2010 Dietary Guidelines Advisory Committee:

Systematic Reviews of the Alcohol Subcommittee

USDA's Nutrition Evidence Library supported the 2010 Dietary Guidelines Advisory Committee as it conducted systematic reviews on diet and health. This document includes archives from www.NEL.gov of the complete evidence portfolios for all NEL systematic reviews conducted by the Alcohol Subcommittee. The *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010* summarizes these systematic review findings and provides interpretations and implications related to these reviews.

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ACKNOWLEDGEMENTS

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CHAPTER 1. OVERVIEW AND NEEDS FOR FUTURE RESEARCH

OVERVIEW

The 2010 Dietary Guidelines Advisory Committee (DGAC) recognized that alcohol affects many health outcomes, due both to the acute effects of alcohol in the bloodstream and to the chronic effects of regular alcohol consumption. Many associations with disease are well known and well documented. Therefore, the sub-committee (SC) examined a few specific questions where a new evidence review could modify conclusions from previous DGAC Reports. In addition, the SC chose those specific health outcomes that would be most influenced by moderate alcohol consumption of up to one drink a day for women and two drinks a day for men, where changes in recommendations would have the broadest impact.

Although the 2005 DGAC summary of the health effects of alcohol consumption were based on an evidence-based review, in many instances these reviews included a substantial number of cross-sectional studies. Since 2005, a large number of prospective studies of alcohol and chronic disease have been published. Thus, to refine the evidence search for each question, the DGAC limited the reviews to studies with greater methodological rigor and only conducted systematic reviews of observational prospective studies and randomized control trials. The exception was the question related to alcohol intake and unintentional injury because cross-sectional or case-control studies are of equal or even better validity. For the question related to alcohol consumption and coronary heart disease (CHD), only systematic reviews and meta-analyses were used, since the Nutrition Evidence Library (NEL) literature search found several recent studies.

NEEDS FOR FUTURE RESEARCH

1. Conduct a comprehensive set of studies in a controlled setting to assess the influences that alcohol may have on factors that affect energy intake and expenditure.
    - **Rationale:** The effects of energy from alcohol on body weight are complex and not completely understood. These studies will clarify whether the lack of association between moderate alcohol consumption and weight gain is due to biological compensation or changes in other behaviors (e.g., diet or physical activity).
2. Conduct research to enhance the currently limited data on changes in markers of bone health in metabolic studies of alcohol consumption.
    - **Rationale:** In large epidemiological studies, a better classification of drinking pattern and a better documentation of the traumatic or non-traumatic cause of fracture are needed, but equally important is the need to study prospectively changes in alcohol consumption and changes in intermediate markers of bone structure and integrity.
3. Focus further research to avoid unintentional injury on effective communication policies that expand current messages on drinking and driving to inform individuals of other unintentional risks associated with alcohol consumption.
    - **Rationale:** The documented benefit of drunk driving campaigns is a public

health success, yet alcohol-related injury is still substantial in other areas and should be addressed with the same vigilance and governmental support.

CHAPTER 2. HEALTH-RELATED OUTCOMES – BONE HEALTH

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL INTAKE AND BONE HEALTH?

Conclusion statement

Moderate evidence suggests a J-shaped association between alcohol consumption and incidence of hip fracture; there was a suggestion that heavy or binge drinking was detrimental to bone health.

Grade

Moderate

Evidence summary paragraphs

Berg et al, 2008 (positive quality) performed a systematic review and meta-analysis involving 33 studies that examined the association between ethanol intake and hip fracture and bone density using a quantitative method and examined qualitatively the association between ethanol consumption and non-hip fracture, bone density loss over time, bone response to estrogen replacement and bone remodeling. MEDLINE, Current Contents, PsychINFO and Cochrane Libraries were searched for studies published before May 14, 2007. Quality of each study was assessed using the internal validity criteria of the US Preventive Services Task Force. Studies were included if they used experimental, cohort or case-control designs; included adults both exposed and not exposed to alcohol; and reported on at least one outcome. Studies were excluded if alcohol consumption and bone density were measured once at the same point in time, and if they were rated as being “poor” quality. Most studies were conducted in white, European or American adults. The results were commonly adjusted for age, body mass index and smoking, but few studies adjusted for dietary calcium, physical activity or estrogen exposure. Meta-analysis involving thirteen studies (eight prospective cohorts and five case-control) with a fair quality rating involving men and women over 20 years of age revealed a J-shaped relationship between alcohol consumption and hip fracture. Compared with abstainers, a lower risk of hip fracture was found among persons consuming up to 0.5 drinks per day (RR=0.84 [95% CI, 0.70-1.01]) and persons consuming from more than 0.5-1.0 drinks per day (RR=0.80 [95% CI, 0.71-0.91]). Those consuming from more than one to two drinks per day did not differ from abstainers (RR=0.91 [95% CI, 0.76-1.09]) and persons consuming more than two drinks per day had a higher risk (RR=1.39, [95%CI 1.08-1.79]). Four cohort studies rated fair quality, involving men and women over 50 years of age followed for 12 to 20 years evaluated the association between alcohol intake and femoral neck bone mineral density. A linear relationship existed between femoral neck bone density and alcohol consumption. Each drink per day was associated with an increase in femoral bone neck density of 0.045g per cm^2 (95% CI, 0.008-0.082g per cm^2, P=0.01). A significant linear relationship was also found at the vertebral spine. Berg indicated that since studies often combined moderate and heavier drinkers in a single category; they could not assess relative associations between alcohol consumption and bone density in moderate compared with heavy drinkers. Even though there is a positive effect of alcohol consumption on hip fracture and bone density, the exact range of beneficial alcohol consumption cannot be

determined.

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Significant Outcomes
Berg et al 2008 Study Design: Cohort Study Class: B Rating: Positive Quality	33 studies (experimental, cohort or case-control designs) among white, European or American adults published before 5/14/07. Studies examined: Quantitatively, the association between ethanol intake and hip fracture and bone density. Qualitatively, the association between ethanol consumption and non-hip fracture, bone density loss over time, bone response to estrogen replacement and bone remodeling.	Meta-analysis involving 13 studies (eight prospective cohorts and five case-control) with a fair quality rating involving men and women >20 years of age showed a J-shaped relationship between alcohol consumption and hip fracture. Compared with abstainers, a ↓ risk of hip fracture was found among persons consuming up to 0.5 drinks per day (RR=0.84 [95% CI, 0.70-1.01]) and persons consuming from >0.5-1.0 drinks per day (RR=0.80 [95% CI, 0.71-0.91]). Those consuming >one to two drinks per day did not differ from abstainers (RR=0.91 [95% CI, 0.76-1.09]) and persons consuming >two drinks per day had a ↑ risk (RR=1.39, [95%CI 1.08-1.79]). Four cohort studies rated fair quality, involving men and women >50 years of age followed for 12 to 20 years, found a linear relationship between femoral neck bone density and alcohol consumption.

Research recommendations

1. Conduct research to enhance the currently limited data on changes in markers of bone health in metabolic studies of alcohol consumption.
    - Rationale: In large epidemiological studies, a better classification of drinking pattern and a better documentation of the traumatic or non-traumatic cause of fracture are needed, but equally important is the need to study prospectively, changes in alcohol consumption and changes in intermediate markers of bone structure and integrity.

Search plan and results

Inclusion criteria

- January 1, 1995 through June 9, 2009
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- Dropout rate: Less than 20%; preference for smaller dropout rates
- Ages: Adults: Adults of legal drinking age (21 and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, Hypertension, Type 2 DM, Osteoporosis, Osteopenia and Obesity) and those with breast cancer, colon cancer and/or prostate cancer.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (exceptions noted)
- Hospitalized patients
- Malnourished and third-world populations or disease incidence not relative to US population, e.g. malaria
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)
- Cross-sectional study design.

