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Estimates of the global reduction in liver disease-related mortality with increased coffee consumption: an analysis of the Global Burden of Disease Data.

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Conflict of Interest Statement

The below authors certify that they have NO affiliations with or involvement in any organisation or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript**.**

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JH and PG conceived and designed the study. MH and TS contributed to study design. JH and TS conducted the statistical analysis. JH, PG, MH and SG wrote the manuscript. All authors reviewed, edited and approved the final manuscript.**Abstract**

Background: Epidemiological data suggests coffee has a dose-dependent protective effect on liver-related mortality.

Aim: To estimate the potential impact of increased per capita coffee consumption on global liver-related mortality.

Methods: Using the Global Burden of Disease 2016 dataset (adults >15 years), we modelled the impact of increased per capita coffee consumption on liver-related mortality in 2016 for 194 countries using published risk ratios for >2 cups coffee/ day (RR 0.54, 95% CI 0.42-0.69) and ≥4 cups/ day (RR 0.29, 95% CI 0.17-0.50), adjusted for confounders and tested model assumptions using sensitivity analyses.

Results: Worldwide, there were an estimated 1,240,201 (95% CI 118,4300-1,354,410) adult liver-related deaths in 2016. Median global liver mortality rate in 2016 was 15 deaths/ 100,000 population/ year (all ages, both genders; IQR 11-21 deaths per 100,000).

If all countries with per capita coffee intake ≤2 cups/ day increased to >2 cups/ day, the predicted total number of liver-related deaths would have been 630,947 in 2016 (95% CI 629,693-631,861) with 452,861 (95% CI 451,948-454116) deaths averted (PPR 7.8 liver-related deaths/ 100,000/ yr). If per capita consumptions was ≥4 cups/ day, the predicted number of liver-related deaths in 2016 would have been 360,523 (95% CI 359,825-361,992)

with 723,287 (95% CI 721,817-723984) deaths averted (PPR 12.1 liver-related deaths/ 100,000/ yr).

Conclusion: Increasing per capita coffee consumption to > 2 cups per day on a population level has the potential to avert hundreds of thousands of liver-related deaths annually if the impact of coffee on liver-related mortality is confirmed in clinical trials.

Introduction

Liver disease is a major cause of morbidity and mortality globally (1). Worldwide, cirrhosis is estimated to be the cause of more than a million deaths annually, equating to more than 2% of all deaths (2). Moreover, hepatocellular carcinoma (HCC) due to liver disease is the third most common cause of cancer deaths worldwide, accounting for 745,000 deaths annually (3). There are numerous efforts to reduce this burden of disease occurring at both national and international levels, including vaccination and treatment strategies for hepatitis B and C(4). However, additional simple, cost-effective interventions are required to reduce the burden of liver disease-related mortality. Coffee is one such intervention that may have a potential role in this area.

For decades, it has been recognised that coffee intake offers some degree of protection against liver disease. The initial reports described an association between coffee intake and improvements in liver function tests(5-8). Over more recent years, there have been a growing number of publications reporting that coffee intake not only improves liver biochemistry, but also slows progression to cirrhosis (9-13) and is associated with a reduced risk of death from liver disease (14-18). The reported magnitude of the protection that coffee offers from liver death in cohort studies is impressive, though the impact on hepatitis B-related mortality is less certain. In one of the largest high quality prospective cohort studies to date, Setiawan and colleagues (14) demonstrated a 46% reduction in death from liver cirrhosis for people assessed at study entry as drinking 2-3 cups/day; and a 71% reduction in death from cirrhosis in those consuming 4 or more cups daily, after adjusting for key confounders including age, BMI, diabetes, gender, race, education level and alcohol intake. The data was drawn from the US Multiethnic Cohort Study, a mixed-race cohort of 162,022 men and women from Hawaii and California, USA (25% Caucasian, 16% African American, 30% Asian, 7% Native Islander and 22% Hispanic) with and without chronic liver

disease of diverse aetiologies, in whom HCC had been excluded at baseline(14). Importantly, the risk ratios in the Setiawan paper were derived from a prospective cohort study where baseline coffee consumption (exposure of interest) was recorded prior to liver-related mortality (outcome of interest), which minimizes recall bias and allows for lag time analysis that reduces but does not remove the possibility of reverse causation due to lower coffee consumption in those with more severe liver disease. Similarly, the Singapore Chinese Health Study prospective cohort also revealed a similar reduction of 66% in liver-related mortality with increased coffee intake to two or more cups per day, however there was no observed impact on liver-related mortality for people with chronic hepatitis B(15). Importantly, published data have shown that reductions in liver-related mortality, liver cirrhosis and liver cancer are reported in Eastern and Western populations(14, 19) supporting the suitability of coffee as a potential global intervention. While preliminary studies in animal models support the protective mechanism of coffee on liver fibrogenesis and liver damage (11, 20, 21), the exact mechanism by which coffee attenuates fibrosis progression remains unclear.

