoea (OSA). The prevalence of daytime sleepiness in the community is as high as 18% as evaluated with the Epworth Sleepiness Scale (ESS). $^{1-\overline{3}}$ Global prevalence of sleep apnoea (apnoea-hypopnoea index $[AHI] \ge 5$ events per h) varies between 711 million and 961 million and is one of the leading causes of daytime sleepiness. Up to 30% of older people globally experience excessive daytime sleepiness (EDS).⁴ Using American Academy of Sleep Medicine (AASM) scoring criteria, and an estimated 272 million to 458 million people have moderate to severe sleep apnea (AHI \geq 15 events per h).⁵ Obesity has been increasing in recent years especially in the developed world. If recent trends continue, an estimated 38% of the world's adult population will be overweight and another 20% will be obese by the end of 2030.⁶ Obesity is one of the important factors for OSA. The prevalence of OSA in an adult population is about 3% to 7% in adult men and 2% to 5% in adult women.⁷ This review will elaborate on some of the most common influencing factors of EDS in OSA individuals.

2. Influencing factors of excessive daytime sleepiness

Excessive daytime sleepiness is a personal and medical burden to the community. EDS is one of the common presentations of OSA. As-

* Corresponding author. *E-mail address:* sushilsah90@yahoo.com (S.Kumar Sah) sessment of EDS is done using an open ESS questionnaire to estimate the severity of daytime sleepiness. The ESS ranges from 0 (indicating no daytime sleepiness) to 3 for (high chance of daytime sleepiness), with a maximum score of 24 (see Table 1).⁸ In 2004, Udaya Seneviratne et al. conducted a study among 195 clinically diagnosed OSA patients, in which clinical symptoms of EDS were present in 87.2%.⁹

3. Obesity

Obesity is a precursor of many diseases including OSA.¹⁰ It outweighs other conditions such as upper airway abnormalities, craniofacial phenotype, and genetics.¹¹ Symptoms of EDS in a patient with OSA commonly include being overweight.^{12,13} Fat deposition is usually around the upper respiratory tract and abdomen leading to hypoxia. Hypoxia is a major contributor to atherosclerosis, leading to cardiovascular disease.¹⁴ Hypersomnolence is associated with obesity even in the absence of sleep-disorder breathing.^{15,16} Overnight sleep monitoring in severely obese patients shows AHI > 10/h, which indicates OSA,¹⁷ and severity increases with a slight gain of weight.¹⁸ OSA severity will decline through a change in lifestyle, weight loss, surgical or medical intervention.^{19–21} A randomized control trial proved that weight loss over a period of 1 to 2 years will significantly lower the severity of OSA in the long-term by reducing AHI score.^{22–24} An increase in neck and waist circumference has been specifically correlated to OSA.^{25–27} Although alteration in functional control of the upper airway is through neurochemical pathways,²⁸ increase in the neck circumference due to fat deposition will further lead to narrowing and collapse of the upper airway; however, no correlation

Table 1

8

Patient questionnaire for rating excessive daytime sleepiness using the Epworth Sleepiness Scale.

	•
Patient Health Questionnaire:	
Excessive Daytime Sleepiness	
0 = No chance of dozing off	1 = Slight chance of dozing off
2 = Moderate chance of dozing off	3 = High chance of dozing off
Rate the chance that you will doze off in the following:	
Sitting and reading	
Watching television	
Sitting inactive in a public place (e.g., in a theatre, during a meeting)	
As a passenger in a car riding for an hour without breaks	
Lying down in the afternoon when circumstance permits	
Sitting and talking someone	
Sitting quietly after lunch without alcohol	
In a car while stopped for a minute in traffic	
Add above for total score	
Less than 8: indicates reported normal daytime alertness	

Less than 8: indicates reported normal daytime alertnes

8 to 11: indicates mild sleepiness

12 to 15: indicates moderate sleepiness

16 to 24: indicates severe sleepiness

Note: you need to discuss your sleepiness with your doctor if you scored higher than 12 on this sleepiness test; regularly fall asleep in class, church meetings; or have ever fallen asleep while driving. Treatment options exist to help alleviate your daytime sleepiness. You should never drive when excessively sleepy - sleepiness is a serious contributing risk factor in many motor vehicle accidents.

