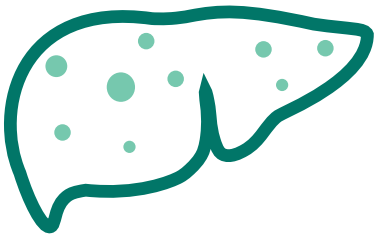
DRINKING AND LIVER CANCER



IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. They are not intended to be exhaustive representations of all scientific research on a given subject and, as research is constantly evolving, they may not include the most recent findings. These materials do not necessarily reflect the views of IARD or its member companies. The reviews report the findings of the referenced studies and are not intended to advise individuals about their drinking. IARD and its member companies do not recommend that anyone drink alcohol for its potential health benefits and would encourage those with specific questions about their drinking to consult their healthcare professionals; together, they can determine what is best based on individual risk factors, including family history, genetics, and lifestyle. For some people, the better choice may be to not drink at all. IARD Health Reviews should be read in their entirety and not misrepresented or taken out of context.

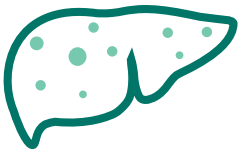
This Health Review focuses on cancer sites associated with alcohol consumption as identified by the World Cancer Research Fund and the International Agency for Research on Cancer. Due to the limited availability of national cancer statistics in many countries, U.S. data – which is publicly available and annually updated – is sometimes used to illustrate cancer risk in this review.

A glossary of key terms used in this review can be found on page 11.

Last literature review: July 2019

Note: Cancers originating in the liver and in the intrahepatic bile ducts (tubes in the liver that carry digestive fluid) are commonly combined when reported in national and international statistics and in some studies. In addition, many studies refer to hepatocellular carcinoma, the most common type of liver cancer, as "liver cancer." Therefore, this review uses the term "liver cancer" to indicate the combination of liver and intrahepatic bile duct cancers, or hepatocellular carcinoma, or both, unless otherwise noted.

Introduction



LIVER CANCER IN MEN AND WOMEN

1%

Lifetime risk of diagnosis (U.S.)