Search terms and electronic databases used

- PubMed

  ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND ("Bone Density"[Mesh] OR "Fractures, Bone"[Mesh] OR "Bone Diseases"[Mesh])

Date searched: 06/09/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 132
- Total articles identified to review from electronic databases: 21
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 0
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 1
- Number of Articles Reviewed but Excluded: 20

Included articles (References)

1. Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA Jr, Malik R, Arnsten JH. Association between alcohol consumption and both osteoporotic

fracture and bone density. *Am J Med.* 2008 May; 121 (5): 406-418. Review. PubMed PMID: 18456037; PubMed Central PMCID: PMC2692368.

Excluded articles

Excluded Citation	Reason for Exclusion
Cawthon PM, Harrison SL, Barrett-Connor E, Fink HA, Cauley JA, Lewis CE, Orwoll ES, Cummings SR. Alcohol intake and its relationship with bone mineral density, falls, and fracture risk in older men. J Am Geriatr Soc. 2006 Nov;54(11):1649-57. PubMed PMID: 17087690.	Cross-sectional study; meets exclusion criteria.
Felson DT, Zhang Y, Hannan MT, Kannel WB, Kiel DP. Alcohol intake and bone mineral density in elderly men and women. The Framingham Study. Am J Epidemiol. 1995 Sep 1;142(5):485-92. PubMed PMID: 7677127.	Primary study included in Berg KM 2008 review.
Feskanich D, Korrick SA, Greenspan SL, Rosen HN, Colditz GA. Moderate alcohol consumption and bone density among postmenopausal women. J Womens Health. 1999 Jan-Feb;8(1):65-73. PubMed PMID: 10094083.	Primary study included in Berg KM 2008 review.
Galindo-Moreno P, Fauri M, Avila-Ortiz G, Fernández-Barbero JE, Cabrera-León A, Sánchez-Fernández E. Influence of alcohol and tobacco habits on peri-implant marginal bone loss: a prospective study. Clin Oral Implants Res. 2005 Oct;16(5):579-86. PubMed PMID: 16164465.	Dental; does not address health outcomes in inclusion criteria
Ganry O, Baudoin C, Fardellone P. Effect of alcohol intake on bone mineral density in elderly women: The EPIDOS Study. Epidémiologie de l'Ostéoporose. Am J Epidemiol. 2000 Apr 15;151(8):773-80. PubMed PMID: 10965974.	Cross-sectional study; meets exclusion criteria.
Gonzalez-Calvin JL, Garcia-Sanchez A, Mundi JL. Effect of alcohol consumption on adult bone mineral density and bone turnover markers. Alcohol Clin Exp Res. 1999 Aug;23(8):1416-7. Erratum in: Alcohol Clin Exp Res 2000 Oct;24(10):1592. Alcohol Clin Exp Res 2001 Dec;25(12):1804. Gonzales-Calvin, JL [corrected to Gonzalez-Calvin, JL]. PubMed PMID: 10470986.	Letter to the Editor

Grainge MJ, Coupland CA, Cliffe SJ, Chilvers CE, Hosking DJ. Cigarette smoking, alcohol and caffeine consumption, and bone mineral density in postmenopausal women. The Nottingham EPIC Study Group. The Nottingham EPIC Study Group. Osteoporos Int. 1998;8(4):355-63. PubMed PMID: 10024906.	Cross-sectional study; meets exclusion criteria.
Høidrup S, Grønbaek M, Gottschau A, Lauritzen JB, Schroll M. Alcohol intake, beverage preference, and risk of hip fracture in men and women. Copenhagen Centre for Prospective Population Studies. Copenhagen Centre for Prospective Population Studies. Am J Epidemiol. 1999 Jun 1;149(11):993-1001. PubMed PMID: 10355374.	Primary study included in Berg KM 2008 review.
Jugdaohsingh R, O'Connell MA, Sripanyakorn S, Powell JJ. Moderate alcohol consumption and increased bone mineral density: potential ethanol and non-ethanol mechanisms. Proc Nutr Soc. 2006 Aug;65(3):291-310. Review. PubMed PMID: 16923313.	Primary study included in Berg KM 2008 review.
Ilich JZ, Brownbill RA, Tamborini L, Crncevic-Orlic Z. To drink or not to drink: how are alcohol, caffeine and past smoking related to bone mineral density in elderly women? J Am Coll Nutr. 2002 Dec;21(6):536-44. PubMed PMID: 12480799.	Cross-sectional study; meets exclusion criteria.
Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A. Alcohol intake as a risk factor for fracture. Osteoporos Int. 2005 Jul;16(7):737-42. Epub 2004 Sep 29. PubMed PMID: 15455194.	Primary study included in Berg KM 2008 review.
Kaukonen JP, Nurmi-Lüthje I, Lüthje P, Naboulsi H, Tanninen S, Kataja M, Kallio ML, Leppilampi M. Acute alcohol use among patients with acute hip fractures: a descriptive incidence study in southeastern Finland. Alcohol Alcohol. 2006 May-Jun;41(3):345-8. Epub 2006 Mar 1. PubMed PMID: 16510531.	This is a descriptive incidence study that only examines 24h alcohol consumption prior to injury. It does not address the effect of alcohol on bone health.
May H, Murphy S, Khaw KT. Alcohol consumption and bone mineral density in older men. Gerontology. 1995;41(3):152-8. PubMed PMID: 7601367.	Cross-sectional study; meets exclusion criteria.

Mukamal KJ, Robbins JA, Cauley JA, Kern LM, Siscovick DS. Alcohol consumption, bone density, and hip fracture among older adults: the cardiovascular health study. Osteoporos Int. 2007 May;18(5):593-602. Epub 2007 Feb 21. PubMed PMID: 17318666.	Primary study included in Berg KM 2008 review.
Perry HM 3rd, Horowitz M, Fleming S, Kaiser FE, Patrick P, Morley JE, Cushman W, Bingham S, Perry HM Jr. Effect of recent alcohol intake on parathyroid hormone and mineral metabolism in men. Alcohol Clin Exp Res. 1998 Sep;22(6):1369-75. PubMed PMID: 9756055.	No data on any measure of bone density or bone health – only provides indirect measures, i.e. parathyroid hormone and calcium levels.
Sampson HW. Alcohol and other factors affecting osteoporosis risk in women. Alcohol Res Health. 2002;26(4):292-8. PubMed PMID: 12875040.	Primary study included in Berg KM 2008 review.
Tucker KL, Jugdaohsingh R, Powell JJ, Qiao N, Hannan MT, Sripanyakorn S, Cupples LA, Kiel DP. Effects of beer, wine, and liquor intakes on bone mineral density in older men and women. Am J Clin Nutr. 2009 Apr;89(4):1188-96. Epub 2009 Feb 25. PubMed PMID: 19244365; PubMed Central PMCID: PMC2667462.	Cross-sectional study; meets exclusion criteria.
Williams FM, Cherkas LF, Spector TD, MacGregor AJ. The effect of moderate alcohol consumption on bone mineral density: a study of female twins. Ann Rheum Dis. 2005 Feb;64(2):309-10. Epub 2004 Jul 1. PubMed PMID: 15231511; PubMed Central PMCID: PMC1755353.	Cross-sectional study; meets exclusion criteria.
Wosje KS, Kalkwarf HJ. Bone density in relation to alcohol intake among men and women in the United States. Osteoporos Int. 2007 Mar;18(3):391-400. Epub 2006 Nov 8. PubMed PMID: 17091218.	Cross-sectional study; meets exclusion criteria.
Zhang N, Yin Y, Chen WS, Xu SJ. Moderate alcohol consumption may decrease risk of intervertebral disc degeneration. Med Hypotheses. 2008 Oct;71(4):501-4. Epub 2008 Jul 15. PubMed PMID: 18632213.	Study not published in a peer review journal.