Coffee ticks many of the boxes when it comes to potential interventions that may play a role in reduction in liver disease mortality at a global level. It is widely available, generally affordable and is associated with minimal side effects. The potential global health impact of coffee intake being advocated as a liver health therapy has not previously been explored and mathematical modelling is one way of exploring the potential impact of novel population-level interventions. The aim of this study was to estimate the potential reduction in liver disease-associated mortality with increased coffee consumption worldwide, using mathematical modelling and published estimates of relative risk reduction in liver-related mortality applied to the Global Burden of Disease 2016 dataset.

Methods

Data

This descriptive cross-sectional study used the Global Burden of Disease (GBD) 2016 adult >15 years dataset (both sexes) (22) to illustrate the potential impact of increasing per capita coffee consumption to more than two and also more than four cups per day on the number of liver-related deaths globally. Annual estimates or absolute number of deaths (both sexes)

due to all liver disease and hepatitis B specifically were extracted for every country in the GBD 2016 dataset. We restricted the dataset to those aged 15 years or older, as those under 15 years are unlikely to be consuming multiple cups of coffee. For regional sub-analyses, World Health Organisation (WHO) regional definitions were used(23). To estimate annual per capita coffee consumption for each country, public-available data were used from the International Coffee Organisation, an international commercial and market interest organisation that records annual estimates of national per capita coffee consumption (kilograms) based on national coffee bean import and export data(24) . Per capita estimates (kilograms/ person/ year) were converted to grams/day and then into a categorical estimate of number of cups consumed per day, based upon standardised measures of coffee content (grams) per cup used in previous publications (7 grams ground coffee per cup) (14, 16, 19, 25). For countries where coffee consumption data were not available, we ascribed a per capita coffee intake of less than two cups per day, a conservative estimate based upon the absence of recorded import and export markets.

Statistical analyses

To estimate the impact of increased coffee consumption on liver-related mortality in 2016, we used the risk reduction ratios published by Setiawan and colleagues(14). These were chosen because they were derived from the largest prospective study to date on the impact of coffee consumption on liver-related mortality, drawn from the US Multiethnic Cohort Study which included 162,022 people from multiple ethnicities and with diverse aetiology of liver disease; and adjusted for key confounders including BMI, obesity, alcohol, age, gender and smoking. In this study, past or current HCC was excluded at baseline and a detailed validated analysis of coffee consumption was conducted prior to measurement of the outcome of liver-related mortality, minimising temporal ambiguity and recall bias. Lag time analysis was also performed to minimise (but not remove) the impact of reverse causation. To estimate the predicted effect on global liver-related mortality in 2016 if per capita coffee consumption were increased globally to more than two cups per day, or four or more cups per day, we applied the risk reduction ratios for liver-related survival calculated by Setiawan and colleagues (14) for drinking more than two cups of coffee per day (RR 0.54, 95% CI 0.42-0.69) and for drinking four or more cups of coffee per day (RR 0.29, 95% CI 0.17-0.50) to the GBD 2016 dataset (both genders, adults >15 years). We then calculated the predicted

number of liver-related deaths and liver related mortality rate for each country and each WHO region in 2016, if per capita coffee intake had been greater than two cups per day, or four or more cups per day.

Only countries with per capita coffee intake less than two cups per day in 2016 would derive a survival benefit from increasing coffee intake to more than 2 cups of coffee per day. Therefore, for countries where per capita coffee consumption is already more than two cups per day, a risk reduction ratio of 1.00 (no change) was used for the analysis assessing impact of increased coffee consumption to more than two cups of coffee per day on mortality. Similarly, for countries with per capita coffee consumption of four or more cups of coffee per day at baseline, an RR of 1.0 (no change) was used for the analysis assessing impact of increased coffee consumption on mortality.

