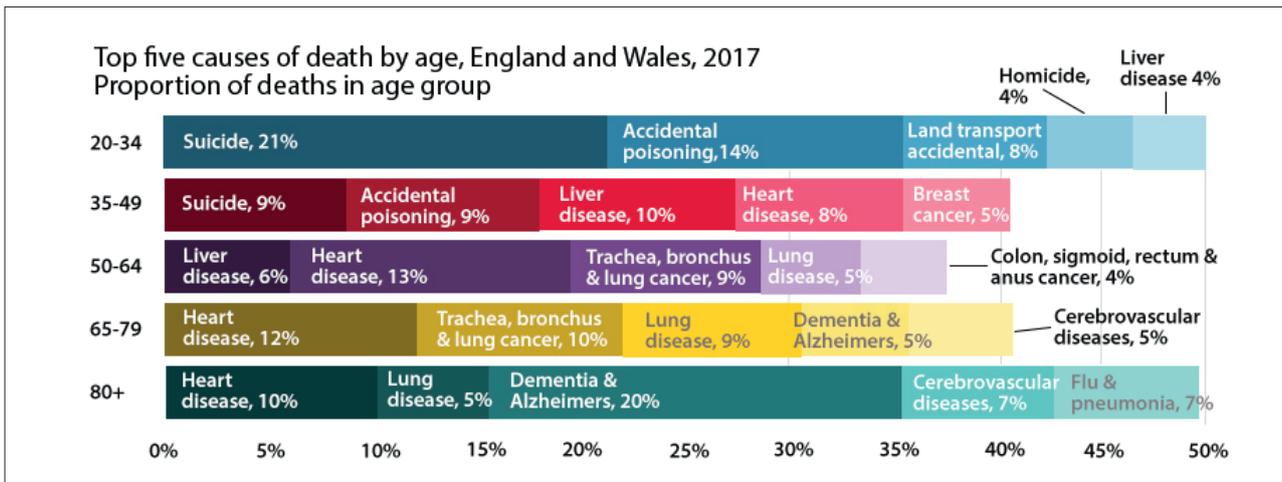


Alcohol and the liver by Helena Conibear



A report from British Liver Trust in June citing that liver disease is now the leading cause of death among 35-45-year olds¹ warrants a close look at the causes of liver disease and its potential prevention and cure, including the role of alcohol. Worldwide estimations show that 844 million people have Chronic Liver Disease, with a mortality rate of 2 million deaths per year. This can be compared with other major public health problems related to chronic diseases such as diabetes (422 million, 1.6 million deaths), pulmonary (650 million, 6.17 million deaths) and cardiovascular diseases (540 million, 17.7 million deaths).²

In the US, non alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in all ethnic groups combined (52%), followed by alcoholic liver disease (ALD) (21%)^{3,4}.

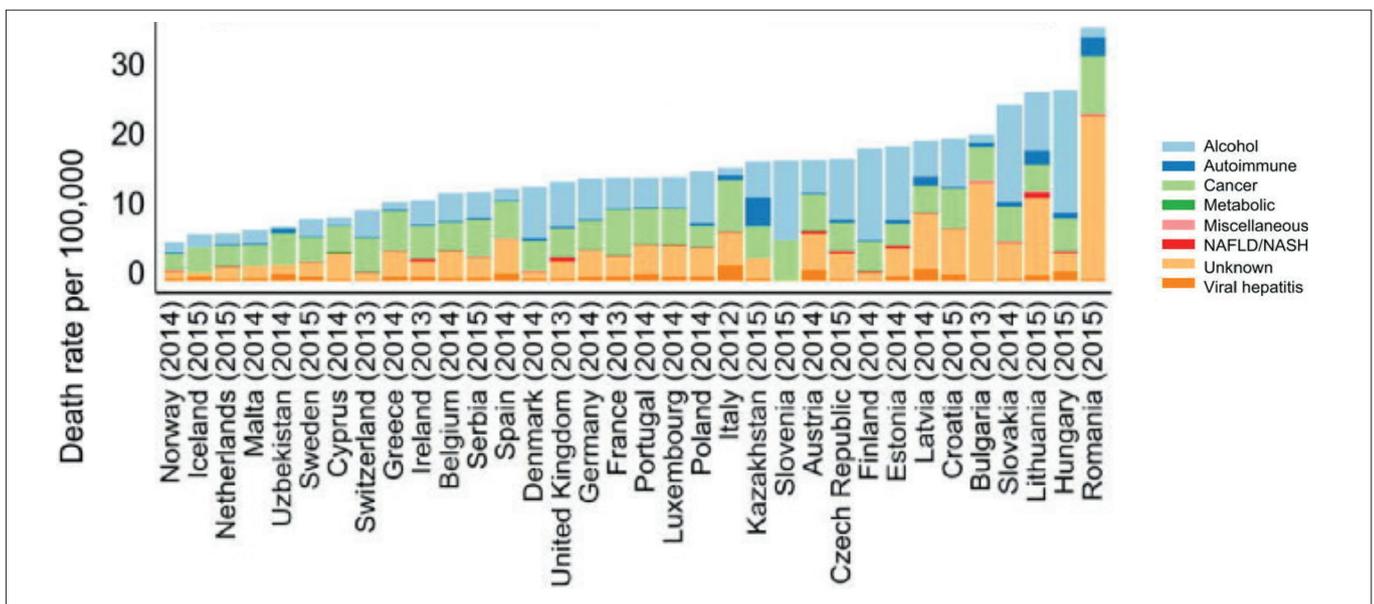
The table below illustrates the recorded liver disease death rates per 100,000 across Europe and the recorded causes.⁵