CHAPTER 3. HEALTH-RELATED OUTCOMES – ALCOHOL INTAKE AND COGNITIVE DECLINE

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL INTAKE AND COGNITIVE DECLINE WITH AGE?

Conclusion statement

Moderate evidence suggests that compared to non-drinkers, individuals who drink moderately have a slower cognitive decline with age. (Grade: Moderate)

Grade

Moderate

Evidence summary overview

Several of the prospective cohort studies (Bond et al, 2005; Deng et al, 2006; Stott et al, 2008; and Wright et al, 2006) found similar results that appear to indicate light to moderate drinking decreases the risk of or lessens the severity of dementia and cognitive decline, especially compared to non-drinkers. Solfrizzi et al, 2007 found no significant (NS) associations between any levels of drinking and the incidence of mild cognitive impairment in non-cognitively impaired individuals vs. abstainers.

In regards to type of alcohol, Deng et al, 2006 found light-to-moderate intake of wine and liquor were related with a reduced risk of dementia compared to non-drinkers, while light-to-moderate intake of beer was associated with a significantly higher risk of dementia than non-drinkers. Mehlig et al, 2008 found that wine was protective for dementia and the association was strongest among women who consumed wine only. Consumption of spirits at baseline was associated with slightly increased risk of dementia.

By gender, Bond et al, 2005 found NS difference in cognitive function, while Stott et al, 2008 found that cognitive function was better for female drinkers than non-drinkers for some cognitive tests. However, no statistically significant differences were found in baseline cognitive function between male drinkers and non-drinkers.

Evidence summary paragraphs

Systematic Review/Meta-Analysis

Peters et al, 2008 (positive quality), a systematic review and meta-analysis of 23 studies, evaluated the evidence for any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption. The majority of the studies were from Europe and North America and Canada. In older people, small to moderate amounts of alcohol consumption were associated with reduced incidence of dementia and Alzheimer's disease. Small amounts of alcohol may be protective against dementia (random effects model, RR=0.63, 95% CI: 0.53 to 0.75) and Alzheimer's disease (RR=0.57, 95% CI: 0.44 to 0.74) but not for vascular dementia (RR=0.82, 95% CI: 0.50 to 1.35) or cognitive decline (R=0.89, 95% CI: 0.67 to 1.17). The evidence is strongest for wine consumption, but it is not conclusive.

Primary Studies

Bond et al, 2005 (neutral quality), a prospective cohort study conducted in the US, investigated the longitudinal relationship between alcohol consumption and cognitive performance in a cohort of 1,624 Japanese American older adults. Structured interviews were conducted at baseline and follow-up every two years for an eight-year period; a questionnaire asked about current and past alcohol patterns by beverage type (beer, wine, sake or liquor), as well as frequency, quantity and number of consumption years. Current alcohol consumers scored significantly higher on the Cognitive Abilities Screening Instrument (mean rate of change of -1.22 CASI units) over the eight-year follow-up period than past consumers or abstainers (mean rate of change of -3.77 CASI units) ($P<0.05$).

Deng et al, 2006 (neutral quality), a prospective cohort study conducted in China, examined the relationship between alcohol intake and dementia and whether this association depended on age, gender, educational level or cigarette smoking. Dementia screening and diagnosis, as well as frequency and quantity of alcohol consumption, were measured at baseline and the two-year follow-up. A total of 2,632 older adults were included in the analysis. Light-to-moderate drinking was associated with a significantly lower risk of dementia compared with non-drinking, while excessive drinking was related to a higher risk of dementia. The effect of light-to-moderate drinking seemed most prominent among vascular dementia, OR=0.63 (95% CI: 0.55 to 0.72) for Alzheimer's disease, OR=0.31 (95% CI: 0.19 to 0.51) for vascular dementia and OR=0.45 (95% CI: 0.12 to 1.69) for other dementia. Light-to-moderate intake of wine and liquor were related with a reduced risk of dementia compared to non-drinkers, while light-to-moderate intake of beer was associated with a significantly higher risk of dementia than non-drinkers.

Mehlig et al, 2008 (neutral quality), the cohort Prospective Population Study of Women in Goteborg, Sweden, assessed the association between different types of alcoholic beverages and 34-year incidence of dementia. Frequency of alcohol intake was recorded and related to dementia at baseline (1968 to 1969, N=1,462) and at four other time points between 1974 and 2002. By 2002, 164 cases of dementia were diagnosed. Wine was protective for dementia (HR=0.6, 95% CI: 0.4, 0.8) in the updated model, and the association was strongest among women who consumed wine only (HR=0.3, 95% CI: 0.1, 0.8); the protective association of wine was stronger among smokers. Consumption of spirits at baseline was associated with slightly increased risk of dementia (HR=1.5, 95% CI: 1.0, 2.2).

Ngandu et al, 2007 (neutral quality), the prospective cohort Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study conducted in Finland, investigated whether midlife alcohol drinking is associated with cognitive function later on in a non-demented population of elderly persons. The average follow-up period was 21 years. A random sample of 2,000 survivors aged 65 to 79 years in 1997 were invited for re-examination in 1998. A total of 1,409 completed re-examination and 68 were excluded due to the diagnosis of dementia, leaving 1,341 subjects in the analysis. A baseline self-administered questionnaire asked for details on frequency of drinking (never, infrequently, or frequently). About 30% of the participants never drank alcohol, 40% drank it infrequently and 30% drank frequently. Participants who did not drink alcohol at mid-life had a poorer performance in episodic memory, psychomotor speed and executive function in late life compared with infrequent and frequent drinkers, after adjustment for sociodemographic and vascular factors, while late-life drinkers had

poorer psychomotor speed and executive function.

Solfrizzi et al, 2007 (positive quality), a prospective cohort study conducted in Italy, examined the impact of alcohol consumption on the incidence of mild cognitive impairment and its progression to dementia in 1,445 non-cognitively impaired participants (630 women, 815 men) aged 65 to 84 years participating in the Italian Longitudinal Study on Aging, with a 3.5-year follow-up. Food frequency (FFQ) and screening questionnaires were used to assess alcohol consumption and health status. Analysis included blood samples and the Mini-Mental State Examination. Analyses were controlled for age and gender and adjusted for education, smoking, coronary artery disease and type 2 diabetes, hypertension, stroke and total cholesterol. Results showed that persons with mild cognitive impairment who were moderate drinkers (less than one drink a day) had a lower rate of progression to dementia than non-drinkers [hazard ratio (HR) 0.15; 95% CI: 0.03 to 0.78]. Also, moderate drinkers with mild cognitive impairment who consumed less than one drink a day of wine showed significantly lower rate of progression to dementia than non-drinkers (HR 0.15; 95% CI: 0.33 to 0.77). No significant association between higher levels of drinking (one or more drink a day) and rate of progression to dementia in patients with mild cognitive impairment vs. non-drinkers. No significant associations were found between any levels of drinking and the incidence of mild cognitive impairment in non-cognitively impaired individuals vs. non-drinkers. Authors concluded that in people with mild cognitive impairment, consuming up to one drink a day of alcohol or wine may decrease the rate of progression to dementia.