The mortality benefit from coffee intake per cup was not perfectly linear in the Setiawan et al paper(14), ie: the risk reduction from four cups of coffee or more per day (RR 0.29) was not twice the risk reduction of two or more cups of coffee per day (RR 0.54). Therefore, countries with baseline per capita coffee consumption of more than two cups of coffee per day would have a lower expected survival benefit from increasing their coffee consumption to four or more cups of coffee per day, compared with countries with baseline per capita coffee consumption of less than two cups of coffee per day. We accounted for this by using a risk ratio of 0.75 (1.00 minus 0.25, the difference in RR for two (RR 0.54) and four cups (RR 0.29) of coffee per day) to calculate the potential number of lives saved by increasing coffee consumption from two to four or more cups per day.

Finally, to calculate the number of predicted lives saved in each country if their baseline per capita coffee intake was increased to more than two cups, or four or more cups of coffee per day, we subtracted the number of predicted deaths from the estimated number of actual deaths in 2016 in the GBD dataset.

For WHO regional analyses, the median per capita coffee intake (cups per day) was estimated using country per capita consumption levels in each region. A baseline coffee intake of two or more cups per day for the Western Europe region was assumed, whereas for all other regions the baseline median per capita coffee intake was less than two cups of coffee per day.

Sensitivity Analyses

A sensitivity analysis was performed to estimate the upper and lower number of predicted lives saved with increased coffee intake, with the lower estimate for predicted lives saved calculated using the lower limit of the 95% confidence interval for number of deaths and the lower limit of the 95% confidence interval for the risk reduction ratio; conversely an upper limit was obtained using the upper limit of the 95% confidence interval for number of liver-related deaths and the upper limit of the 95% CI for the risk ratio. As some studies have suggested there may not be a strong protective effect of coffee among people with hepatitis B- related liver disease(15), a second calculation was performed excluding all HBV related liver deaths from the analysis. We also performed additional sensitivity analyses to test our assumptions, restricting the dataset in turn to only those aged 55-79 years; and presuming that coffee intake in countries with no reported import and export coffee data already drink four or more cups per capita per day, therefore would not benefit from an increase in coffee consumption. All analyses were performed using Excel for Mac v 15.29 (Microsoft, CA USA) and Stata v14.1 (StataCorp, College Station, Texas USA).

Results

Per capita coffee consumption data were available for 112 of the 194 countries listed in the GBD dataset (58%). (**Supplementary Table 1** and **Figure 1**). Worldwide, there were an estimated total of 1,240,201 (95% CI 118,4300-1,354,410) deaths due to liver disease in 2016 among people aged >15 years (22). The median global liver mortality rate in 2016 was 15 deaths per 100,000 population per year (all ages, both genders; IQR 11-21 deaths per 100,000).

If worldwide per capita coffee was more than two cups per day, the total number of liver-related deaths among those aged > 15 years would reduce to an estimated 714,942 (95% CI 713,811-716,289) in 2016 (best case scenario 451,219 – worst case scenario 914,788 liver-related deaths), translating to an estimated 524,413 deaths averted (95% CI 522,966-525,444 deaths averted) and a population preventable rate of 7.8 liver-related deaths per 100,000 per year.

If all countries increased their per capita coffee intake to four or more cups per day, the total global number of deaths would have been 405,632 (95% CI 403997-406,476), with a

best-case scenario of 227,829 liver-related deaths and a worst-case scenario 771,794 deaths. 833,725 (95% CI 832,779-835,258) liver-related deaths would have been averted and the population preventable rate would be 12.1 liver-related deaths per 100,000 per year (**Tables 1 and 2 and Supplementary Table 2**).

Tables 1 and 2 illustrates the potential impact in global regions of increased coffee consumption.

Sensitivity Analyses

We used sensitivity analyses to explore some of the limitations in the assumptions used to generate our data. First, we have assumed that countries with no import or export data for coffee have per capita consumption levels of 0-2 cups of coffee per capita per day. We therefore performed a sensitivity analysis where we instead assumed that all countries with no import and export coffee data were drinking more than two cups of coffee daily and would therefore not derive mortality benefit from a population-based increase of coffee consumption to two or more cups of coffee per day (**Supplementary Table 3**). Making this assumption, the estimated number of liver-related deaths averted in 2016 by an increase in coffee consumption of more than two cups per capita per day would be 452,861 (95% CI 451,948-454,116) and with four or more cups per capita per day, an estimated 723,287 (95% CI 721817-723,984) liver-related deaths would be averted.