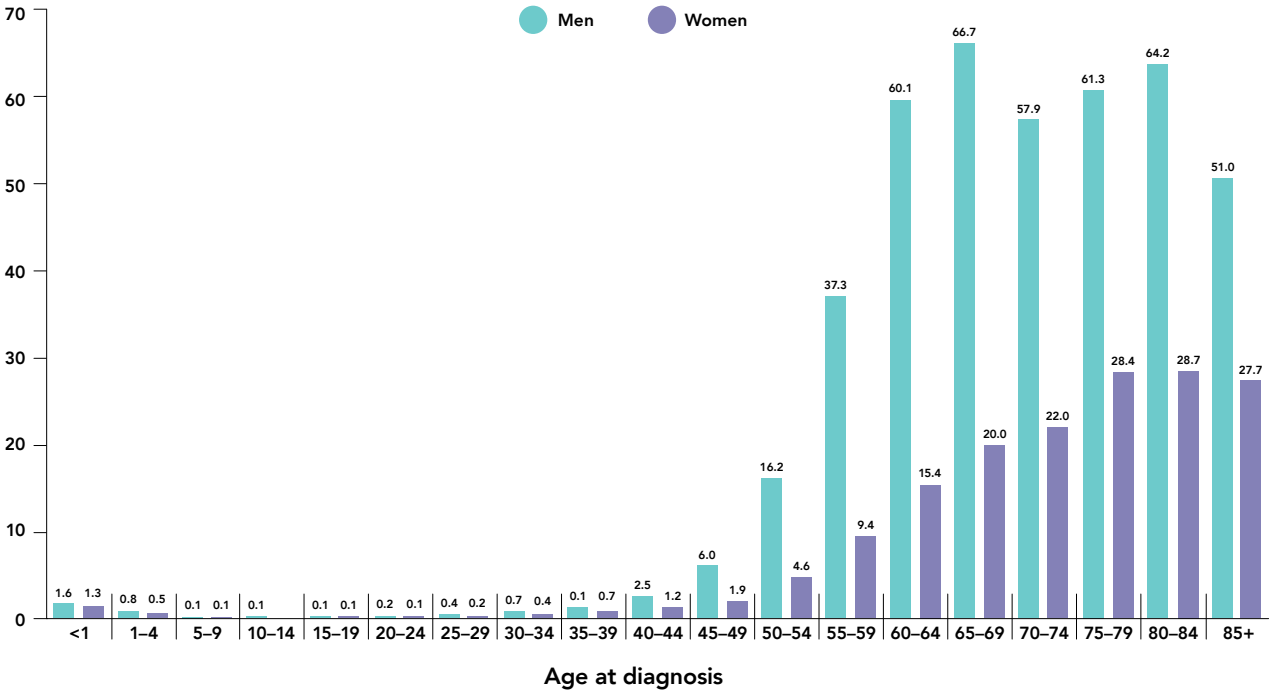
6.5

Global incidence per 100,000

Sources: *Global Burden Disease study 2019 (age-standardized data) [1] and the National Cancer Institute SEER Report [2]*

Liver cancer is the sixth most common cancer in the world for men and women combined and accounts for 4.7% of all incident cancer cases globally [3]. Incidence rates vary across countries, from a high of 85.6 per 100,000 persons in Mongolia to a low of 1.2 per 100,000 persons in Sri Lanka [3]. Liver cancer incidence increases with age [4]. In the U.S., 88% of new diagnoses occur among those aged 55 years and older; incidence rates are nearly three-times higher among men (13.8 per 100,000) than women (4.9 per 100,000) (see Figure 1) [2].

Figure 1. Age-specific incidence of liver cancer among men and women in the U.S. per 100,000



Source: *SEER 21 Areas, Liver and Intrahepatic Bile Duct SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [2]*

According to the World Cancer Research Fund (WCRF), alcohol consumption is a risk factor for liver cancer [5]. In addition, several other risk factors are associated with liver cancer risk, some of which may mediate or modify the relationship between alcohol consumption and liver cancer risk (see Table 1).

Table 1. Common risk factors for liver cancers*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption Body mass index Caffeine Chronic viral hepatitis B and C Cirrhosis Dietary aflatoxins (toxins produced by fungi) Oral contraceptives Smoking	Age Genetics Inherited metabolic diseases Race Sex
Type 2 Diabetes	

Source: *American Cancer Society [6] and The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018 [4]*

**Items are listed alphabetically and not according to importance or magnitude of risk.*

The importance (that is, magnitude or prevalence) of any given risk factor relative to other risk factors may differ by population due to environmental, socio-economic, behavioral, or genetic differences.

BIOLOGICAL MECHANISMS OF LIVER CANCER

Researchers are continuing to explore several plausible biological mechanisms that explain the potential role of alcohol as a risk factor for liver cancer [4], and some of these include:

Acetaldehyde

Alcohol (ethanol) is primarily metabolized in the liver by two important families of enzymes: *alcohol dehydrogenase* (ADH) and *acetaldehyde dehydrogenase* (ALDH), as well as the enzyme CYP2E1 to a lesser extent. Alcohol is converted to *acetaldehyde* by ADH, which is then converted to acetate by ALDH [7, 8]. Several studies have shown that acetaldehyde is a *carcinogen* and may increase DNA damage to the liver by interfering with DNA repair, or promoting cell growth, or both [8, 9]. According to some studies, acetaldehyde may be a co-carcinogen (an agent that promotes but does not initiate cell growth) because DNA damage is an early stage in carcinogenesis [10].

- The microsomal ethanol oxidizing system, another metabolic pathway, accounts for a small percentage of ethanol metabolism and is significantly induced at chronic heavy levels of consumption (after a single week of consuming 40g/day or more) [8, 11]. The main component of this system is the enzyme *CYP2E1*, which breaks down alcohol into acetaldehyde and results in increased production of both acetaldehyde and *reactive oxygen species (ROS)*, which can lead to DNA damage [12, 13].

- Clinical research has demonstrated that individuals with certain gene mutations in ADH, ALDH, and CYP2E1 accumulate higher levels of acetaldehyde in saliva and in the liver and other tissues during alcohol metabolism than individuals without these mutations [14].

- Epidemiologic research has found that individuals who carry these genetic mutations have an increased risk of certain cancers [9, 12, 13, 15-18].

Nutritional deficiencies

The role of alcohol in liver cancer risk may also be related to the effect of alcohol on dietary intake, or on malabsorption, or utilization of dietary nutrients [19]. The inability to support these processes may independently and jointly increase susceptibility for cancer growth [9, 20].