Stott et al, 2008 (neutral quality), a prospective cohort study in Ireland, Netherlands and Scotland investigated whether low to moderate alcohol intake was protective against cognitive decline in older people (N=5,804; 3,000 women, 2,804 men) aged 70 to 82 years with vascular risk factors or known vascular disease randomized to pravastatin or placebo in the Prospective Study of Pravastatin in the Elderly at Risk. Alcohol intake was assessed one time at baseline and quantified in terms of usual alcohol intake in units per week for the previous month. Cognitive function was measured using the Mini-Mental State Examination (MMSE), speed of information processing (Stroop and Letter-Digit Coding tests [LDCT]) and immediate and delayed memory (Picture-Work Learning test [PWLT]) over 3.2 years. Results showed cognitive performance was better for female drinkers than non-drinkers for all cognitive tests over the 3.2-year follow-up. However, when adjusted for potential confounders, results remained statistically significant only for the LDCT ($P<0.001$) and delayed recall in the PWLT ($P=0.001$), with borderline significance for the MMSE (P5.05). No statistically significant differences were found in baseline cognitive function between male drinkers and non-drinkers. The rate of cognitive decline was similar for drinkers and non-drinkers for all cognitive tests, except for MMSE, which declined significantly less in female drinkers than non-drinkers (linear mixed model attenuated rate of decline = 0.05 MMSE units per year, $P=0.001$). The authors concluded that drinking low to moderate amounts of alcohol may delay age-associated cognitive decline in older women; however, these benefits were not evident in older men. Limitations of this study include no data on the type of alcohol consumed or lifetime alcohol consumption and the relatively short follow-up time of 3.2 years to assess cognitive decline.

Wright et al, 2006 (positive quality), a prospective cohort study conducted in the US

examined the effect of alcohol intake on cognitive performance over time in a younger, multi-ethnic, community-based sample (N=1,428; 43% of initial N) participating in the Northern Manhattan Study. The study also examined the role of the APOE-4allele. Participants were 40 or more years with mean age of 71 years, with 62% Hispanic, 19% black and 19% white. Data were collected through telephone interviews, physical and neurological examinations, review of medical records and fasting blood samples. Alcohol intake (average amount consumed in past year and during drinking lifetime) was assessed using a structured interview adapted from a food frequency questionnaire. Results showed a positive relationship between reported alcohol intake and cognition. Drinking less than one drink a week (P=0.09), between one drink weekly up to two drinks daily (P=0.001), and more than two drinks daily (P=0.003) were associated with less cognitive decline on the modified Telephone Interview for Cognitive Status compared to never drinkers. The dose-response relationship was not changed by the presence of an APOE-4allele in a sub-sample.

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Significant Outcomes
Bond GE et al 2005 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=1,624 Japanese American older adults. Duration: Eight years. Location: United States.	Current alcohol consumers (N=480) scored significantly higher (P<0.05) on the Cognitive Abilities Screening Instrument (mean rate of Δ of 1.22 CASI units) than past consumers or abstainers (N=1,144, mean rate of Δ of -3.77 CASI units).

Deng et al 2006 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=2,632 older adults. Duration: Two years. Location: China.	Light-to-moderate drinking associated with a significantly ↓ risk of dementia, compared with non-drinking, while excessive drinking related to a ↑ risk of dementia. Effect of light-to-moderate drinking seemed most prominent among vascular dementia, 0.63 (0.55 to 0.72) for Alzheimer's disease, 0.31 (0.19 to 0.51) and for vascular dementia and 0.45 (0.12 to 1.69) for other dementia. Light-to-moderate intake of wine/liquor related with ↓ risk of dementia compared to non-drinkers, while light-to-moderate intake of beer associated with significantly ↑ risk of dementia than non-drinkers.
Mehlig et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	Participants from the Prospective Population Study of Women in Goteborg, Sweden. Frequency of alcohol intake recorded and related to dementia at baseline (1968 to 1969, N=1,462), as well as in 1974 to 1975 (N=91%), 1980 to 1981 (83%), 1992 to 1993 (70%) and 2000 to 2001 (71%). Duration: 34 years. Location: Sweden.	By 2002, 164 cases of dementia were diagnosed. Wine was protective for dementia (HR=0.6; 95% CI: 0.4, 0.8) in the updated model. Association strongest among women who consumed wine only (HR=0.3, 95% CI: 0.1, 0.8); protective association of wine stronger among smokers. Consumption of spirits at baseline associated with slightly ↑ risk of dementia (HR=1.5, 95% CI: 1.0, 2.2).

Ngandu et al 2006 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	Participants in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study. Random sample of 2,000 survivors aged 65 to 79 years in 1997 were invited for re-examination in 1998. N=1,409 completed re-examination; 68 excluded due to diagnosis of dementia. Final N=1,341 subjects. Duration: Average follow-up was 21 years. Location: Finland.	~30% of participants never drank alcohol, 40% drank infrequently and 30% drank frequently. Participants who did not drink alcohol at mid-life had poorer performance in episodic memory, psychomotor speed and executive function in late life, compared with infrequent and frequent drinkers, after adjustment for sociodemographic and vascular factors, while late-life drinkers had poorer psychomotor speed and executive function.
Peters et al 2008 Study Design: Systematic Review / Meta-Analysis Class: M Rating: Positive Quality	N=23 studies evaluating evidence for any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption. Duration: Varied by study. Location: Primarily Europe and North America/Canada.	In older people, small to moderate amounts of alcohol consumption associated with ↓ incidence of dementia and Alzheimer's disease. Small amounts of alcohol may be protective against dementia (random effects model, RR=0.63, 95% CI: 0.53 to 0.75) and Alzheimer's disease (RR=0.57, 95% CI: 0.44 to 0.74), but not for vascular dementia (RR=0.82, 95% CI: 0.50 to 1.35) or cognitive decline (RR=0.89, 95% CI: 0.67 to 1.17). Evidence is strongest for wine consumption, but it is not conclusive.

Solfrizzi V, D'Introno A et al, 2007 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	N=1,445 non-cognitively impaired participants (630 women; 815 men) aged 65 to 84 years participating in Italian Longitudinal Study on Aging. Duration: 3.5-year follow-up. Location: Italy.	Patients with mild cognitive impairment who were moderate drinkers (i.e., those who consumed <one drink a day (~15g of alcohol), had a ↓ rate of progression to dementia than abstainers (HR 0.15; 95% CI: 0.03 to 0.78). Moderate drinkers with mild cognitive impairment who consumed <one drink a day of wine showed a significantly ↓ rate of progression to dementia than abstainers (HR 0.15; 95% CI: 0.03 to 0.77). NS association between ↑ levels of drinking (≥one drink a day) and rate of progression to dementia in patients with mild cognitive impairment vs. abstainers. NS associations found between any levels of drinking and incidence of mild cognitive impairment in non-cognitively impaired individuals vs. abstainers.

Stott DJ, Falconer A et al, 2008 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=5,804 (3,000 women; 2,804 men) aged 70 to 82 years with vascular risk factors or known vascular disease participating in Prospective Study of Pravastatin in the Elderly at Risk. Duration: 3.2-year follow-up. Location: Ireland, Netherlands and Scotland.	Cognitive function better for female drinkers than non-drinkers for all cognitive tests over the 3.2-year follow-up. When adjusted for potential confounders, results remained statistically significant only for LDCT (P<0.001) and delayed recall in PWLT (P=0.001), with borderline significance for MMSE (P=5.05). NS differences found in baseline cognitive function between male drinkers and non-drinkers. Rate of cognitive decline similar for drinkers and non-drinkers for all cognitive tests, except for MMSE, which ↓ significantly less in female drinkers than non-drinkers (linear mixed model attenuated rate of ↓ = 0.05 MMSE units per year, P=0.001).
Wright CB, Elkind MS et al, 2006 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	N=1,428; 43% of initial N were aged ≥40 years (mean age 71 years), participating in Northern Manhattan Study. 62% Hispanic, 19% black and 19% white. Duration: Mean follow-up 2.2 years; range 0.5 to 4.4 years. Location: United States.	Positive relationship between reported alcohol intake and cognition. Drinking <one drink a week (P=0.09), between one drink weekly, up to two drinks daily (P=0.001), and >two drinks daily (P=0.003) associated with ↓ cognitive decline, compared to never drinkers. No Δ in dose-response relationship by the presence of an APOE-4allele.