Adapted with permission from the American Academy of Sleep Medicine, and Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14(6):541.

was found between the fat pad and OSA severity.^{29,30} Sutherland K. conducted research on middle-aged obese men with moderate to severe OSA on a 24-week weight loss program. Sutherland found that weight loss increases the velopharyngeal airway resulting in a drop in sleep apnoea. Caudal traction is another cause of upper respiratory collapse due to excess fat deposition around the chest and abdomen.³¹ Daniel L. piloted research on 15 obese (body mass index: 34.5 \pm 1.1 kg/m²) male obstructive sleep apnoea patients aged 50 years (apnoea-hypopnea index: 58.1 ± 6.8 events/h) over a period of 2.6 years and showed that central obesity is the cause of caudal traction leading to upper airway collapse. A recent study showed that upper respiratory collapse in females is mainly due to the deposition of fat around the neck whereas in males it is around the abdomen.³² A study piloted by Liala S. that included 60 men and 36 women demonstrated that localized obesity was responsible for upper airway collapse in males whereas it was neck fat in females. Aging influences central obesity, a major contributor to insulin resistance and metabolic disorder.33

4. Morphology of head and neck

Anatomical variation of the face and cranium is another crucial factor in the pathogenesis of OSA.^{34,35} A meta-analysis done by Bala C.N. supports the relationship between OSA and craniofacial deformity. Craniofacial includes mandible, maxilla, cranial base, hyoid bone, and head position including soft tissue morphology, which decides the morphology of the airway. Any abnormalities among these structures may lead to narrowing of the upper respiratory airway. Anatomical variants may be due to genetic factors, ethnicity, congenital abnormality due to folic acid deficiency during pregnancy, and the environment. Research conducted by Sutherland and Villaneuva showed that every ethnicity has a typical physical appearance including head and neck. Craniofacial skeletal restriction in Asians, overweight in African Americans, and bony and soft tissue abnormalities in Caucasians are triggering factors in OSA development.^{10,36}

5. Gender

OSA is more prevalent in the geriatric population compared

with young adults.³⁷ OSA is predominant in men.³⁷ Sah et al. found the male/female ratio was 5:1 and Quintana-Gallego E, in a study total of 1166 people, found the male/female ratio was 4.9:1. A possible explanation for this is hormonal influence on upper airway muscle and collapsibility, distribution of body fat in the different gender, and anatomical variation and function of the pharyngeal muscle.³⁷ Incidence of OSA is minimal in pre-menopausal due to hormonal protection.¹⁵ Bixler E. conducted a study in two phases including 13,219 women and 5105 men aged 20-100 years that showed a significant risk of OSA among menopausal women. In 2008, Young T. piloted research on sleep-disordered breathing (SDB) among 1522 individuals, which showed high mortality in SDB patients. The role of hormones was imprecise, as gender differences remain the same in the elderly.³⁸ According to Hader C., elderly males aged above 65 showed all types of apnoea more often than women.³⁹ According to Franklin et al.'s study, 50% of women aged 20-70 years have OSA.⁴⁰ In addition, compared with men, women with OSA shows more signs of hypertension and obesity than daytime sleepiness.

6. Age

The chance of developing OSA increases with growing age (geriatric population) irrespective of other risk factors such as overweight.^{41,42} A study piloted by Timo et al. on patients (1090) with AHI > 5 found that the incidence of OSA increases to 60 years of age then gradually drops or remains the same. A cohort study (randomized sample of 16,583) piloted by Bixler E.O. showed young individuals (age < 30 years) and old-aged groups (age > 75 years) have higher EDS.⁴³ Cooke JR conducted research suggesting that the geriatric have a decreased ability to sleep, which leads to an increase in day-time sleepiness.⁴⁴

7. Smoking

Smoking is another risk factor for OSA. Several cross-sectional studies revealed a strong association between smoking and snoring or sleep apnoea.⁴⁵ A study conducted by Krishnan V. revealed that smoking increases the severity of OSA through alteration in sleep

architecture, upper airway neuromuscular function, and upper airway inflammation. Philips et al. studied 484 individuals aged from 14–84 years (99 school going children and 385 adults from a random sample of 1000 completed a small survey), which revealed cigarette smokers have symptoms like EDS.⁴⁶

