Kardiologia Polska 2014; 72, 9: 771–776; DOI: 10.5603/KP.a2014.0149 ISSN 0022–9032

ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Wine, alcohol and cardiovascular diseases

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VARIOUS FACES OF THE FRENCH PARADOX

Since the first reports on the cardioprotective effects of low and moderate alcohol ingestion, not only on the cardiovascular (CV) system but also on all-cause mortality, were published several years ago, this issue has generated unabated interest from both researchers and public opinion. This is easily explained, as the prevention of CV conditions is necessary for most adult citizens from developed countries. A pleasurable habit and/or a habit which is ascribed a number of unfavourable biological effects is rarely associated with potential health benefits. Individuals drinking small or moderate amounts of alcohol constitute a large percentage of the adult population and, therefore, can benefit from these potentially beneficial effects. However, alcohol abuse is not only a social issue, but a medical one as well, as it can significantly increase morbidity and mortality. Previous studies have documented an association between the consumption of alcohol and increased mortality due to several types of neoplasms, accidents and trauma, liver cirrhosis and other causes. Moreover, alcohol abuse is associated with increased incidence of haemorrhagic stroke; furthermore, it can increase the risk of ischaemic stroke [1].

In 1981, French researchers, Richard, Cambien and Ducimetière, coined the term 'the French paradox' to describe a certain epidemiological phenomenon [2]. Population-based studies showed that the incidence of cardiovascular diseases (CVDs) among people living in the south of France is markedly lower than in northern Europeans, e.g. Scottish people, despite similar exposure to CVD risk factors [3–5]. In 1992, Renaud and de Lorgeril [6] identified the consumption of wine as an independent variable distinguishing between regions characterised by low and high incidences of coronary heart disease (CHD). Another attempt to explain the French paradox was undertaken by Criqui and Ringel [7]. Based on statistical data from 26 countries worldwide, they revealed that France is characterised by the highest consumption of wine per capita and by one of the lowest mortality rates due to CHD among all analysed populations. Further analyses conducted by these authors revealed an inverse correlation between mortality due to CHD and the ingestion of vegetables, fruit and alcohol; the relationship turned out to be the strongest in the case of wine.

The hypothesis on the lower incidence of heart disease among Frenchmen has a long history, dating back to the early 19th century. In 1819, Samuel Black, an Irish physician from Newry who was particularly interested in angina pectoris, published the first report on the 'French phenomenon' in his monograph entitled 'Clinical and Pathological Reports'. He described the disproportion between the lower incidence of CHD in France and its frequent occurrence among the British to *"the French habits and modes of living, coinciding with the benignity of their climate and the peculiar character of their moral affections"* [8]. It is worth noting that these conclusions were published 160 years before the results of the first international study which showed that the incidence of CHD in countries with a predominant consumption of wine

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Received: 09.06.2014 **Accepted:** 11.06.2014 **Available as AoP:** 04.07.2014

is lower than in countries characterised by a preference for beer or spirits [9].

The above mentioned findings were confirmed by a number of population-based studies conducted in the last 2 decades of the 20th century. A Danish study, analysing the causes of mortality during several years of follow-up period, revealed that the risk of all-cause mortality, including deaths due to CVD, decreased inversely to the ingestion of wine and was the lowest for persons consuming 3–5 glasses of wine daily. In contrast, the risk of all-cause mortality increased proportionally to the ingestion of spirits. This was one of the first large observational studies that documented the superiority of wine over other types of alcoholic beverages in the prevention of CVDs [10].

Obviously, the reports of low CV mortality and high consumption of wine in France do not necessarily suggest that drinking wine decreases CVD-related mortality. This relationship is suggested by comparisons with other countries, rather than by an analysis of individual causative relationships. Unfortunately, analyses of this type cannot be controlled for any sources of bias or confounders. For example, the causes of mortality can be identified and encoded differently in various countries; moreover, potential study-to-study differences in socioeconomic characteristics, patterns of health-seeking behaviours, dietary habits, availability and quality of healthcare, etc. should also be considered. Another, more serious, problem associated with this kind of 'data' is the so-called 'ecological fallacy' [11]. Regarding the French paradox, no-one can ascertain whether individuals at low risk of CHD living in countries characterised by a high consumption of wine in fact consume large amounts of this beverage. Ecological studies are based on the assumption that a relationship observed at a population (country) level does also exist in most individuals forming this population. Furthermore, unbiased meta-analysis of the results of numerous epidemiological studies can be hindered by different methodologies of measurement, potential measurement bias in alcohol ingestion, and individual variability in biological 'responses' to alcohol. Moreover, consumption of alcohol by a given individual can change with time. In view of these doubts, a number of critical opinions emerged shortly after acknowledging the important role of alcohol in the aetiology of the French paradox, and the potential involvement of other variables was suggested for this phenomenon. For example, Renaud emphasised that the diet of an average Frenchman is rich in fruits and vegetables; furthermore, most French people use olive oil for cooking, and neither eat in a hurry nor snack between meals [6]. The aetiology of the French paradox was also analysed by Goldberg et al. [12], who concluded that it is probably the healthy lifestyle of wine drinkers which plays an important role in the prevention of CVD; these authors observed that such persons are less often obese, usually do not smoke, more frequently practice sports, eat more vegetables, fruits and fish, and drink wine with food [13].