Search plan and results

Inclusion criteria

- January 1, 1995 to June 22, 2009
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes if available
- Dropout rate: Less than 20%; preference for smaller dropout rates

- Ages: Adults of legal drinking age (21 years and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, hypertension, type 2 diabetes, osteoporosis, osteopenia and obesity) and those with breast cancer, colon cancer or prostate cancer.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (exceptions noted)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)
- Cross-sectional study design.

Search terms and electronic databases used

- PubMed

  ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND "Cognition Disorders"[Mesh]

Date searched: 06/22/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 320
- Total articles identified to review from electronic databases: 37
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 7
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 8
- Number of Articles Reviewed but Excluded: 29

Included articles (References)

Reviews/Meta-analysis

1. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing.* 2008 Sep; 37(5): 505-512. Epub 2008 May 16. Review. PMID: 18487267.

Primary Research

2. Bond GE, Burr RL, McCurry SM, Rice MM, Borenstein AR, Larson EB. Alcohol and cognitive performance: A longitudinal study of older Japanese Americans. The Kame Project. *The Kame Project. Int Psychogeriatr.* 2005 Dec; 17(4): 653-668. Epub 2005 Sep 27. PMID: 16185373.
3. Deng J, Zhou DH, Li J, Wang YJ, Gao C, Chen M. A two-year follow-up study of alcohol consumption and risk of dementia. *Clin Neurol Neurosurg.* 2006 Jun; 108(4): 378-383. Epub 2005 Aug 9. PMID: 16084641.

4. Mehlig K, Skoog I, Guo X, Schütze M, Gustafson D, Waern M, Ostling S, Björkelund C, Lissner L. Alcoholic beverages and incidence of dementia: 34-year follow-up of the prospective population study of women in Goteborg. *Am J Epidemiol.* 2008 Mar 15; 167(6): 684-691. Epub 2008 Jan 24. PMID: 18222934.
5. Ngandu T, Helkala EL, Soininen H, Winblad B, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking and cognitive functions: findings from the Cardiovascular Risk Factors Aging and Dementia (CAIDE) Study. *Dement Geriatr Cogn Disord.* 2007; 23(3): 140-149. Epub 2006 Dec 14. PMID: 17170526.
6. Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Baldassarre G, Scapicchio P, Scafato E, Amodio M, Capurso A, Panza F; Italian Longitudinal Study on Aging Working Group. Alcohol consumption, mild cognitive impairment and progression to dementia. *Neurology*. 2007 May 22; 68 (21): 1,790-1,799.
7. Stott DJ, Falconer A, Kerr GD, Murray HM, Trompet S, Westendorp RG, Buckley B, de Craen AJ, Sattar N, Ford I. Does low to moderate alcohol intake protect against cognitive decline in older people? *J Am Geriatr Soc.* 2008 Dec; 56(12): 2, 217-2, 224. PMID: 19093921.
8. Wright CB, Elkind MS, Luo X, Paik MC, Sacco RL. Reported alcohol consumption and cognitive decline: The Northern Manhattan study. *Neuroepidemiology.* 2006; 27(4): 201-207. Epub 2006 Oct 16. PMID: 17047373; PMCID: PMC1756459.

Excluded articles

Excluded Citations	Reason for Exclusion
Anttila T, Helkala EL, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B, Soininen H, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ.* 2004 Sep 4;329(7465):539. Epub 2004 Aug 10. PMID: 15304383; PMCID: PMC516103.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Brust JC. A 74-year-old man with memory loss and neuropathy who enjoys alcoholic beverages. *JAMA.* 2008 Mar 5; 299(9): 1, 046-1, 054. Epub 2008 Feb 5. PMID: 18252872.	Only one subject with cognitive impairment.
Christian JC, Reed T, Carmelli D, Page WF, Norton JA Jr, Breitner JC. Self-reported alcohol intake and cognition in aging twins. *J Stud Alcohol.* 1995 Jul; 56(4): 414-416. PMID: 7674676.	Some subjects were diagnosed as alcoholics.

den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, van Duijn CM, Hofman A, Breteler MM. Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. *Am J Clin Nutr.* 2004 Oct; 80(4): 992-997. PMID: 15447910.	Cross-sectional study.
Espeland MA, Coker LH, Wallace R, Rapp SR, Resnick SM, Limacher M, Powell LH, Messina CR; Women's Health Initiative Study of Cognitive Aging. Association between alcohol intake and domain-specific cognitive function in older women. *Neuroepidemiology.* 2006; 27(1): 1-12. Epub 2006 May 24. PMID: 16717476.	Included in Peters et al, 2008 systematic review.
Espeland MA, Gu L, Masaki KH, Langer RD, Coker LH, Stefanick ML, Ockene J, Rapp SR. Association between reported alcohol intake and cognition: Results from the Women's Health Initiative Memory Study. *Am J Epidemiol.* 2005 Feb 1; 161(3): 228-238. PMID: 15671255.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Alcohol consumption and cognitive function in late life: A longitudinal community study. *Neurology.* 2005 Oct 25; 65(8): 1, 210-1, 217. PMID: 16247047.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
González-Muñoz MJ, Peña A, MeseguerI. Role of beer as a possible protective factor in preventing Alzheimer's disease. *Food Chem Toxicol.* 2008 Jan; 46(1): 49-56. Epub 2007 Jul 7. PMID: 17697731.	Cross-sectional study.
Huang W, Qiu C, Winblad B, Fratiglioni L. Alcohol consumption and incidence of dementia in a community sample aged 75 years and older. *J Clin Epidemiol*. 2002 Oct; 55(10): 959-964. PMID: 12464371.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Järvenpää T, Rinne JO, Koskenvuo M, Räihä I, Kaprio J. Binge drinking in midlife and dementia risk. *Epidemiology.* 2005 Nov; 16(6): 766-771. PMID: 16222166.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Kasahara H, Karasawa A, Ariyasu T, Thukahara T, Satou J, Ushijima S. Alcohol dementia and alcohol delirium in aged alcoholics. *Psychiatry Clin Neurosci.* 1996 Jun; 50(3): 115-123. PMID: 9201756.	Study population is alcoholics.

Leibovici D, Ritchie K, Ledésert B, Touchon J. The effects of wine and tobacco consumption on cognitive performance in the elderly: A longitudinal study of relative risk. *Int J Epidemiol.* 1999 Feb; 28(1): 77-81. PMID: 10195668.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Lemeshow S, Letenneur L, Dartigues JF, Lafont S, Orgogozo JM, Commenges D. Illustration of analysis taking into account complex survey considerations: the association between wine consumption and dementia in the PAQUID study. Personnes Ages Quid. *Am J Epidemiol.* 1998 Aug 1; 148(3): 298-306. PMID: 9690368.	Does not address the question. Looks at statistical software packages to best analyze data.
Leroi I, Sheppard JM, Lyketsos CG. Cognitive function after 11.5 years of alcohol use: relation to alcohol use. *Am J Epidemiol.* 2002 Oct 15; 156(8): 747-752. PMID: 12370163.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. *J Am Geriatr Soc.* 2004 Apr; 52(4): 540-546. PMID: 15066068.	Included in Peters et al, 2008 systematic review.
McDougall GJ Jr, Becker H, Areheart KL. Older males, cognitive function, and alcohol consumption. *Issues Ment Health Nurs.* 2006 May; 27(4): 337-353. PMID: 16546934; PMCID: PMC2535769.	Cross-sectional study.
Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA.* 2003 Mar 19; 289(11): 1, 405-1, 413. PMID: 12636463.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Müller-Thomsen T, Haasen C. Alcohol consumption in Alzheimer's disease. A case report. *Eur Addict Res.* 2003 Jan; 9(1): 51-52. PMID: 12566798.	Subjects diagnosed with Alzheimer’s disease.
Orgogozo JM, Dartigues JF, Lafont S, Letenneur L, Commenges D, Salamon R, Renaud S, Breteler MB. Wine consumption and dementia in the elderly: A prospective community study in the Bordeaux area. *Rev Neurol (Paris).* 1997 Apr; 153(3): 185-192. PMID: 9296132.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Panza F, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Santamato A, Ranieri M, Fiore P, Vendemiale G, Seripa D, Pilotto A, Capurso A, Solfrizzi V. Vascular risk factors, alcohol intake, and cognitive decline. *J Nutr Health Aging.* 2008 Jun-Jul; 12(6): 376-381. Review. PMID: 18548174.	Narrative review.