8. Alcohol

It is well established that alcohol diminishes motor function especially in the upper respiratory tract. A systemic review and metaanalysis by Kolla B.P. of 14 eligible studies (n = 422) found a significant increase in AHI after alcohol intake (weighted mean differences [WMD] = 2.33; 95% CI = 1.41 to 3.25, I2 = 62%) and significant decline in mean Spo₂ (WMD = -0.60; 95% CI = -0.72 to -0.49, I2 = 0%). Thus, alcohol is a modifiable risk factor for the development of OSA.⁴⁷ Research done by Chakravorty et al. during 2007–2008 (n = 2919) showed that an increased probability of daytime sleepiness was predicted by declined log drinks per day [OR = 0.74 (95% CI, 0.58–0.95)], a decreased log drinking frequency [0.90 (95% CI, 0.83– 0.98)], and lower sleep duration [OR = 0.75 (95% CI, 0.67–0.84)]. Therefore, alcohol use influences daytime sleepiness.⁴⁸

9. Internet overuse

The growing use of the internet and its easy availability makes many people addicted to it. An enormous amount of time is spent on web browsing, leading to sleep deficit and increasing the possibility of daytime sleepiness.⁴⁹ Research conducted by Singh et al. using a web-based questionnaire (www.surveymonkey.com) with 1782 individuals aged between 18–64 years asked about sleep-related symptoms and found that a significant relationship existed between internet overuse and EDS.⁴⁹

10. Sleep deficit

Sleep deficit is very common and increasing in recent years due to medical illness or non-medical problems. A systematic review and meta-analysis that included 26 studies involving 4684 participants by Guang et al. revealed that sleep disturbance due to medical illness can be treated with gabapentin in adults.⁵⁰ Non-medical problems such as stress, caffeine overuse, unhealthy lifestyle (internet overuse) may also cause sleep disturbance. Insufficient sleep is common in school-going children, which leads to EDS and decreased school performance.⁵¹ A research study conducted on 12 men (aged 63 to 86) and 12 women (ages 63 to 82) by Carskadon M.A. shows that fragmented sleep during the night has significant influence on daytime well-being and sleepiness in elderly individuals.⁵² It also showed sleep deficit increases with age and is a leading cause of EDS. A study by Stepnowsky et al. showed that in men aged between 16 and 83, total sleep time reduced on average by 27 minutes per decade from mid-life until the eighth decade. This sleep deficit makes elderly people sleepy during the daytime.⁵³

11. Co-morbid medical conditions

Depression may be a possible cause of excessive daytime sleepiness.⁵⁴ Slater G. conducted a study that revealed there were several risk factors for excessive daytime sleepiness including depression, obesity, extremes of age, and insufficient sleep. Type 2 diabetes mellitus or syndrome of diabetes mellitus can be common problems that coexist with sleep disorders.^{55,56} According to Jacobsen et al., people with a score greater than 13 on the ESS had a significantly lower (3%) oxygen saturation index and a notably lower Spo₂ during sleep (p < 0.05). Moreover, patients with severe OSA had symptoms of depression and EDS.⁵⁵ Individuals with EDS and OSA should be evaluated for depression. Chronic illnesses such as cardiovascular disease and diabetes mellitus are common in the geriatric group and increase with age. Research done by Sahdeo et al. showed that prevalence of chronic illness increased in the elderly. Chronic illness associated with sleep disorders leads to EDS.⁵⁷

12. Conclusion

Daytime sleepiness is highly prevalent in the general population and poses mounting concerns for global health, especially in elderly people. An increase in the prevalence of daytime sleepiness will increase with growing age, medical conditions such as OSA, and influencing factors described above. The current studies on EDS will allow us to understand the disease in-depth and assist the physician in diagnosis and timely treatment.

Acknowledgment

Thanks to my parents, sister and brother for their continuous support and love.

Funding/support statement

Self-funded.

Conflict of interest

Declare none.