THE PATTERN OF ALCOHOL CONSUMPTION AND CVD

CVDs represent the main health threat for the Polish population and constitute the most frequent cause of mortality, being responsible for nearly 48% of all deaths documented in our country, *inter alia* about 20% of deaths among individuals younger than 65 years of age [14–16]. CHD is expected to be the leading cause of mortality by 2020 [17]. Although the association between the consumption of alcohol and the incidence of CVDs is complex and not completely understood, the ingestion of alcoholic beverages cannot be neglected in epidemiologic studies and reports, due to its potentially preventive role.

Since an inverse association between the consumption of alcohol and the incidence of CHD was postulated [9], the problem has been widely discussed both in specialist and popular literature. One of the first meta-analyses of the issue was conducted by Marmot [18] in 1984. This author summarised the current body of evidence and the existing controversies, and outlined the directions for future research. On the basis of the available evidence, they concluded that moderate ingestion of alcohol is beneficial in decreasing CV mortality risk [18]. Importantly, most of the conclusions from this paper remain valid today, and the results of further observational studies and meta-analyses dealing with the problem in question are surprisingly consistent. Most of them have shown that a relationship between the consumption of alcohol and the incidence of CHD and stroke can be illustrated by a U- or L-shaped curve. Nearly all of the studies have shown that the risk of CVD is the lowest for individuals drinking moderate amounts of alcohol, and increases in non-drinkers and (albeit not universally) in heavy drinkers. Moreover, heavy drinkers are at an increased risk of morbidity and mortality due to trauma, intoxication, suicide, liver cirrhosis, neoplasms and stroke [19].

The association between all-cause mortality and alcohol ingestion has been illustrated by a U- or J-shaped curve in virtually all prospective studies [19–22]. This suggests that

mortality among individuals drinking moderate amounts of alcohol is lower than among non-drinkers. In contrast, the slope of the curve is higher in heavier drinkers, corresponding to a higher mortality risk than in abstainers. This relation was well documented by the results of the American Cancer Prevention Study II, which analysed lifestyle and consumption of alcohol in a group of nearly half a million adult Americans, as well as the causes of deaths documented in this group during a consecutive 9 years of follow-up. In this study, mortality risk turned out to be the lowest among men and women who ingested 1–2 alcoholic drinks on a daily basis [19]. In their meta-analysis, Ronksley et al. [22] showed that consuming at least 50–60 g alcohol daily is associated with an increased mortality risk and a higher incidence of stroke; in contrast, they observed beneficial health effects from lower alcohol ingestion.

Also the analysis of data from 245,207 Americans taking part the National Health Interview Survey conducted between 1987 and 2000 confirmed that low and moderate ingestion of alcohol can reduce CV mortality risk. Mortality risk due to CVD in lifetime abstainers, lifetime infrequent drinkers and former drinkers turned out to be higher than in individuals consuming moderate amounts of alcohol, namely more than one alcoholic drink a day [23].

Estimating the level of alcohol ingestion associated with the strongest protective effect against CHD is difficult due to the variety of measures and definitions of alcohol consumption used in previous studies. Nevertheless, the regular consumption of about 30 g of ethanol a day has been shown to reduce mortality risk and the incidence of CHD or stroke [24]. Furthermore, a meta-analysis of 51 studies, conducted by Corrao et al. [20], revealed that the risk of CHD is the lowest in persons consuming 20–25 g ethanol daily, and the beneficial effects of alcohol consumption are observed up to 72 g per day. In another meta-analysis of 42 studies, Rimm et al. [25] found that the daily consumption of 30 g of ethanol is associated with favourable changes in the concentrations of high density lipoprotein, apolipoprotein A-I, triglycerides and selected haemostatic risk factors, leading to a nearly 25% decrease in CHD risk. Therefore, the protective effect of alcohol seems to be the strongest in individuals consuming 20–30 g of ethanol daily, which corresponds to 2–3 servings of alcoholic beverages, or so-called drinks. According to most authors, one unit of alcohol corresponds to 250 mL of beer, 150 mL of wine, or one 30-mL glass of vodka, each containing approximately 12 g ethanol (Fig. 1) [26].