Piguet O, Cramsie J, Bennett HP, Kril JJ, Lye TC, Corbett AJ, Hayes M, Creasey H, Broe GA. Contributions of age and alcohol consumption to cerebellar integrity, gait and cognition in non-demented very old individuals. *Eur Arch Psychiatry Clin Neurosci.* 2006 Dec; 256(8): 504-511. Epub 2006 Aug 17. PMID: 16917683.	Cross-sectional study.
Red wine might prevent Alzheimer's disease. Moderate consumption could be a factor in reducing or slowing the incidence of AD. *Health News.* 2007 Jan; 13(1): 7-8. PMID: 17299887.	Not peered reviewed; article.
Reid MC, Maciejewski PK, Hawkins KA, Bogardus ST Jr. Relationship between alcohol consumption and Folstein mini-mental status examination scores among older cognitively impaired adults. *J Geriatr Psychiatry Neurol.* 2002 Spring; 15(1): 31-37. PMID: 11936241.	Subjects were cognitively-impaired adults.
Rozzini R, Trabucchi M. Re: "Association between reported alcohol intake and cognition: Results from the Women's Health Initiative Memory Study". *Am J Epidemiol.* 2005 Aug 1; 162(3): 294-295; author reply 295-296. Epub 2005 Jun 29. PMID: 15987726.	Letter to the editor.
Ruitenberg A, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, Breteler MM. Alcohol consumption and risk of dementia: The Rotterdam Study. *Lancet.* 2002 Jan 26; 359(9, 303): 281-286. PMID: 11830193.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. *N Engl J Med.* 2005 Jan 20; 352(3): 245-253. PMID: 15659724.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Truelsen T, Thudium D, Grønbaek M; Copenhagen City Heart Study. Amount and type of alcohol and risk of dementia: The Copenhagen City Heart Study. *Neurology.* 2002 Nov 12; 59(9): 1, 313-1, 319. PMID: 12427876.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Xu G, Liu X, Yin Q, Zhu W, Zhang R, Fan X. Alcohol consumption and transition of mild cognitive impairment to dementia. *Psychiatry Clin Neurosci.* 2009 Feb; 63(1): 43-49. PMID: 19154211.	Subjects studied had suspected cognitive impairment.

Zuccalà G, Onder G, Pedone C, Cesari M, Landi F, Bernabei R, Cocchi A; Gruppo Italiano di Farmacoepidemiologia nell'Anziano Investigators. Dose-related impact of alcohol consumption on cognitive function in advanced age. *Alcohol Clin Exp Res.* 2001 Dec; 25(12): 1, 743-1, 748. PMID: 11781507. Results of a multicenter survey.	Cross-sectional study.

CHAPTER 4. HEALTH-RELATED OUTCOMES – HEAVY ALCOHOL INTAKE/BINGE DRINKING AND COGNITIVE DECLINE

WHAT IS THE RELATIONSHIP BETWEEN HEAVY ALCOHOL INTAKE OR BINGE DRINKING AND COGNITIVE DECLINE WITH AGE?

Conclusion statement

Although limited, evidence suggests that heavy or binge drinking is detrimental to age-related cognitive decline. (Grade: Limited).

Grade

Limited

Evidence summary overview

Several of the prospective cohort studies (Bond et al, 2005; Deng et al, 2006; Stott et al, 2008; and Wright et al, 2006) found similar results that appear to indicate light to moderate drinking decreases the risk of or lessens the severity of dementia and cognitive decline, especially compared to non-drinkers. Solfrizzi et al, 2007 found no significant (NS) associations between any levels of drinking and the incidence of mild cognitive impairment in non-cognitively impaired individuals vs. abstainers.

In regards to type of alcohol, Deng et al, 2006 found light-to-moderate intake of wine and liquor were related with a reduced risk of dementia compared to non-drinkers, while light-to-moderate intake of beer was associated with a significantly higher risk of dementia than non-drinkers. Mehlig et al, 2008 found that wine was protective for dementia and the association was strongest among women who consumed wine only. Consumption of spirits at baseline was associated with slightly increased risk of dementia.

By gender, Bond et al, 2005 found NS difference in cognitive function, while Stott et al, 2008 found that cognitive function was better for female drinkers than non-drinkers for some cognitive tests. However, no statistically significant differences were found in baseline cognitive function between male drinkers and non-drinkers.

Evidence summary paragraphs

Systematic Review/Meta-Analysis

Peters et al, 2008 (positive quality), a systematic review and meta-analysis of 23 studies, evaluated the evidence for any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption. The majority of the studies were from Europe and North America and Canada. In older people, small to moderate amounts of alcohol consumption were associated with reduced incidence of dementia and Alzheimer's disease. Small amounts of alcohol may be protective against dementia (random effects model, RR=0.63, 95% CI: 0.53 to 0.75) and Alzheimer's disease (RR=0.57, 95% CI: 0.44 to 0.74) but not for vascular dementia (RR=0.82, 95% CI: 0.50 to 1.35) or cognitive decline (R=0.89, 95% CI: 0.67 to 1.17). The evidence is strongest for wine consumption, but it is not conclusive.

Primary Studies

Bond et al, 2005 (neutral quality), a prospective cohort study conducted in the US, investigated the longitudinal relationship between alcohol consumption and cognitive performance in a cohort of 1,624 Japanese American older adults. Structured interviews were conducted at baseline and follow-up every two years for an eight-year period; a questionnaire asked about current and past alcohol patterns by beverage type (beer, wine, sake or liquor), as well as frequency, quantity and number of consumption years. Current alcohol consumers scored significantly higher on the Cognitive Abilities Screening Instrument (mean rate of change of -1.22 CASI units) over the eight-year follow-up period than past consumers or abstainers (mean rate of change of -3.77 CASI units) ($P<0.05$).

Deng et al, 2006 (neutral quality), a prospective cohort study conducted in China, examined the relationship between alcohol intake and dementia and whether this association depended on age, gender, educational level or cigarette smoking. Dementia screening and diagnosis, as well as frequency and quantity of alcohol consumption, were measured at baseline and the two-year follow-up. A total of 2,632 older adults were included in the analysis. Light-to-moderate drinking was associated with a significantly lower risk of dementia compared with non-drinking, while excessive drinking was related to a higher risk of dementia. The effect of light-to-moderate drinking seemed most prominent among vascular dementia, OR=0.63 (95% CI: 0.55 to 0.72) for Alzheimer's disease, OR=0.31 (95% CI: 0.19 to 0.51) for vascular dementia and OR=0.45 (95% CI: 0.12 to 1.69) for other dementia. Light-to-moderate intake of wine and liquor were related with a reduced risk of dementia compared to non-drinkers, while light-to-moderate intake of beer was associated with a significantly higher risk of dementia than non-drinkers.