The importance of the liver

The liver is the largest gland, and the largest solid organ in the body, weighing an average of 1.8 kgs in men and 1.3 kgs in women. It holds approximately 13% (about one pint or 0.57 litres) of our total blood supply at any given moment and is estimated to have over 500 functions. One of the many jobs it has to deal with is breaking down, or ‘metabolizing’ alcohol.

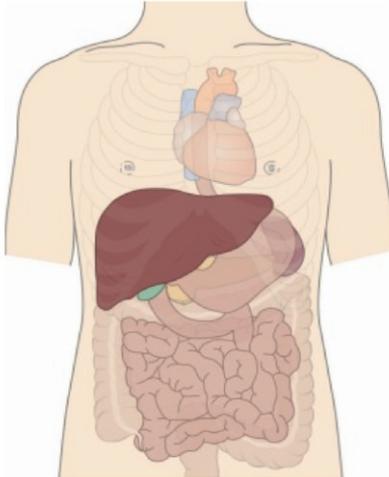
How does the liver break down alcohol?

The liver cannot store alcohol, it metabolizes about 90 per cent of the alcohol consumed and the rest is excreted through urine and sweat. The liver can process about 10g - or a small drink an hour, any remaining alcohol circulates in the blood until it can be broken down - this is what is measured to assess ‘blood alcohol concentration’ for drink drive limits for example.



The efficiency of alcohol metabolism in the liver depends on several factors like heritage, whether you drink alcohol on an empty stomach or with food and your usual drinking pattern. A BAC of 1.0 ‰ = 1000 mg alcohol/litre body water = 100 mg/100 ml. The metabolism of alcohol is measured in mg alcohol/100 ml body water per hour with these typical results:

- In fasting condition: 10-15 mg/100 ml/hour.
- After a meal: 15-20 mg/100 ml/hour.
- Heavy drinkers: 25-35 mg/100 ml/hour.



On average a person with a moderate, regular consumption of alcohol can metabolise 15 mg alcohol/100 ml body water/hour = 150 mg (0.15 g) alcohol/litre body water per hour. The amount of body water = weight (kg) x 0.68 for men or weight (kg) x 0.55 for women. An average man (75 kg) will break down $0.15 \text{ g} \times 75 \times 0.68 = 7.65 \text{ g}$ alcohol per hour, while an average woman (50 kg) will break down $0.15 \text{ g} \times 50 \times 0.55 = 4.12 \text{ g}$ alcohol per hour.

When the liver processes alcohol, the first step is conversion into a toxic substance called acetaldehyde. Acetaldehyde is subsequently broken down into a harmless chemical called acetate, which is broken down further into carbon dioxide and water, which are excreted via the normal route.

What is liver disease?