- Heavy alcohol consumption may be associated with certain nutrient deficiencies (such as vitamins A, B9 (folate), C, and E, glutathione and zinc) [14, 21-23] and other nutrients that support the processes of repairing DNA damage and neutralizing ROS [24].

Tissue integrity

Alcohol may act as a solvent by changing the proteins involved in maintaining tissue integrity, which could lead to increased invasiveness of carcinogens such as tobacco or nitrosamines (compounds formed by nitrates and nitrites) into liver and other tissues [23, 25, 26].

- Heavy consumption may also increase the permeability of molecules, which increases the production of pro-inflammatory substances that interfere with DNA repair [21, 27].

Cirrhosis

Another important mechanism is related to the effect of ROS on increased *oxidative stress* and cirrhosis [13].

- Increased production of ROS due to iron overload and enzymatic activity such as CYP2E1 induction results in alcohol-induced oxidative stress in liver cells and subsequent liver injury [13, 21, 28, 29]. This may increase cell growth and repair [13, 21, 28, 29], potentially leading to fibrosis (excess repair) and the replacement of damaged liver cells with scar tissue resulting in cirrhosis [28, 29], a risk factor for liver cancer [7, 13, 30].

Interaction with hepatitis infection

The process by which liver cancer develops may also be related to the joint effect of heavy alcohol consumption and hepatitis infection [9, 27, 29, 31, 32].

- As described by Dolganiuc in a 2015 review, alcohol-exposed liver cells are prone to several changes that make the cells more susceptible to hepatitis B and C infection [27].

- Prevalence of hepatitis C is three to 30 times higher among patients with alcoholism, compared with the general population, as described by Singal and Anand in their 2007 review [31].

- Chronic heavy drinking may compromise the body's immune response and aggravate damage from hepatitis infection, resulting in a faster progression of disease [29, 32].

- Patients with both hepatitis C infection and alcohol abuse develop more severe fibrosis and higher rates of cirrhosis and liver cancer compared with nondrinkers [31] and experience faster progression from cirrhosis to cancer, as described in a 2002 review by Stickel and colleagues [32].

Summary of recent liver cancer research

This chapter of the *IARD Health Review: Drinking and Cancer* includes studies that examine the association between alcohol consumption and risk of being diagnosed with liver cancer.

For this chapter, the following criteria were used to select studies following a literature search using the IARD Research Database and PubMed.

Study designs: meta-analyses (a type of study that pools data from multiple studies), pooled cohort studies, pooled case-control studies, prospective cohort studies, and case-control studies; systematic reviews were excluded from the summary of results section because of the absence of new or pooled risk estimates
Publication dates: from 2007 through June 2019
Outcomes: liver cancer incidence; combined incidence and mortality (for meta-analyses only)
Exposure: at least three quantified levels of alcohol consumption; or at least two quantified levels of alcohol consumption if a study examined a limited range of alcohol consumption (for example, up to one drink per day only)
Sample size: 1,000+

When multiple analyses were presented in a study, we included results from models that were fully adjusted, used a lifetime alcohol consumption assessment (versus a single assessment), and separated former drinkers from lifetime abstainers. Results of meta-analyses and pooled cohort studies are presented first, followed by results of individual studies to allow comparison of risk estimates across both types of study designs.

Note: The time frame of alcohol exposure assessment varies from study to study (for example, researchers could assess a study participant's lifetime, recent past, or current consumption), making it difficult to determine whether risk estimates reflect recent drinking patterns or the accumulation of drinking patterns over a lifetime. *This topic is discussed in the chapter "**Discussion of conceptual and methodological issues**".*

LIVER CANCER

In this section we present results of studies reporting relative risk estimates for liver cancer. *(Please see the Glossary on page 12 for a definition of relative risk (RR) and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)*

According to the WCRF, there is "convincing" evidence of an increased risk of liver cancer associated with alcohol consumption above 45g/day [4]. *(Please see **Background chapter** for an explanation on the WCRF definitions of strength of evidence.)*

Meta-analyses and pooled prospective cohort studies
Six meta-analyses or pooled prospective cohort studies met the inclusion criteria for this review (see Table 2).