The results of a recently published meta-analysis conducted by Costanzo et al. [27] confirmed the beneficial effects of moderate alcohol consumption on the CV system of individuals with a history of CVD. The analysis included all papers published up to 2009 and indexed in the PubMed and EMBASE databases. Eight reports from prospective studies of patients with a history of CVD were chosen from 54 identified publications, and 2 meta-analyses were conducted, one

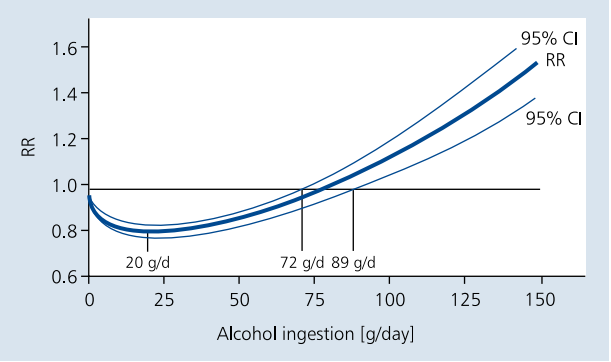

Figure 1. Relationship between alcohol ingestion and relative risk (RR) of coronary heart disease determined on the basis of meta-analysis of 28 cohort studies. Minimum and maximum protective doses and harmful dose were identified [22]; CI — confidence interval

regarding the CV mortality risk (data from 12,819 individuals), and the second referring to all-cause mortality (data from 16,398 persons). Consumption of alcohol was shown to have a protective effect in patients with documented CVD; low or moderate ingestion of alcoholic beverages (5–26 g/day) was associated with a marked reduction in both all-cause and CV mortality risk [27]. This relationship was illustrated by a J-shaped curve. In 2011, the same authors analysed the effects of various types of alcoholic beverages on the incidence of CV episodes. In a meta-analysis of 16 prospective studies, they documented a J-shaped association between the consumption of wine and the risk of CV episodes. The lowest risk was associated with consuming 21 g of ethanol a day; this beneficial effect could be observed up to 72 g ethanol daily. Another meta-analysis, including 13 studies of beer drinkers, also documented a J-shaped relationship between the risk of vascular episodes and the ingestion of beer. Unfortunately, a similar association was not observed in the case of spirits [28]. Another study showed that the mortality risk among heavy drinkers is not higher than in abstainers. Moreover, the cumulative risk of CVD among people drinking alcohol was about 20% lower than in non-drinkers. Interestingly, no significant differences were observed between the risk among heavy drinkers and abstainers [19].

Consumption of alcohol can reduce the risk of sudden cardiac death (SCD). The US Physicians Health Study of individuals without CHD showed that the relative risk of SCD among men consuming 2–4 or 5–6 alcoholic drinks a week corresponds to 0.4 or 0.2 of that in non-drinkers, respectively; in contrast, a markedly higher relative risk (close to 1) was observed in individuals who consumed 2 alcohol units a day. This study revealed a typical U-shaped relationship between the incidence of the SCD episodes and alcohol ingestion. However, the curve illustrating this relationship was more L-shaped when 'non-sudden' cardiac deaths were included in