As the liver is such a complex organ, performing over 500 functions, it is not surprising that liver function can be damaged in a number of ways, through viral infection - Acute viral hepatitis A and Chronic viral hepatitis B and C in particular, through illegal drug use, legal drug overuse especially paracetamol or acetaminophen. What many do not realise is that there are many types of cirrhosis

Liver functions

Liver functions include:

- processing digested food from the intestine
- controlling levels of fats, amino acids and glucose in the blood
- combating infections
- clearing the blood of particles and infections, including bacteria
- neutralising and destroying all drugs and toxins
- manufacturing bile
- storing iron, vitamins and other essential chemicals
- breaking down food and turning it into energy
- manufacturing, breaking down and regulating numerous hormones including sex hormones
- making enzymes and proteins which are responsible for most chemical reactions in the body, for example those involved in blood clotting and repair of damaged tissues.

including autoimmune, biliary, cryptogenic and post hepatic. There are also congenital liver diseases.

The majority of liver cancer can be linked to cirrhosis of the liver. Many liver diseases eventually cause cirrhosis, most notably hepatitis B and C.

When is alcohol implicated?

Scientists are not sure exactly why drinking too much alcohol can damage your liver but the reasons include:

1. Oxidative stress. When our liver tries to break down alcohol, the resulting chemical reaction can damage its cells. This damage can lead to inflammation and scarring as the liver tries to repair itself.
2. Toxins in gut bacteria. Alcohol can damage our intestine which lets toxins from our gut bacteria get into the liver. These toxins can also lead to inflammation and scarring.

Alcohol related liver damage

The liver has become known as 'the canary of drinking' i.e. it becomes damaged through excessive drinking. Due to its huge functional reserve, fatty liver or cirrhosis can often be advanced before symptoms arise - hence liver disease is known as 'a silent disease'.

Drinking excessively over a long period harms the liver and makes it very fatty, with the liver cells becoming bloated. This can result in swelling and inflammation of the liver – known as alcoholic hepatitis or alcoholic steatohepatitis – and can lead to scarring, known as fibrosis. Extensive scarring, combined with development of nodules, is known as cirrhosis (affecting between 10% and 20% of excessive drinkers)- a disease we have all come to associate with heavy long-term drinking of alcohol.

The NHS identifies the following two groups as at a high risk of developing serious types of alcoholic liver disease:

1. Men who drink more than 35 units (8g) of alcohol a week for 10 years or more
2. Women who drink more than 28 units (8g) of alcohol a week for 10 years or more.

“Alcohol use and abuse is widespread and end stage liver disease is the result of prolonged heavy alcohol intake in only a small proportion of users. Nevertheless, these patients make up a significant proportion of the workload of most liver units in the western world.”
 Professor Chris P Day MD hepatologist

Fatty Liver

Fatty liver is a condition in which too much fat builds up in the liver. The liver turns glucose into fat which it sends around the body to store for use when we need it. Alcohol affects the way the liver handles fat so that liver cells retain it. The risk of alcohol fatty liver (AFL) is increased with intake of >20-30 grams of alcohol, and nearly half of persons drinking >60 grams of alcohol per day have AFL. People are more at risk who tend to put on weight around their middle. Fatty liver is also associated with high blood fat hyperlipidemia and diabetes irrespective of any alcohol use. You can get a fatty liver without drinking and ‘non-alcoholic fatty liver’ (NAFL) is the most common type of liver disease today.

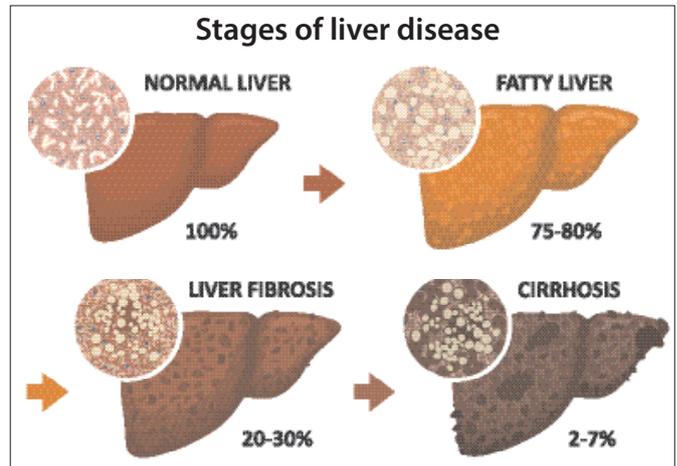
Research is increasingly proving a link between an increased risk of liver disease with obesity. Body weight determines the serum level of liver enzymes.