Some published data suggest that hepatitis B infected people derive less mortality benefit from coffee consumption compared with other aetiologies of chronic liver disease (14, 15, 17). To account for this, we performed an additional sensitivity analysis to determine the impact of excluding all hepatitis B- related liver deaths (**Supplementary Table 4**). Taking the conservative assumption that coffee intake does not impact HBV related liver mortality, the global number of non-HBV related liver deaths averted in 2016 if per capita coffee intake increased to more than two cups per day would have been 478,059 deaths averted (95% CI 476,876-479,044 deaths averted) and 761,702 deaths averted (95% CI 760,834-763,002 deaths averted) if coffee consumption increased to four or more cups per day.

Finally, chronic liver disease-related mortality increases with increasing age and some studies suggest mortality benefits may be less in those aged < 57 years (26). We therefore restricted our analysis to individuals aged 55-79 years (**Supplementary Table 5)**. Even when the survival benefits of coffee were restricted to those aged 55-79 years, increasing global

coffee consumption to more than two cups, and four or more cups, per capita per day averted an estimated 242,959 deaths (95% CI 241,689-243,857) and 406,863 deaths (95% CI 405345-407,512) respectively.

Discussion

Liver disease is responsible for greater than one million deaths globally each year (2, 27), with the greatest burden in low-middle income countries due to viral hepatitis. Therefore, cost-effective, affordable and accessible initiatives to implement at an international population level to reduce this figure are urgently needed. The last two decades have seen a significant number of important publications that have consolidated the evidence that coffee drinking plays an important and powerful role in reducing the risk of death from cirrhosis and/or HCC (19, 28, 29). This current paper estimates that nearly half a million lives may be able to be saved annually if moderate coffee drinking became embraced globally as a health initiative to reduce the risk of premature death from liver disease.

Projections of potential lives saved if a two cup/day coffee intake could be widely implemented varies markedly on a geographical basis. Our projections estimate that there would be few if any lives saved in Europe with this policy, as in this region the current mean coffee intake is already two or more cups daily (24). However, outside of Europe rates of coffee drinking are relatively low. In South-East Asia alone we estimate that greater than 150,000 lives could be saved annually with the implementation of a 2 cup/day policy. Similar large numbers of lives could be saved in other global regions where coffee drinking is low and rates of underlying liver disease are relatively high. Notably, these countries most likely to derive liver-related mortality benefit on a population level are also coffee producers (South-East Asia, Sub-Saharan Africa, Latin America) (24).

Our data also estimate that greater than 720,000 lives could be saved annually if worldwide coffee intake increased to four or more cups daily. The paper by Setiawan (14) and other published series (26, 28, 30) have demonstrated a dose-response effect for coffee intake and protection from mortality from both cirrhosis and HCC. The magnitude of the reduction in mortality rates from both cirrhosis and HCC of course varies between case series. In this current paper we chose to use the risk reduction estimates generated from the paper by Setiawan and colleagues (14). Their cohort study was prospective and included the largest

data set with information for more than 162,000 individuals and was ethnically mixed. Though their data were derived from an exclusively US population with a median age of 60 years which may not be generalizable to the global population, the study included patients with diverse aetiology of liver disease. The relative risks derived from the study were also appropriately adjusted for confounding by gender, age, alcohol, smoking, BMI, race, education level and diabetes status (14). Moreover, there has not been a systematic review and meta-analysis on the impact of coffee drinking on liver-related mortality to our knowledge from which we could derive a pooled RR to use for our study.