Mehlig et al, 2008 (neutral quality), the cohort Prospective Population Study of Women in Goteborg, Sweden, assessed the association between different types of alcoholic beverages and 34-year incidence of dementia. Frequency of alcohol intake was recorded and related to dementia at baseline (1968 to 1969, N=1,462) and at four other time points between 1974 and 2002. By 2002, 164 cases of dementia were diagnosed. Wine was protective for dementia (HR=0.6, 95% CI: 0.4, 0.8) in the updated model, and the association was strongest among women who consumed wine only (HR=0.3, 95% CI: 0.1, 0.8); the protective association of wine was stronger among smokers. Consumption of spirits at baseline was associated with slightly increased risk of dementia (HR=1.5, 95% CI: 1.0, 2.2).

Ngandu et al, 2007 (neutral quality), the prospective cohort Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study conducted in Finland, investigated whether midlife alcohol drinking is associated with cognitive function later on in a non-demented population of elderly persons. The average follow-up period was 21 years. A random sample of 2,000 survivors aged 65 to 79 years in 1997 were invited for re-examination in 1998. A total of 1,409 completed re-examination and 68 were excluded due to the diagnosis of dementia, leaving 1,341 subjects in the analysis. A baseline self-administered questionnaire asked for details on frequency of drinking (never, infrequently, or frequently). About 30% of the participants never drank alcohol, 40% drank it infrequently and 30% drank frequently. Participants who did not drink alcohol at mid-life had a poorer performance in episodic memory, psychomotor speed and executive function in late life compared with infrequent and frequent drinkers, after adjustment for sociodemographic and vascular factors, while late-life drinkers had

poorer psychomotor speed and executive function.

Solfrizzi et al, 2007 (positive quality), a prospective cohort study conducted in Italy, examined the impact of alcohol consumption on the incidence of mild cognitive impairment and its progression to dementia in 1,445 non-cognitively impaired participants (630 women, 815 men) aged 65 to 84 years participating in the Italian Longitudinal Study on Aging, with a 3.5-year follow-up. Food frequency (FFQ) and screening questionnaires were used to assess alcohol consumption and health status. Analysis included blood samples and the Mini-Mental State Examination. Analyses were controlled for age and gender and adjusted for education, smoking, coronary artery disease and type 2 diabetes, hypertension, stroke and total cholesterol. Results showed that persons with mild cognitive impairment who were moderate drinkers (less than one drink a day) had a lower rate of progression to dementia than non-drinkers [hazard ratio (HR) 0.15; 95% CI: 0.03 to 0.78]. Also, moderate drinkers with mild cognitive impairment who consumed less than one drink a day of wine showed significantly lower rate of progression to dementia than non-drinkers (HR 0.15; 95% CI: 0.33 to 0.77). No significant association between higher levels of drinking (one or more drink a day) and rate of progression to dementia in patients with mild cognitive impairment vs. non-drinkers. No significant associations were found between any levels of drinking and the incidence of mild cognitive impairment in non-cognitively impaired individuals vs. non-drinkers. Authors concluded that in people with mild cognitive impairment, consuming up to one drink a day of alcohol or wine may decrease the rate of progression to dementia.

Stott et al, 2008 (neutral quality), a prospective cohort study in Ireland, Netherlands and Scotland investigated whether low to moderate alcohol intake was protective against cognitive decline in older people (N=5,804; 3,000 women, 2,804 men) aged 70 to 82 years with vascular risk factors or known vascular disease randomized to pravastatin or placebo in the Prospective Study of Pravastatin in the Elderly at Risk. Alcohol intake was assessed one time at baseline and quantified in terms of usual alcohol intake in units per week for the previous month. Cognitive function was measured using the Mini-Mental State Examination (MMSE), speed of information processing (Stroop and Letter-Digit Coding tests [LDCT]) and immediate and delayed memory (Picture-Work Learning test [PWLT]) over 3.2 years. Results showed cognitive performance was better for female drinkers than non-drinkers for all cognitive tests over the 3.2-year follow-up. However, when adjusted for potential confounders, results remained statistically significant only for the LDCT ($P<0.001$) and delayed recall in the PWLT ($P=0.001$), with borderline significance for the MMSE (P5.05). No statistically significant differences were found in baseline cognitive function between male drinkers and non-drinkers. The rate of cognitive decline was similar for drinkers and non-drinkers for all cognitive tests, except for MMSE, which declined significantly less in female drinkers than non-drinkers (linear mixed model attenuated rate of decline = 0.05 MMSE units per year, $P=0.001$). The authors concluded that drinking low to moderate amounts of alcohol may delay age-associated cognitive decline in older women; however, these benefits were not evident in older men. Limitations of this study include no data on the type of alcohol consumed or lifetime alcohol consumption and the relatively short follow-up time of 3.2 years to assess cognitive decline.

Wright et al, 2006 (positive quality), a prospective cohort study conducted in the US

examined the effect of alcohol intake on cognitive performance over time in a younger, multi-ethnic, community-based sample (N=1,428; 43% of initial N) participating in the Northern Manhattan Study. The study also examined the role of the APOE-4allele. Participants were 40 or more years with mean age of 71 years, with 62% Hispanic, 19% black and 19% white. Data were collected through telephone interviews, physical and neurological examinations, review of medical records and fasting blood samples. Alcohol intake (average amount consumed in past year and during drinking lifetime) was assessed using a structured interview adapted from a food frequency questionnaire. Results showed a positive relationship between reported alcohol intake and cognition. Drinking less than one drink a week (P=0.09), between one drink weekly up to two drinks daily (P=0.001), and more than two drinks daily (P=0.003) were associated with less cognitive decline on the modified Telephone Interview for Cognitive Status compared to never drinkers. The dose-response relationship was not changed by the presence of an APOE-4allele in a sub-sample.

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Significant Outcomes
Bond GE et al 2005 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=1,624 Japanese American older adults. Duration: Eight years. Location: United States.	Current alcohol consumers (N=480) scored significantly higher (P<0.05) on the Cognitive Abilities Screening Instrument (mean rate of Δ of 1.22 CASI units) than past consumers or abstainers (N=1,144, mean rate of Δ of -3.77 CASI units).

Deng et al 2006 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=2,632 older adults. Duration: Two years. Location: China.	Light-to-moderate drinking associated with a significantly ↓ risk of dementia, compared with non-drinking, while excessive drinking related to a ↑ risk of dementia. Effect of light-to-moderate drinking seemed most prominent among vascular dementia, 0.63 (0.55 to 0.72) for Alzheimer's disease, 0.31 (0.19 to 0.51) and for vascular dementia and 0.45 (0.12 to 1.69) for other dementia. Light-to-moderate intake of wine/liquor related with ↓ risk of dementia compared to non-drinkers, while light-to-moderate intake of beer associated with significantly ↑ risk of dementia than non-drinkers.
Mehlig et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	Participants from the Prospective Population Study of Women in Goteborg, Sweden. Frequency of alcohol intake recorded and related to dementia at baseline (1968 to 1969, N=1,462), as well as in 1974 to 1975 (N=91%), 1980 to 1981 (83%), 1992 to 1993 (70%) and 2000 to 2001 (71%). Duration: 34 years. Location: Sweden.	By 2002, 164 cases of dementia were diagnosed. Wine was protective for dementia (HR=0.6; 95% CI: 0.4, 0.8) in the updated model. Association strongest among women who consumed wine only (HR=0.3, 95% CI: 0.1, 0.8); protective association of wine stronger among smokers. Consumption of spirits at baseline associated with slightly ↑ risk of dementia (HR=1.5, 95% CI: 1.0, 2.2).