Furthermore, obesity is thought to slow intestinal motility, enabling bacterial overgrowth and other noxious factors in the intestine.

There should be little or no fat in a healthy liver. Too much of this fat can build up by drinking

more than the liver can cope with over a sustained period of time, leading to fatty liver disease.

Alcoholic Fatty livers should return to normal if drinking is limited to within responsible drinking guidelines of one to two drinks a day. 90-100% of heavy drinkers have alcoholic fatty liver disease and one in five drinkers with fatty liver disease will go on to develop cirrhosis.



Alcoholic hepatitis

If you have a fatty liver and continue to drink, there is a one in four chance of getting alcoholic hepatitis. This is a condition where the liver becomes puffy, swollen and tender. Alcoholic hepatitis can happen at an early stage or after many years of excessive drinking. Up to 35% of heavy drinkers develop alcoholic hepatitis. Symptoms may include loss of appetite, nausea, vomiting, abdominal pain and tenderness, fever and jaundice. The damage maybe reversible with drinking cessation. In its severe form, the disease may occur suddenly and it can quickly lead to life-threatening complications. One in four drinkers with fatty liver disease will develop alcoholic hepatitis.

Alcoholic Cirrhosis

The final stage of alcoholic liver disease is cirrhosis. This is usually the result of long-term, continuous damage to the liver. Irregular bumps, known as nodules, replace the smooth liver tissue and the liver becomes harder. The effect of this, together with continued scarring from fibrosis, means that the liver will run out of healthy cells to support normal functions. This can lead to complete liver failure.

Between 10 and 20% of heavy drinkers develop cirrhosis, usually after 10 or more years of high levels of drinking, but it may be much less. Symptoms of cirrhosis are completely silent. The damage from

cirrhosis is not reversible, but patients who stop drinking can live near normal lives.

Many heavy drinkers will progress from fatty liver to alcoholic hepatitis and finally to alcoholic cirrhosis, though the progression may vary from patient to patient. The risk of developing cirrhosis is particularly high for people who drink heavily and have another chronic liver disease such as viral hepatitis C.

Those with cirrhosis of the liver of any cause are also at higher risk of development of liver cancer, nearly always fatal. In addition to causing liver damage by excess, alcohol, at least when abused, inhibits liver regeneration (healing) from any damage, whether from viral hepatitis, toxins, medication overdose (acetaminophen), hemochromatosis (hereditary iron overload), or alcohol itself.

If cirrhosis develops, cutting out alcohol is essential to prevent death from liver failure. People who have had no previous symptoms who stop drinking when they have cirrhosis, have an 80% chance of being alive after 10 years.

Does drinking moderately increase your risk of alcoholic liver disease and cirrhosis?

As is most often the case, it appears once again to be a matter of dose, even for those of us who are overweight and at increased risk of NALFD. At high doses, however, alcohol synergises with other risk factors for liver disease such as obesity and viral infections. For a body mass index (BMI) over 35 kg/m², it is estimated that the hepatotoxicity of alcohol doubles. Similarly, with hepatitis C virus (HCV) infection, alcohol consumption of more than 20 g per day may increase mortality risk.

In the Million Women Study, the combination of obesity and alcohol consumption of 150g or more each week was associated with a marked increased risk of cirrhosis (about fivefold) compared with that seen in obese women who drank less than 70g of alcohol a week. Hart and colleagues also showed that being overweight or obese and drinking 15 units of alcohol or more each week had a synergistic effect, which amplified the insult to the liver and greatly increased the risk of liver-related morbidity and mortality.

A study published in the August 2018 edition of Hepatology suggested that among a cohort of 4,568 US patients with non-alcoholic fatty liver disease (NAFLD), modest alcohol consumption was associated with a reduction in all-cause

mortality, while drinking 1.5 or more drinks (14g) per day was found to increase mortality.