The data from Setiawan and colleagues (14) revealed that compared to non-coffee drinkers, those who drank 2-3 cups daily has a 38% reduction in HCC risk and a 46% reduction in risk of death from chronic liver disease (CLD). If individuals drank four or more cups daily the risk reduction for HCC was 41% and for death from CLD 71%. Other cohort studies have reported risk reductions of similar magnitude (5, 15, 28, 30). In the Singapore Chinese Health study involving data from 63,257 middle aged Chinese, Goh and colleagues reported a risk reduction in death from non-viral CLD of 38% in those drinking two or more cups of coffee daily(15). Lai et al (26) also reported mortality reduction in patients with liver disease from increased coffee consumption in a Norwegian adult population-based cohort, with an adjusted RR of 0.55 (95% CI 0.48-0.63) per extra cup consumed per capita, however this cohort was exclusively male smokers from Finland, therefore the generalisability of the results beyond this population is unclear. Klatsky et al also reported a dose-response effect between coffee intake and cirrhosis-related mortality in a US population-based cohort(5). A further meta-analysis by Kennedy and colleagues(30) explored the impact of coffee consumption on the risk of cirrhosis, but not chronic liver disease-related mortality. They found the risk of cirrhosis was reduced by 41% (pooled RR0.59, 95% CI 0.41-0.76). There have also been several case-control studies supporting the association between coffee drinking and improved liver-related survival (9, 31), though causation cannot be established from these studies. Collectively, these data have been considered compelling enough that for the first time the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for both hepatocellular carcinoma (2018)(32) and non-alcoholic fatty liver disease (2015)(33) recommend increased coffee consumption in people with chronic liver disease to reduce liver disease progression, HCC incidence and liver-related mortality. Moreover, coffee appears a safe intervention for people with chronic liver disease: as

highlighted in the EASL HCC CPG, adverse events in people with chronic liver disease have not been identified in the studies conducted to date. An umbrella review of several meta-analyses by Poole and colleagues found minimal adverse events reported for usual consumption levels including in patients with chronic liver disease (34).

However, the paper by Goh and colleagues (15) raises the important point that it is not clear if the benefits of coffee on liver mortality risk reduction are uniformly spread between all aetiologies of liver disease (15, 17). In this paper, the positive impact of coffee on liver related mortality was exclusively in those with non-viral hepatitis related liver disease. However, only two of 63,257 subjects had hepatitis C-related liver mortality and these were excluded from the analysis, therefore the majority of those with viral hepatitis were hepatitis B infected, suggesting coffee may not have a benefit in those with hepatitis B. However, other papers have not supported this finding.

In the Setiawan paper (14), the protective effect of coffee on both HCC risk reduction and CLD mortality was not specifically examined in patients with underlying viral hepatitis as a subgroup analysis. However, they did not find evidence to support interaction between coffee drinking and viral hepatitis aetiology of liver disease. The only other publication to specifically explore the benefits of coffee drinking in people with hepatitis B found coffee to be protective against HCC development, but did not examine CLD mortality as an endpoint (17). Importantly in our study, there were still significant benefits associated with coffee drinking even after people living with hepatitis B were excluded from our global mortality estimates.

Although the data supporting the potential benefits of coffee for reducing HCC risk are compelling (14, 17), cancer registry data is unreliable in many parts of the world, particularly in low-middle income countries with high prevalence of HCC and low coffee intake, such as Africa and Asia(35). Therefore, we did not explore the potential impact of increased coffee consumption on risk of HCC.

The mechanism by which coffee offers protection from liver disease has not been clearly demonstrated, but it appears that caffeine is not the protective chemical (15). Of the many compounds in coffee, diterpenes and chlorogenic acids are the most studied in liver disease(21). High coffee consumption has been correlated with improved insulin sensitivity, suggesting coffee may exert protective effects through attenuating insulin-induced hepatic fibrosis and/or NAFLD as a co-factor in liver disease progression(36). Coffee intake has also

been associated with lower rates of biochemical inflammation in human cross sectional studies and in animal studies, liver enzymes and pro-inflammatory cytokines IFN-γ and TNF-α were lower with coffee intake (21).

This current paper and projections of lives saved has many potential biases. First, this is a hypothetical study that models the potential lives saved based on published risk reduction ratios from one study, in the absence of published risk reduction ratios derived from a systematic review and meta-analysis. Moreover, a common limitation of cohort studies (including the one by Setiawan and colleagues) is that while evaluation of coffee consumption (exposure) occurred prior to the outcome of interest, the impact of severe chronic liver disease on coffee intake has not been taken into consideration, therefore reverse causation cannot be excluded. The paper by Setiawan and colleagues was able to exclude prior or current history of HCC at baseline, however detail of underlying liver disease and severity at study entry was limited. Overall, the ecological study design means derived data are population-based and cannot be extrapolated to the individual – this is ecological fallacy. The predicted numbers of liver-related deaths averted by the modelling used here have wide ranges from best case to worst case scenario. Although we project that over 450,000 lives may be saved annually with more than 2 cups of coffee daily, this number may be as high as 630,00 or as low as 169,000 based on our sensitivity analysis. Similar wide confidence intervals are also predicted for greater than 4 cups daily and with respect to lives saved from liver-related mortality reduction. Although the racial spectrum included in the Setiawan paper was quite broad the numbers of Asian and African (non-American) participants were negligible. Whether the estimates of protection from liver mortality reported from the Setiawan paper can be predicted to all ethnic groups remains unclear. The Setiawan data were also developed from a population of people living in the USA, where there are high background rates of obesity, non-alcoholic fatty liver disease and alcohol use (37) – whether these estimates can be broadened to communities in other counties with different liver disease risk factors also remains unanswered. Although adjustment of the models has been made to account for obvious confounding and interaction, residual confounders for the apparent association between coffee intake and liver related mortality need careful exclusion. For example, wealth was measured at baseline in the Setiawan paper but often changes over time, which may have impacted the