References

- Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis. 2012;4(6):608–616.
- Gislason T, Tómasson K, Reynisdóttir H, et al. Medical risk factors amongst drivers in single-car accidents. J Intern Med. 1997;241(3):213–219.
- Ohayon MM, Caulet M, Philip P, et al. How sleep and mental disorders are related to complaints of daytime sleepiness. Arch Intern Med. 1997; 157(22):2645–2652.
- Empana JP, Dauvilliers Y, Dartigues JF, et al. Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the three city study. *Stroke.* 2009;40(4):1219– 1224.
- Grote L. The global burden of sleep apnoea. Lancet Respir Med. 2019; 7(8):645–647.
- Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008;32(9):1431–1437.
- Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):136–143.
- Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. *Chest.* 1993;103(1):30–36.
- Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. *Sleep Med.* 2004; 5(4):339–343.
- Sutherland K, Lee RW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. *Respirology*. 2012;17(2):213–222.
- Durán J, Esnaola S, Rubio R, et al. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med.* 2001;163(3 Pt 1):685–689.
- Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. Sleep. 1996;19(2):104–115.
- Steier J, Jolley CJ, Seymour J, et al. Neural respiratory drive in obesity. *Thorax.* 2009;64(8):719–725.
- 14. Chen X, Pensuksan WC, Lohsoonthorn V, et al. Obstructive sleep apnea

and multiple anthropometric indices of general obesity and abdominal obesity among young adults. *Int J Soc Sci Stud*. 2014;2(3):89–99.

- Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med.* 2001; 163(3 Pt 1):608–613.
- Resta O, Foschino Barbaro MP, Bonfitto P, et al. Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. J Intern Med. 2003;253(5):536–543.
- Schwartz AR, Patil SP, Laffan AM, et al. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc.* 2008;5(2):185–192.
- Newman AB, Foster G, Givelber R, et al. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med. 2005;165(20):2408–2413.
- Grunstein RR, Stenlöf K, Hedner JA, et al. Two year reduction in sleep apnea symptoms and associated diabetes incidence after weight loss in severe obesity. *Sleep.* 2007;30(6):703–710.
- Johansson K, Hemmingsson E, Harlid R, et al. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. *BMJ*. 2011;342:d3017.
- Yee BJ, Phillips CL, Banerjee D, et al. The effect of sibutramine-assisted weight loss in men with obstructive sleep apnoea. *Int J Obes (Lond)*. 2007;31(1):161–168.
- Johansson K, Neovius M, Lagerros YT, et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. *BMJ.* 2009;339:b4609.
- Tuomilehto H, Gylling H, Peltonen M, et al. Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postinterventional follow-up. Am J Clin Nutr. 2010; 92(4):688–696.
- Tuomilehto HP, Seppä JM, Partinen MM, et al. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med.* 2009;179(4):320–327.
- Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002; 165(9):1217–1239.
- Carmelli D, Swan GE, Bliwise DL. Relationship of 30-year changes in obesity to sleep-disordered breathing in the Western Collaborative Group Study. Obes Res. 2000;8(9):632–637.
- 27. Shinohara E, Kihara S, Yamashita S, et al. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *J Intern Med.* 1997;241(1):11–18.
- Schwartz AR, Patil SP, Squier S, et al. Obesity and upper airway control during sleep. J Appl Physiol (1985). 2010;108(2):430–435.
- Hora F, Nápolis LM, Daltro C, et al. Clinical, anthropometric and upper airway anatomic characteristics of obese patients with obstructive sleep apnea syndrome. *Respiration*. 2007;74(5):517–524.
- Sutherland K, Lee RW, Phillips CL, et al. Effect of weight loss on upper airway size and facial fat in men with obstructive sleep apnoea. *Thorax*. 2011;66(9):797–803.
- Stadler DL, McEvoy RD, Sprecher KE, et al. Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. *Sleep.* 2009;32(12):1579–1587.
- 32. Simpson L, Mukherjee S, Cooper MN, et al. Sex differences in the association of regional fat distribution with the severity of obstructive sleep apnea. *Sleep.* 2010;33(4):467–474. Erratum in: *Sleep.* 2010;33(8): preceding 1003. Hillman Fanzca, David R [corrected to Hillman, David R].
- Jura M, Kozak LP. Obesity and related consequences to ageing. Age (Dordr). 2016;38(1):23.
- Neelapu BC, Kharbanda OP, Sardana HK, et al. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: A systematic review and meta-analysis of cephalometric studies. *Sleep Med Rev.* 2017; 31:79–90.