The researchers found that drinking 0.5 to 1.5 US drinks of 14g per day was associated with a decreased risk for overall mortality compared with not drinking (hazard ratio [HR], 0.59; 95% confidence interval, 0.4 to 0.85; P = 0.005) in a model adjusted for age, sex, and smoking history. The protective effect of drinking 0.5 to 1.5 drinks per day remained significant after further adjustment for race, physical activity, education level, diabetes, fibre and polyunsaturated fat intake (HR, 0.64; 95% CI, 0.42 to 0.97; P = 0.035), and drinking 20g per day or more was associated with an increase in mortality.⁶

Another bigger study of 219,279 men and women aged 30-67 years who attended cardiovascular screening in Norway from 1994 to 2003 published in the August 2018 edition of the Annals of Epidemiology investigated the association between coffee and alcoholic beverage consumption and alcoholic liver disease mortality. The research found that coffee and moderate wine consumption were inversely associated with alcoholic liver disease death, whereas higher levels of consumption were not.⁷

In a study by Schwimmer et al which found that modest alcohol consumption was associated with better outcomes for patients with NALFD, the author stated wisely that the findings indicate patients with liver disease should be treated individually, with nuance. "Forty million Americans have NAFLD. Physicians need to look at their patient's overall health, their CVD risk, their liver status, whether they're already drinking modestly or not. They need to put all of these things into a framework to determine risk. I suspect modest alcohol consumption will be an appropriate recommendation for many patients, but clearly not all," he said.⁸

Women and chronic liver disease

An important meta-analysis on alcohol consumption and risk of fatty liver disease by Cao et al in 2016 found that for light to moderate alcohol consumption, there was a 22.6% reduction in risk of Fatty Liver Disease with a greater reduction in risk among female drinkers (30.2%) and especially female drinkers with a high BMI ≥ 25 kg/m² (31.3%) compared with the male drinkers (22.6%) and the drinkers with BMI <25 kg/m² (21.3%), respectively.⁹



A UK study on chronic liver disease in postmenopausal women found that a High BMI and both heavy alcohol consumption and abstinence were risk factors for CLD in postmenopausal women. They found that BMI and alcohol didn't interact significantly in this group.¹⁰

The health harm paradox

A paper describing a dramatic change during the 20th century in England and Wales in the association between social class and mortality from liver cirrhosis was published in *Alcohol and Alcoholism*. While deaths from cirrhosis were more common among higher social classes in the early part of the century, the pattern changed so that deaths from cirrhosis were much more common among the lower social classes by the end of the century. The authors of this paper state that more recent research suggests that alcohol drinking may not be the reason for this change over time, as surveys in the UK have shown that lower-social-class individuals do not drink more than those at higher social classes.

"Alcohol-related diseases," especially cirrhosis of the liver, are much more common among individuals with less education, lower income, and other components of what has been defined as lower "social class." This has been attributed to a number of causes, including poorer diet, more obesity, and fewer of the other aspects of a healthy lifestyle, as well as less access to health care. The main explanation usually given, however, relates to alcohol drinking pattern: people classified as being of lower social class tend to report less-frequent but larger amounts of alcohol per occasion (a binge-drinking pattern). Also, many studies show poorer health effects associated with the consumption of spirits and beer, especially when consumed infrequently and in large amounts, than with the consumption of wine. This is a pattern that may be more common among lower social-class individuals.

It should always be remembered that there are multiple risk factors for hepatic cirrhosis: While alcohol is generally considered the most important risk factor for hepatic cirrhosis, there are a number of other factors apart from excessive alcohol consumption and obesity. This includes autoimmune diseases, viral hepatitis, and metabolic diseases." Another factor is the over use of medications, such as paracetamol or

acetaminophen, which break down to more toxic metabolites. Heavy use of acetaminophen has been shown to relate to cirrhosis in a large study in the United States.

There is no doubt that if you drink heavily you increase your risk, not only of alcoholic liver disease, but for many cancers and all cause mortality. If you combine heavy drinking with obesity, poor diet and a sedentary lifestyle, the risks increase further. The message, as ever, is to enjoy drinking in moderation, and if you believe you are drinking too heavily, cut back, and with care, your liver can recover.