results through unmeasured factors associated with coffee consumption and liver-related mortality. Data on the underlying mean coffee intake in many counties was also not available. In this situation we presumed the coffee intake to be less than 2 cups daily. This may have led to an overestimate of the predicted effects of coffee intake on mortality in these populations. However, when a sensitivity analysis was performed to instead assume that countries without available coffee import and export data have higher coffee consumption (four or more cups per day), there was still over 400,000 deaths averted by more than two cups of coffee consumed per capita per day and over 700,000 lives saved if four or more cups of coffee were consumed per capita per day. Similarly, some data suggest that only those aged over 57 years may derive mortality benefit from increased coffee consumption(26) and chronic disease related mortality increases with increasing age. While data on the duration of consumption needed to derive survival benefits from coffee are unavailable, we performed a further sensitivity analysis to estimate the number of lives potentially saved in 2016 with increased coffee consumption, restricted to those aged 55-79, which showed there were still hundreds of thousands of liver-related deaths that could be averted with increased coffee consumption. We therefore conclude that even with adjustments for confounding and assumptions, an increase in coffee intake has the potential to save hundreds of thousands of lives on a global scale. As liver related mortality data is of poor quality in many counties due to inaccuracy of recording cause of death data, it is likely that our data may under report the benefits of coffee as many of the counties with limited quality death data are in regions with high rates of viral hepatitis.

Despite these caveats, this population-based ecological study has demonstrated the potential positive impact of global increased coffee consumption on liver related mortality. Our results suggest that increased coffee drinking may reduce worldwide liver disease related mortality. However, to date the key reported studies have been observational cohorts and until a mortality benefit is observed in randomised controlled trials enthusiasm to embrace coffee consumption policy should be tempered. Our findings suggest further research into the protective mechanisms of coffee in liver disease and data from a randomised controlled trial would be beneficial, particularly given its low cost, wide accessibility and good safety profile. Public health intervention studies are also warranted to explore how best to deliver the potential impact that coffee could have in terms of global reduction in the burden of liver disease.

Conclusion

Based on available data, coffee represents a simple, relatively safe and accessible public health intervention that may reduce liver-related mortality globally. If the impact of coffee on liver-related mortality shown in cohort studies is confirmed in clinical trials, increasing per capita coffee consumption to more than two cups per capita per day on a population level has the potential to avert hundreds of thousands of deaths from liver disease annually. Further research is urgently needed to confirm the benefits and cost-effectiveness of coffee on liver-related mortality.

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Table 1. Estimated number of current liver-related deaths and predicted number of liver-related deaths with increased per capita coffee consumption or more than two cups per day, and four or more cups per day among people aged 15 years or older in each global region in 2016*

	Current coffee consumption (2015-2016)		**More than two cups coffee consumed per capita[a]**				**Four or more cups coffee consumed per capita[a]**			
	Actual deaths 2016		**Predicted Impact in 2016**		**Sensitivity Analysis**		**Predicted Impact in 2016**		**Sensitivity Analysis**	
Region	**Number liver-related deaths**	**Population percentage liver-**	**Predicted number liver-**	**Predicted number of liver-**	**Predicted number liver-**	**Predicted number liver-**	**Predicted number liver-**	**Predicted number of liver-**	**Predicted number liver-**	**Predicted number liver-**