- For men and women combined, three meta-analyses reported an increased risk of liver cancer starting at ≥37.5g/day [33], ≥50g/day [34], or ≥98g/day [35], compared to non-drinkers.
- Two meta-analyses found no association between any level of alcohol consumption and liver cancer [36, 37].
- One pooled cohort study, conducted by Petrick and colleagues, reported a reduced risk associated with consumption less than 42g/day, compared to nondrinkers [35].
- None of the six meta-analyses or pooled prospective cohorts reported an increased risk of liver cancer associated with light or moderate drinking level categories, including two studies that exclusively examined drinking levels up to 12.5g/day [36] and up to 30g/day [37].
- The studies that reported results separately for each sex found similar results as those that combined men and women in their analysis [33-38].

Table 2. Relative risk (RR) estimates for alcohol consumption associated with liver cancer from meta-analyses and pooled cohort studies*

Study reference	Nondrinker	Occasional drinker	Average alcohol grams per day
Combined sexes			
Bagnardi et al., 2013	ref.†		ns
Choi et al., 2018	ref.†		ns ns
Turati et al., 2014	ref.†		ns 1.16
Bagnardi et al., 2015	ref.†		ns ns 2.07
Petrick et al., 2018	ref.†		0.77 0.57 0.71 ns ns 1.87
Men			
Bagnardi et al., 2013	ref.†		ns
Turati et al., 2014	ref.†		ns ns
Bagnardi et al., 2015	ref.†		ns ns 1.59
Shimazu et al., 2012	1.88‡	ref.	ns ns ns 2.18 ns
Petrick et al., 2018	ref.†		0.74 ns 1.45
Women			
Bagnardi et al., 2013	ref.†		ns
Turati et al., 2014	ref.†		ns
Choi et al., 2018	ref.†		ns ns
Shimazu et al., 2012	ns‡	ref.	ns 3.6
Bagnardi et al., 2015	ref.†		ns ns 3.89
Petrick et al., 2018	ref.†		0.7 ns 2.48

*All meta-analysis or pooled cohort study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
† Nondrinker (may include former or occasional drinkers or both)
‡ Nondrinker (includes former drinkers)

Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Purple shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk, compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- "ns" indicates that risk for that drinking level was not statistically different from risk for the reference group.
- Dashed line indicates that upper and lower limits of two drinking categories overlapped (Table 2 only).
- Under the "Study Designs" column, "P" indicates prospective studies and "C-C" indicates case-control studies (Table 3).

Results from these meta-analyses or pooled prospective cohorts indicate that the magnitude of the risk estimates measuring the association between alcohol consumption and liver cancer appears to grow larger as alcohol consumption increases. Compared to nondrinkers, the lowest categories of average alcohol consumption as defined by these studies (up to 7g/day) are associated with a 23% decrease in risk (this is equivalent to a relative risk of 0.77, which would be described as "weak" [39] in magnitude), while the highest levels of consumption (more than 98g/day) are associated with an 87% increase in risk (this is equivalent to a relative risk of 1.87 which would be described as "moderate" in magnitude [39]). See, for example, Schoenbach and Rosamond (2000) [39] and the Glossary for additional resources on magnitude of risk.

Individual prospective cohort and case-control studies

Eleven individual prospective cohort or case-control studies met the review criteria for examining the association between alcohol consumption and liver cancer, including two studies that reported results for men only [40] or women only [41] (see Table 3).

- Most (seven) of the nine studies that reported results for men and women combined found an increased risk of liver cancer associated with drinking categories starting at ≥20g/day [42], at various points between 40 and 50 g/day [43-47], and ≥50g/day [48].

- One study found no association between any alcohol consumption category and liver cancer risk, compared to nondrinkers [49].

- One case-control study reported a reduced risk associated with alcohol consumption less than 40g/day, compared to up to 10g/day, for men and women combined and no increase in risk associated with other drinking categories. The association with reduced risk of liver cancer was found among men, but not women, when results were stratified by sex [50].

- Some of the studies included in Table 3 defined alcohol consumption categories spanning wide ranges (see for example Koh et al.'s (2011) [42] category of >0 to <50g/day or Hassan et al.'s (2009) [46] ≥20g/day category) and should be interpreted with caution. Such wide ranges make it difficult to precisely determine where a change in risk begins.