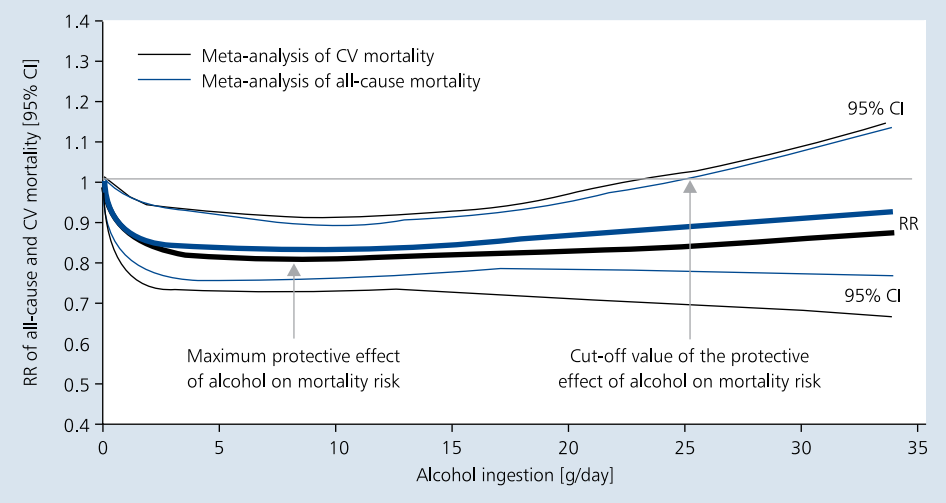

Figure 2. Relationships between all-cause/cardiovascular (CV) mortality and alcohol ingestion in persons with established CV conditions (coronary heart disease or a history of a cerebrovascular accident). Maximum protective effect on all-cause and CV mortality was observed for 5–10 g alcohol a day. Significant protective effects on all-cause and CV mortality were observed up to 24 g/day and up to 26 g/day, respectively. Modified on the basis of Costanzo et al. [28]; CI — confidence interval; RR — relative risk

the analysis [29]. Also another study documented a U-shaped relationship between alcohol ingestion and SCD [30]. The mechanism through which the consumption of alcohol can modulate the risk of SCD is still not understood; perhaps it is associated with a lower risk of arrhythmia in the case of acute coronary episodes (Fig. 2).

While analysing the health effects of alcohol, one cannot neglect the problem of 'binge drinking', i.e. consuming large amounts of alcohol within a short period of time, e.g. having ≥ 5 drinks during one day of a week and refraining from drinking during subsequent days. The beneficial effects of alcohol are not observed among persons who declare such drinking patterns [23, 31]. Based on a nearly 8-year observation, Murray et al. [32] revealed that sporadic consumption of large amounts of alcoholic beverages increases the risk of CHD in both men and women, as well as the risk of arterial hypertension in men. In contrast, the regular consumption of small amounts of alcohol exerted a significant cardioprotective effect in both genders. The hypothesis on the unfavourable effect of irregularly consuming large amounts of alcohol was also confirmed by Mukamal et al. [33]; they showed that the mortality risk in myocardial infarction patients is 2-fold higher in persons who occasionally consume ≥ 3 'drinks' within a short period of 1–2 hours.

The Global Burden of Disease project, using the so-called disability-adjusted-life-years (DALY) to measure the burden of various diseases, identified arterial hypertension (7% DALY), tobacco smoking (6.3%) and drinking alcohol (5.5%) as 3 main determinants of health loss in 2010 [17, 34]. However, the effects of alcohol on mortality differed depending on age category. Evidently unfavourable effects were documented in younger age groups (below 50 years of age), mostly due to the increased risk of mortality from trauma and accidents (especially among 15- to 29-year-olds). Among the elderly, however, the number of deaths (especially due to CVD) that could be avoided due to moderate consumption of alcohol turned out to be higher than the number of fatal outcomes resulting from drinking [35]. Nevertheless, the number of people with alcohol dependence is estimated at about 76 million worldwide, and the consequences of alcohol abuse contribute to 14.6% of preterm deaths in this group [36, 37].

Most of the previous studies analysing the association between the consumption of alcohol and mortality risk have included middle- and old-aged participants rather than younger persons; this raises many doubts regarding the role of alcohol in the latter age category. The results of the few available studies point to the lack of protective effect of moderate alcohol ingestion in young adults [38]. Probably, the beneficial effects of alcohol consumption are more evident in older persons in whom CVDs represent the predominant cause of mortality. In contrast, they are not observed in younger people as such conditions rarely occur in this age category. Furthermore, the ingestion of alcohol can even increase the risk of mortality among the young as they more frequently die due to trauma or accidents [39]. These findings are supported by the results of the American Cancer Prevention Study II [19], which showed an L-shaped association between the consumption of alcohol and mortality risk solely in persons with established CVDs; a more J-shaped relationship was documented among individuals without CV conditions.