	2016 (95% CI)	related deaths 2016 (95% CI)	related deaths in 2016 (95% CI)	related deaths averted in 2016 (95% CI)	related deaths: worst case scenario	related deaths best case scenario	related deaths in 2016 (95% CI)	related deaths averted in 2016 (95% CI)	related deaths: worst case scenario	related deaths: best case scenario
African Region	128211 (110383-150341)	1.5% (1.508-1.525)	69234 (68722-69750)	58977 (58503-59453)	103736	46361	37181 (36805-37560)	91030 (90443-91620)	75171	18765
South-East Asia Region	331317 (309508-369818)	2.2% (2.182-2.196)	178911 (178088-179737)	152406 (151645-153170)	255174	129993	96082 (95477-96689)	235235 (234293-236181)	184909	52616
European Region**	216998 (199512-236478)	1.6% (1.634-1.648)	216998 (199512-236478)	0	236478	199512	162749 (162315-163182)	54249 (53816-54683)	196277	131678
Region of the Americas	193201 (185484-199516)	1.3% (1.276-1.287)	104328 (103698-104960)	88872 (88280-89457)	137666	77903	56028 (55566-56493)	137172 (136451-137897)	99758	31532
Western Pacific Region	243822 (228643-283232)	2.4% (2.429-2.448)	131664 (130959-132372)	112158 (111506-112812)	195430	96030	70708 (70189-71229)	173114 (172307-173925)	141616	38869

Eastern Mediterranean Region	118559 (106018-135463)	2.4% (2.429-2.448)	64022 (63530 - 64517)	54337 (53884 - 54793)	93469	44527	34382 (34021 - 34746)	84177 (83614 - 84742)	67731	18023
Global	1240201 (1184300-1354410)	1.4% (1.362-1.367)	669709 (668113-671312)	570493 (569019-571973)	934543	49740 6	359658 (358483-360836)	880543 (878714-882376)	677205	201331

**Source: Global Burden of Disease Collaborative Network: Global Burden of Disease Study 2016 (GBD 2016) Results; Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017; accessed February 2nd, 2018; http://ghdx.healthdata.org/gbd-results-tool.*

** Median per capita coffee intake in Europe greater than two cups of coffee per day but less than four cups of coffee per day, therefore additional mortality benefit only derived for an increase in per capita consumption to more than four cups of coffee per day.

a- Relative risk (RR) applied for more than two, and four or more cups of coffee per day from Setiawan et al.

Table 2. Estimated current liver-related mortality and predicted liver-related mortality with increased per capita coffee consumption of more than two cups per day, and four or more cups per day (mortality rate per 100,000 per year) for each global region in 2016*

	Current coffee consumption (2015-2016)	**More than two cups (>14 g) of coffee consumed per capita**	**Four or more cups (≥28g) coffee consumed per capita**

Region	Liver-related mortality rate per 100,000 per year (95% CI)	Predicted liver-related mortality rate per 100,000 per year	Predicted liver-related mortality: worst case scenario	Predicted number liver-related deaths best case scenario	Population preventable rate (PPR) per 100,000 per year	Predicted liver-related mortality rate per 100,000 per year	Predicted liver-related mortality: worst case scenario	Predicted number liver-related deaths best case scenario	Population preventable rate (PPR) per 100,000 per year
African Region	13 (11.3-15.6)	7.1 (6.1-8.4)	10.8	4.8	6.1	3.8 (3.3-4.5)	7.8	1.9	9.2
South-East Asia Region	17 (16.2-19.4)	9.4 (8.7-10.5)	13.4	6.8	8	5 (4.7-5.6)	9.7	2.8	12
European Region**	24 (21.7-25.8)	24.0 (21.7-25.8)	25.8	21.7	0	12.8 (11.7-13.9)	17.8	9.1	10.9
Region of the Americas	19 (18.7-20.1)	10.5 (10.1-10.9)	13.9	7.9	9	5.6 (5.4-5.8)	10.1	3.2	13.4
Western Pacific Region	13 (12.5-15.4)	7.2 (6.8-8.3)	10.7	5.2	6.1	3.9 (3.6-4.5)	7.7	2.1	9.1
Eastern Mediterranean Region	19 (16.6-21.5)	10 (9.0-11.6)	14.8	7	8.6	5.4 (4.8-6.2)	10.7	2.8	13.6
Global	17 (16.2-18.6)	9.2 (8.7-10.0)	12.9	6.8	7.8	4.9 (4.7-5.4)	9.3	2.8	12.1

**Source: Global Burden of Disease Collaborative Network: Global Burden of Disease Study 2016 (GBD 2016) Results; Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017; accessed February 2nd, 2018; http://ghdx.healthdata.org/gbd-results-tool.*

** Median per capita coffee intake in Europe greater than two cups of coffee per day but less than four cups of coffee per day, therefore additional mortality benefit only derived for an increase in per capita consumption to more than four cups of coffee per day.

a- Relative risk (RR) applied for more than two, and four or more cups of coffee per day from Setiawan et al.