- Cakirer B, Hans MG, Graham G, et al. The relationship between craniofacial morphology and obstructive sleep apnea in whites and in African-Americans. Am J Respir Crit Care Med. 2001;163(4):947–950.
- 36. Villaneuva AT, Buchanan PR, Yee BJ, et al. Ethnicity and obstructive sleep apnoea. *Sleep Med Rev.* 2005;9(6):419–436.
- Quintana-Gallego E, Carmona-Bernal C, Capote F, et al. Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. *Respir Med.* 2004;98(10):984–989.
- Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep.* 2008; 31(8):1071–1078.
- Hader C, Schroeder A, Hinz M, et al. Sleep disordered breathing in the elderly: comparison of women and men. J Physiol Pharmacol. 2005;56 Suppl 4:85–91.
- Franklin KA, Sahlin C, Stenlund H, et al. Sleep apnoea is a common occurrence in females. *Eur Respir J.* 2013;41(3):610–615.
- Leppänen T, Töyräs J, Mervaala E, et al. Severity of individual obstruction events increases with age in patients with obstructive sleep apnea. *Sleep Med.* 2017;37:32–37.
- Shigeta Y, Ogawa T, Tomoko I, et al. Soft palate length and upper airway relationship in OSA and non-OSA subjects. *Tex Dent J.* 2013;130(3):203– 211.
- Bixler EO, Vgontzas AN, Lin HM, et al. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab. 2005;90(8):4510–4515.
- Cooke JR, Ancoli-Israel S. Normal and abnormal sleep in the elderly. Handb Clin Neurol. 2011;98:653–665.
- Krishnan V, Dixon-Williams S, Thornton JD. Where there is smoke... there is sleep apnea: exploring the relationship between smoking and sleep apnea. *Chest.* 2014;146(6):1673–1680.
- Phillips BA, Danner FJ. Cigarette smoking and sleep disturbance. Arch Intern Med. 1995;155(7):734–737.
- Kolla BP, Foroughi M, Saeidifard F, et al. The impact of alcohol on breathing parameters during sleep: A systematic review and meta-analysis. *Sleep Med Rev.* 2018;42:59–67.
- Chakravorty S, Jackson N, Chaudhary N, et al. Daytime sleepiness: associations with alcohol use and sleep duration in Americans. *Sleep Disord*. 2014;2014:959152.
- Singh LK, Suchandra KHH, Pattajoshi A, et al. Internet addiction and daytime sleepiness among professionals in India: A web-based survey. *Indian* J Psychiatry. 2019;61(3):265–269.
- Liu GJ, Karim MR, Xu LL, et al. Efficacy and tolerability of gabapentin in adults with sleep disturbance in medical illness: A systematic review and meta-analysis. *Front Neurol.* 2017;8:316.
- Li S, Arguelles L, Jiang F, et al. Sleep, school performance, and a schoolbased intervention among school-aged children: a sleep series study in China. *PLoS One.* 2013;8(7):e67928.
- Carskadon MA, Brown ED, Dement WC. Sleep fragmentation in the elderly: relationship to daytime sleep tendency. *Neurobiol Aging*. 1982; 3(4):321–327.
- Stepnowsky CJ, Ancoli-Israel S. Sleep and its disorders in seniors. Sleep Med Clin. 2008;3(2):281–293.
- Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis. 2012;4(6):608–616.
- Jacobsen JH, Shi L, Mokhlesi B. Factors associated with excessive daytime sleepiness in patients with severe obstructive sleep apnea. *Sleep Breath*. 2013;17(2):629–635.
- Karim MR, Syeda A. The influencing factors associated with ketosis-prone type 2 diabetes mellitus: a syndrome of diabetes mellitus. *International Journal of Diabetes and Endocrinology*. 2018;3(1):1–6.
- Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old medicine: role of chronic inflammation. *Prev Med.* 2012;54 Suppl (Suppl):S29–S37.