To prevent liver disease:

- *Drink alcohol in moderation.*
- *Avoid risky behaviour.* Get help if you use illicit intravenous drugs, and don't share needles used to inject drugs. Use a condom during sex. If you choose to have tattoos or body piercings, be picky about cleanliness and safety when selecting a shop.
- *Get vaccinated.* If you're at increased risk of contracting hepatitis or if you've already been infected with any form of the hepatitis virus, talk to your doctor about getting the hepatitis A and hepatitis B vaccines.
- *Use medications wisely.* Take prescription and non-prescription drugs only when needed and only in recommended doses.
- *Don't mix alcohol with these three kinds of drugs:*
 - A. Acetylsalicylic acid (aspirin) and NSAIDs (nonsteroidal anti-inflammatory drugs).
 - B. Depressant drugs (e.g. sedatives, tranquillizers, antihistamines and opioids = drugs where the label advises against driving and operating heavy machinery).
 - C. Sulfonylureas (medication used to control type 2 diabetes like Glimepiride, Glyburide and Glipizide).
- *Talk to your doctor/pharmacist before mixing new prescription or non-prescription drugs with alcohol.*
- *Avoid contact with other people's blood and body fluids.* Hepatitis viruses can be spread by accidental needle sticks or improper clean-up of blood or body fluids.
- *Take care with aerosol sprays.* Make sure the room is ventilated, and wear a mask when spraying insecticides, fungicides, paint and other toxic chemicals. Always follow the manufacturer's instructions.
- *Protect your skin.* When using insecticides and other toxic chemicals, wear gloves, long sleeves, a hat and a mask.
- *Maintain a healthy weight.* Obesity can cause non-alcoholic fatty liver disease.

References

1. britishlivertrust.org.uk/wp-content/uploads/The-alarming-impact-of-liver-disease-FINAL-June-2019.pdf - statistic based on a Health Foundation analysis using ONS Deaths registered in England and Wales 2017
2. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. Patrick Marcellin, Blaise K. Kutal. *Liver Int.* 2018 Feb;38 Suppl 1:2-6. doi.org/10.1111/liv.13682
3. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. V.W. Setiawan, D.O. Stram, J. Porcel, S.C. Lu, L. Le Marchand, M. Nouredin. *Hepatology*. Published online 2016 Jul 17. doi.org/10.1002/hep.28677.
4. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. Elliot B Tapper, Neehar D Parikh. *BMJ* 2018; 362 doi.org/10.1136/bmj.k2817.
5. marlin-prod.literatumonline.com/cms/attachment/3376962d-b5a7-4973-9a2f-686240517e28/fx1_lrg.jpg
6. Effect of Alcohol Consumption on Survival in Non-alcoholic Fatty Liver Disease: A National Prospective Cohort Study. Kaveh Hajifathalian, Babak Torabi Sagvand, Arthur J. McCullough. *Hepatology*, first published: 19 August 2018. doi.org/10.1002/hep.302267.
7. Coffee and wine consumption is associated with reduced mortality from alcoholic liver disease: follow-up of 219,279 Norwegian men and women aged 30-67 years. Tverdal A, Skurtveit S, Selmer R, Myhre R, Thelle D. *Ann Epidemiol.* 2018 Aug 28. pii: S1047-2797(18)30539-8. doi.org/10.1016/j.annepidem.2018.08.010.
8. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with nonalcoholic fatty liver disease (NAFLD). Winston Dunn, Arun J. Sanyal, Elizabeth M. Brunt, Aynur Unalp-Arida, Michael Donohue, Arthur J. McCullough, Jeffrey B. Schwimmer. *Journal of Hepatology*, 2012. doi.org/10.1016/j.jhep.2012.03.024.
9. Alcohol consumption and risk of fatty liver disease: a meta-analysis. Cao G, Yi T, Liu Q, Wang M, Tang S. *PeerJ.* 2016 Oct 27;4:e2633. eCollection 2016. doi.org/10.7717/peerj.2633
10. Risk of chronic liver disease in post-menopausal women due to body mass index, alcohol and their interaction: a prospective nested cohort study within the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Trembling PM, Apostolidou S, Gentry-Maharaj A, Parkes J, Ryan A, Tanwar S, Burnell M, Jacobs I, Menon U, Rosenberg WM. *BMC Public Health.* 2017 Jun 28;17(1):603. doi.org/10.1186/s12889-017-4518-y.