One can speculate that the evidence of the protective effect of alcohol results from a selection bias; namely, a num-

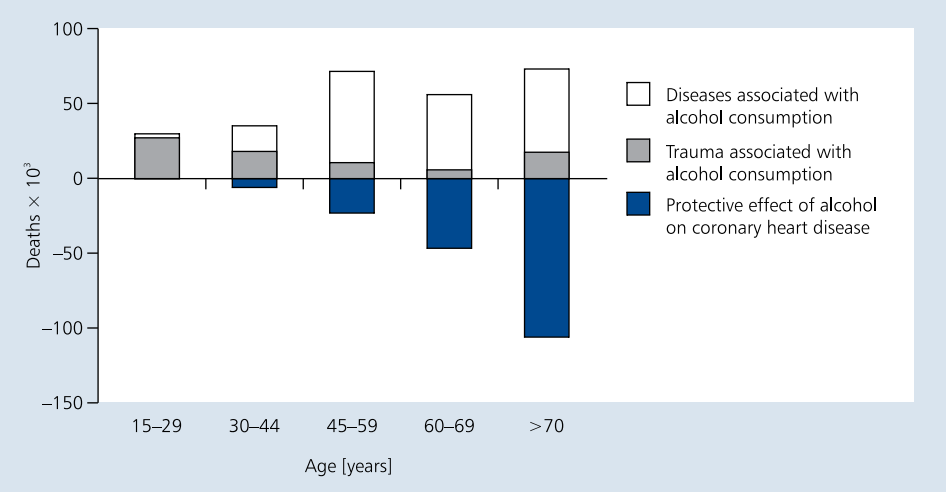

Figure 3. Estimated age-specific mortality of men from developed countries, stratified according to the consequences of alcohol consumption. Values higher than 0 — deaths due to diseases or trauma associated with alcohol consumption; values lower than 0 — deaths that could be prevented due to alcohol consumption [34]

ber of individuals could have stopped drinking due to various comorbidities, which was reflected by an overestimation of mortality among non-drinkers. However, this hypothesis is not supported by available data [40]. In several studies, non-drinkers were divided into those who stopped drinking due to various reasons and lifetime abstainers. CV mortality risk in both abstainers and former drinkers was higher than in moderate drinkers, with no significant differences between the two former groups [34]. Furthermore, the results of most of the analyses remained unchanged after excluding patients who died during the early follow-up period, i.e. those who could have died due to earlier comorbidities (Fig. 3) [41].

Confirmation of the protective role of alcohol in CVDs would be vital for public health, as CV conditions constitute the main cause of mortality worldwide. Therefore, even a small reduction of the relative risk of CVDs could be reflected by a marked decrease in the absolute number of new diagnoses or deaths.

Although alcohol ingestion is associated with a number of health threats and it is not recommended in the prevention of CVD [26], one should be aware that regular consumption of alcoholic beverages in reasonable amounts, while maintaining a healthy lifestyle (physical activity, proper diet, lack of addictions) and appropriate pharmacotherapy can reduce the risk of CV morbidity and mortality.

CONCLUSIONS

In conclusion, Hippocrates's statement: *"Wine is a matter which in a miraculous way intended for men to apply in good and bad health in the proper quantities"* is surprisingly accurate and still valid in view of the hereby presented research findings.

Conflict of interest: *none declared*

References

1. Gronbaek M. Factors influencing the relation between alcohol and cardiovascular disease. Curr Opin Lipidol, 2006; 17: 17–21.
2. Richard JL, Cambien F, Ducimetiere P. Particularités épidémiologiques de la maladie coronarienne en France. Nouv Presse Med, 1981; 10: 1111–1114.
3. Kuulasmaa K, Tunstall-Pedoe H, Dobson A et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet, 2000; 355: 675–687.
4. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet, 1999; 353: 1547–1557.
5. Tunstall-Pedoe H, Vanuzzo D, Hobbs M et al. Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. Lancet, 2000; 355: 688–700.
6. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet, 1992; 339: 1523–1526.
7. Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? Lancet, 1994; 344: 1719–1723.
8. Black S. Clinical and Pathological Reports. Alexander Wilkinson, 1819: 46–47.
9. St Leger AS, Cochrane AL, Moore F. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. Lancet, 1979; 1: 1017–1020.
10. Gronbaek M, Deis A, Sorensen TI et al. Mortality associated with moderate intakes of wine, beer, or spirits. BMJ, 1995; 310: 1165–1169.
11. Piantadosi S, Byar DP, Green SB. The ecological fallacy. Am J Epidemiol, 1988; 127: 893–904.
12. Goldberg IJ, Mosca L, Piano MR et al. AHA Science Advisory: Wine and your heart: a science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. Circulation, 2001; 103: 472–475.
13. Tjonneland A, Gronbaek M, Stripp C et al. Wine intake and diet in a random sample of 48763 Danish men and women. Am J Clin Nutr, 1999; 69: 49–54.