Table 3. Relative risk estimates for alcohol consumption associated with liver cancer from individual prospective cohort and case-control studies*

Study reference	Study design	Former drinker	Non-drinker	Average alcohol grams per day
Combined sexes				
Klatsky et al., 2015	P	1.9	ref.‡	ns (0.5–99+)
Koh et al., 2011	C-C		ref.†	ns (0.5–19); 2.24 (20–99+)
Yi et al., 2018	P		ref.†	ns (0.5–39); 1.37 (40–79); 1.75 (80–99+)
Ohishi et al., 2008	C-C		ref.†	ns (0.5–39); 4.36 (40–99+)
Kunzmann et al., 2018	P		ref.‡	ns (0.5–4); ns (5–9); ns (10–14); ns (15–19); ns (20–34); ns (35–39); 3.53 (40–99+)
Persson et al., 2013	P		1.71	ref. (0.5–19); ns (20–39); 1.92 (40–99+)
Hassan et al., 2009	C-C		ref.†	ns (0.5–44); 3.2 (45–99+)
Zhao et al., 2017	C-C		ref.†	ns (0.5–49); 1.50 (50–99+)
Trichopoulos et al., 2011	C-C		ref.†	ref. (0.5–24); 0.48 (25–39); ns (40–99+)
Men				
Benedetti et al., 2009	C-C		ref.†	ns (0.5–24); ns (25–39); 4.3 (40–94); 4.65 (95–99+)
Trichopoulos et al., 2011	C-C		ref.†	ref. (0.5–24); 0.41 (25–39); ns (40–99+)
Women				
Trichopoulos et al., 2011	C-C		ref.†	ns (0.5–24); ns (25–99+)
Allen et al., 2009	P		1.41	ref. (0.5–4); ns (5–9); ns (10–39); 1.70 (40–99+)

* All individual prospective cohort or case-control study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
† Nondrinker (may include former or occasional drinkers or both)
‡ Nondrinker (lifetime abstainers)

JOINT EFFECT OF ALCOHOL AND HEPATITIS OR OBESITY

The WCRF and other organizations, such as the American Cancer Society, have identified obesity and hepatitis as risk factors for liver cancer. Several studies that investigate the relationship between alcohol consumption and liver cancer included in this review adjust for obesity [41, 42, 50] or hepatitis B or C infection [29, 33, 47] in their multivariate analyses. Only a few studies have examined the joint effect of alcohol and obesity or hepatitis on the risk of liver cancer (see Table 4). Although a full analysis of studies examining the joint effect and magnitude of risk was outside the scope of this review, some of the results reported include:

- One study reported a "strong" joint effect of hepatitis infection and alcohol use on the risk of liver cancer [RR = 25.4; 95%CI (9.6–41.2)]. As individual risk factors, this study reported relative risks of 2.15 associated with alcohol consumption and 13.7 associated with hepatitis [29]. *(Please see also the Biological mechanisms section for a discussion of the effect of heavy alcohol consumption and hepatitis infection on liver cancer risk.)*

- One of two studies reported a "strong" joint effect of obesity and alcohol use on the risk of liver cancer [RR = 3.82; 95%CI (1.94–7.52)] [51]. As individual risk factors, both studies reported an increased risk of 1.68 and 1.46 associated with alcohol consumption, but no association with obesity [29, 51].

(Please see the Glossary on page 12 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)

Table 4. Joint effect analyses of alcohol consumption and hepatitis infection and obesity

Risk factor	Study reference	Alcohol use only	Risk factor only	Joint effect
Hepatitis	Chuang et al., 2015	2.15	13.68	25.4
Obesity (>30kg/m²)	Chuang et al., 2015	1.68	ns	ns
Obesity (>30kg/m²)	Loomba et al., 2013	1.46	ns	3.82

FUTURE RESEARCH

Further research is needed to understand the joint effect of alcohol and obesity, or hepatitis, or both on the risk of liver cancer. In addition, more research is needed to understand how a cluster of modifiable risk factors can impact liver cancer risk. For example, Luu et al. (2021), found that adhering to "healthier" behaviors (having a BMI <23kg/m2, never having smoked, not drinking ≥15 drinks/week for men and ≥8 drinks/week for women, having a Mediterranean diet score within the fourth quartile, and regularly getting six to eight hours of sleep) compared to a few or no healthy behaviors was associated with an 87% reduced risk for liver cancer [52].