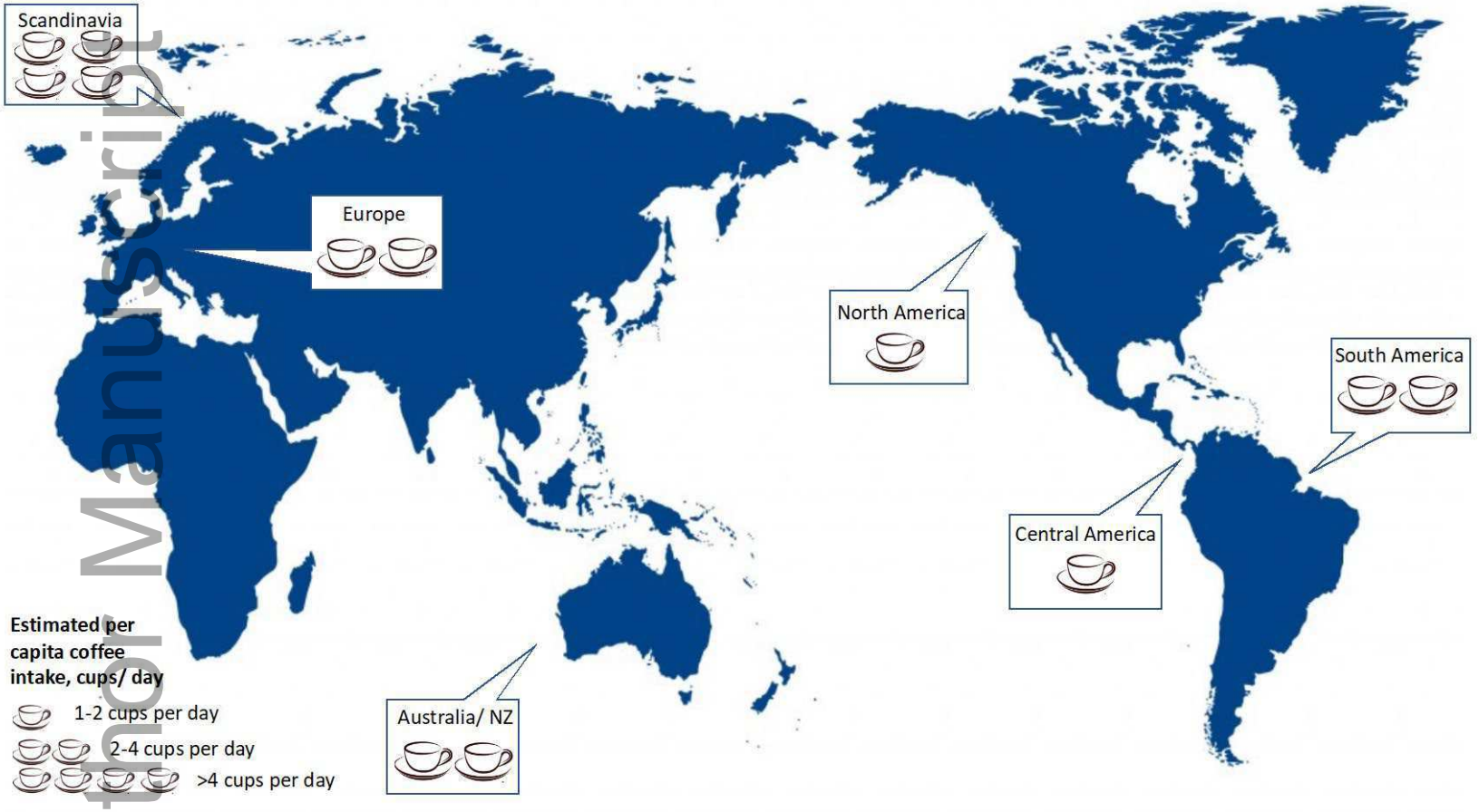

Figure 1. Global map of estimated per capita daily coffee intake in cups/ day

Daily estimated per capita coffee intake (cups/day) is demonstrated for South, Central and North America, Australia and New Zealand, Europe and Scandinavia. All other world regions had estimated per capita daily coffee intake of less than one cup per day.