14. WHO Regional Office for Europe. The European Health Report 2002. WHO Regional Publications, European Series 2002; 97: 3.
15. Wojtyniak B, Goryński P. Sytuacja zdrowotna ludności Polski. Narodowy Instytut Zdrowia Publicznego, Państwowy Zakład Higieny 2008.
16. Zdrojewski T, Ignaszewska-Wyrzykowska A, Wierucki Ł et al. Modelowy projekt prewencji chorób układu krążenia na przykładzie doświadczeń Programu SOPKARD. Choroby Serca i Naczyń, 2004; 2: 115–129.
17. Murray J, Lopez A. The Global Burden of Disease: A Comprehensive Assessment of Global Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. World Health Organization, 1996.
18. Marmot MG. Alcohol and coronary heart disease. Int J Epidemiol, 1984; 13: 160–167.
19. Thun MJ, Peto R, Lopez AD et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med, 1997; 337: 1705–1714.
20. Corrao G, Rubbiati L, Bagnardi V et al. Alcohol and coronary heart disease: a meta-analysis. Addiction, 2000; 95: 1505–1523.
21. Marmot M, Brunner E. Alcohol and cardiovascular disease: the status of the U shaped curve. BMJ, 1991; 303: 565–568.
22. Ronksley PE, Brien SE, Turner BJ et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ, 2011; 342: 671.
23. Mukamal KJ, Chen CM, Rao SR et al. Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. J Am Coll Cardiol, 2010; 55: 1328–1335.
24. Sinkiewicz W, Dudziak J, Kubica A et al. Czy wzorzec konsumpcji alkohol ma wpływ na układ sercowo-naczyniowy? Folia Cardiol Excerpta, 2007; 2: 292–296.
25. Rimm EB, Williams P, Fosher K et al. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ, 1999; 319: 1523–1528.
26. Mamcarz A, Podolec P, Pająk A et al. Konsensus rady redakcyjnej Polskiego Forum Profilaktyki Chorób Układu Krążenia dotyczący znaczenia alkoholu w profilaktyce chorób układu krążenia. Forum Profilaktyki, 2006; 1: 1.
27. Costanzo S, Di Castelnuovo A, Donati MB et al. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. J Am Coll Cardiol, 2010; 55: 1339–1347.
28. Costanzo S, Di Castelnuovo A, Donati MB et al. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. Eur J Epidemiol, 2011; 26: 833–850.
29. Albert CM, Manson JE, Cook NR et al. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. Circulation, 1999; 100: 944–950.
30. Chiuve SE, Rimm EB, Mukamal KJ et al. Light-to-moderate alcohol consumption and risk of sudden cardiac death in women. Heart Rhythm, 2010; 7: 1374–1380.
31. Banach J, Żekanowska E, Sinkiewicz W et al. Short-term alcohol consumption may have detrimental effect on fibrinolysis and endothelial function: preliminary report of prospective randomised study. Kardiol. Pol, 2013; 71: 1161–1167.
32. Murray RP, Connett JE, Tyas SL, et al. Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? Am J Epidemiol, 2002; 155: 242–248.
33. Mukamal KJ, Maclure M, Muller JE et al. Binge drinking and mortality after acute myocardial infarction. Circulation, 2005; 112: 3839–3845.
34. Lim SS, Vos T, Flaxman AD et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 2012; 380: 2224–2260.
35. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet, 1997; 349: 1436–1442.
36. Rehm J, Mathers C, Popova S et al. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet, 2009; 373: 2223–2233.
37. Schuckit MA. Alcohol-use disorders. Lancet, 2009; 373: 492–501.
38. Andreasson S, Allebeck P, Romelsjo A. Alcohol and mortality among young men: longitudinal study of Swedish conscripts. Br Med J (Clin Res Ed), 1988; 296: 1021–1025.
39. Jones SN, Waite RL. Underage drinking: an evolutionary concept analysis. Nurs Clin North Am, 2013; 48: 401–413.
40. Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. Am J Cardiol, 1990; 66: 1237–1242.
41. Rehm J, Fichter MM, Elton M. Effects on mortality of alcohol consumption, smoking, physical activity, and close personal relationships. Addiction, 1993; 88: 101–112.