This review did not evaluate risk of bias or overall study quality as this was out of the scope of the review, and instead left interpretation of study quality and findings to the reader. However, future systematic reviews could contribute to a greater understanding of the relationship between alcohol consumption and liver cancer risk by assessing study quality. Such an exercise may help readers interpret individual study results in the context of other published research and assess the overall quality of evidence from the existing body of research.

Glossary

- **Acetaldehyde** is a product of the metabolism of ethanol, which begins in the mouth and digestive tract but takes place primarily in the liver. Acetaldehyde is a carcinogen and can damage DNA and increase cell proliferation.

- **Acetaldehyde dehydrogenase (ADH)** is an enzyme that breaks down acetaldehyde into smaller molecules such as acetate, which are further broken down into carbon dioxide and water molecules.

- **Alcohol dehydrogenase (ALDH)** is an enzyme involved in metabolism of ethanol which breaks down alcohol into acetaldehyde molecules.

- **Carcinogen** is any agent or substance that can cause cancer.

- **CYP2E1** is a protein that is induced by ethanol, diabetes, and starvation and metabolizes ethanol and other endogenous and exogenous substances.

- **Oxidative stress** is an imbalance of free radicals and the body's inability to neutralize them. It is the precursor to oxidative damage, which results in cell damage.

- **Reactive oxygen species (ROS)** are a group of highly-reactive molecules containing oxygen that, at low levels, are an important part of metabolism and inflammatory response. An excess of reactive oxygen species can damage cellular proteins, lipids, or DNA, and has been linked with chronic diseases, such as cancer, diabetes, and cardiovascular disease.

- **Relative risk (RR)** is a measure that compares the probability of a given outcome (for example, breast cancer) among a group of people with a given risk factor (for example, alcohol consumption) with the probability of that outcome among a group of people without the risk factor (for example, nondrinkers). A risk estimate above one (RR>1) indicates an increased risk of the outcome associated with the exposure and a risk estimate below one (RR<1) indicates a reduced risk of the outcome associated with the exposure. If the risk estimate is equivalent to one (RR=1) then there is no association between the outcome and the exposure.

    - The magnitude of relative risk describes the strength of the association between the exposure and outcome of interest, or the relative risk estimate. There are several terms used to describe or interpret different relative risk estimates. Some commonly used descriptors are weak, small, moderate, medium, strong, or large [39, 53-56], however, the risk estimates associated with each term may differ or overlap (see Figures 2A–C). For example, according to Schoenbach and Rosamond 2000 [39], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon n.d., states that moderate to strong risk is equivalent to a relative risk greater than 1.5 [53, 54].

Figure 2A. Descriptions of magnitude of risk

1.0	No association (null value)
1.1–1.3	Weak
1.4–1.7	Modest
1.8–3.0	Moderate
3–8	Strong
For inverse associations (risk ratio is less than 1.0), take the reciprocal and look in above table, for example, the reciprocal of 0.5 is 2.0, which corresponds to a "moderate" association.	

Source: *Schoenbach and Rosamond 2000 [39]*

Figure 2B. Descriptions of magnitude of risk

	Trivial	Small	Moderate	Large	Very Large	Nearly perfect	Perfect
Correlation	0.0	0.1	0.3	0.5	0.7	0.9	1
Diff. in means	0.0	0.2	0.6	1.2	2.0	4.0	infinite
Freq. diff.	0	10	30	50	70	90	100
Rel. risk	1.0	1.2	1.9	3.0	5.7	19	infinite
Odds ratio	1.0	1.5	3.5	9.0	32	360	infinite

Source: *Hopkins 2002 [55]*

Figure 2C. Descriptions of magnitude of risk

Effect size: Interpretation suggestions for social science data

Type of effect size estimate	Included indices	RMPE	Moderate effect	Strong effect
Group difference	d, Δ, g	0.41	1.15	2.70
Strength of association	r, R, ϕ, p, partial r, β, r_{pb}, tau	0.2	0.5	0.8
Squared association indices	r^2, R^2, η^2, adjusted R^2, ω^2 ε^2	0.04	0.25	0.64
Risk estimates	RR, OR	2.0*	3.0	4.0

Note. RMPE = recommended minimum effect size representing a "practically" significant effect for social science data. For effects with highly valid dependent measures (e.g., death) and using rigorous controlled outcomes trials, lower values may have practical value. RR = relative risk; OR = odds ratio.

*These are not anchored to *r* and should be interpreted with caution

Source: *Ferguson 2016 [56]*

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