Ngandu et al 2006 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	Participants in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study. Random sample of 2,000 survivors aged 65 to 79 years in 1997 were invited for re-examination in 1998. N=1,409 completed re-examination; 68 excluded due to diagnosis of dementia. Final N=1,341 subjects. Duration: Average follow-up was 21 years. Location: Finland.	~30% of participants never drank alcohol, 40% drank infrequently and 30% drank frequently. Participants who did not drink alcohol at mid-life had poorer performance in episodic memory, psychomotor speed and executive function in late life, compared with infrequent and frequent drinkers, after adjustment for sociodemographic and vascular factors, while late-life drinkers had poorer psychomotor speed and executive function.
Peters et al 2008 Study Design: Systematic Review / Meta-Analysis Class: M Rating: Positive Quality	N=23 studies evaluating evidence for any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption. Duration: Varied by study. Location: Primarily Europe and North America/Canada.	In older people, small to moderate amounts of alcohol consumption associated with ↓ incidence of dementia and Alzheimer's disease. Small amounts of alcohol may be protective against dementia (random effects model, RR=0.63, 95% CI: 0.53 to 0.75) and Alzheimer's disease (RR=0.57, 95% CI: 0.44 to 0.74), but not for vascular dementia (RR=0.82, 95% CI: 0.50 to 1.35) or cognitive decline (RR=0.89, 95% CI: 0.67 to 1.17). Evidence is strongest for wine consumption, but it is not conclusive.

Solfrizzi V, D'Introno A et al, 2007 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	N=1,445 non-cognitively impaired participants (630 women; 815 men) aged 65 to 84 years participating in Italian Longitudinal Study on Aging. Duration: 3.5-year follow-up. Location: Italy.	Patients with mild cognitive impairment who were moderate drinkers (i.e., those who consumed <one drink a day (~15g of alcohol), had a ↓ rate of progression to dementia than abstainers (HR 0.15; 95% CI: 0.03 to 0.78). Moderate drinkers with mild cognitive impairment who consumed <one drink a day of wine showed a significantly ↓ rate of progression to dementia than abstainers (HR 0.15; 95% CI: 0.03 to 0.77). NS association between ↑ levels of drinking (≥one drink a day) and rate of progression to dementia in patients with mild cognitive impairment vs. abstainers. NS associations found between any levels of drinking and incidence of mild cognitive impairment in non-cognitively impaired individuals vs. abstainers.

Stott DJ, Falconer A et al, 2008 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=5,804 (3,000 women; 2,804 men) aged 70 to 82 years with vascular risk factors or known vascular disease participating in Prospective Study of Pravastatin in the Elderly at Risk. Duration: 3.2-year follow-up. Location: Ireland, Netherlands and Scotland.	Cognitive function better for female drinkers than non-drinkers for all cognitive tests over the 3.2-year follow-up. When adjusted for potential confounders, results remained statistically significant only for LDCT (P<0.001) and delayed recall in PWLT (P=0.001), with borderline significance for MMSE (P=5.05). NS differences found in baseline cognitive function between male drinkers and non-drinkers. Rate of cognitive decline similar for drinkers and non-drinkers for all cognitive tests, except for MMSE, which ↓ significantly less in female drinkers than non-drinkers (linear mixed model attenuated rate of ↓ = 0.05 MMSE units per year, P=0.001).
Wright CB, Elkind MS et al, 2006 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	N=1,428; 43% of initial N were aged ≥40 years (mean age 71 years), participating in Northern Manhattan Study. 62% Hispanic, 19% black and 19% white. Duration: Mean follow-up 2.2 years; range 0.5 to 4.4 years. Location: United States.	Positive relationship between reported alcohol intake and cognition. Drinking <one drink a week (P=0.09), between one drink weekly, up to two drinks daily (P=0.001), and >two drinks daily (P=0.003) associated with ↓ cognitive decline, compared to never drinkers. No Δ in dose-response relationship by the presence of an APOE-4allele.

Search plan and results

Inclusion criteria

- January 1, 1995 to June 22, 2009
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes if available
- Dropout rate: Less than 20%; preference for smaller dropout rates

- Ages: Adults of legal drinking age (21 years and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, hypertension, type 2 diabetes, osteoporosis, osteopenia and obesity) and those with breast cancer, colon cancer or prostate cancer.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (exceptions noted)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)
- Cross-sectional study design.

Search terms and electronic databases used

- PubMed

  ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND "Cognition Disorders"[Mesh]

Date searched: 06/22/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 320
- Total articles identified to review from electronic databases: 37
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 7
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 8
- Number of Articles Reviewed but Excluded: 29

Included articles (References)

Reviews/Meta-analysis

1. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing.* 2008 Sep; 37(5): 505-512. Epub 2008 May 16. Review. PMID: 18487267.

Primary Research

2. Bond GE, Burr RL, McCurry SM, Rice MM, Borenstein AR, Larson EB. Alcohol and cognitive performance: A longitudinal study of older Japanese Americans. The Kame Project. *The Kame Project. Int Psychogeriatr.* 2005 Dec; 17(4): 653-668. Epub 2005 Sep 27. PMID: 16185373.
3. Deng J, Zhou DH, Li J, Wang YJ, Gao C, Chen M. A two-year follow-up study of alcohol consumption and risk of dementia. *Clin Neurol Neurosurg.* 2006 Jun; 108(4): 378-383. Epub 2005 Aug 9. PMID: 16084641.

4. Mehlig K, Skoog I, Guo X, Schütze M, Gustafson D, Waern M, Ostling S, Björkelund C, Lissner L. Alcoholic beverages and incidence of dementia: 34-year follow-up of the prospective population study of women in Goteborg. *Am J Epidemiol.* 2008 Mar 15; 167(6): 684-691. Epub 2008 Jan 24. PMID: 18222934.
5. Ngandu T, Helkala EL, Soininen H, Winblad B, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking and cognitive functions: findings from the Cardiovascular Risk Factors Aging and Dementia (CAIDE) Study. *Dement Geriatr Cogn Disord.* 2007; 23(3): 140-149. Epub 2006 Dec 14. PMID: 17170526.
6. Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Baldassarre G, Scapicchio P, Scafato E, Amodio M, Capurso A, Panza F; Italian Longitudinal Study on Aging Working Group. Alcohol consumption, mild cognitive impairment and progression to dementia. *Neurology*. 2007 May 22; 68 (21): 1,790-1,799.
7. Stott DJ, Falconer A, Kerr GD, Murray HM, Trompet S, Westendorp RG, Buckley B, de Craen AJ, Sattar N, Ford I. Does low to moderate alcohol intake protect against cognitive decline in older people? *J Am Geriatr Soc.* 2008 Dec; 56(12): 2, 217-2, 224. PMID: 19093921.
8. Wright CB, Elkind MS, Luo X, Paik MC, Sacco RL. Reported alcohol consumption and cognitive decline: The Northern Manhattan study. *Neuroepidemiology.* 2006; 27(4): 201-207. Epub 2006 Oct 16. PMID: 17047373; PMCID: PMC1756459.

Excluded articles

Excluded Citations	Reason for Exclusion
Anttila T, Helkala EL, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B, Soininen H, Tuomilehto J, Nissinen A, Kivipelto M. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. *BMJ.* 2004 Sep 4;329(7465):539. Epub 2004 Aug 10. PMID: 15304383; PMCID: PMC516103.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Brust JC. A 74-year-old man with memory loss and neuropathy who enjoys alcoholic beverages. *JAMA.* 2008 Mar 5; 299(9): 1, 046-1, 054. Epub 2008 Feb 5. PMID: 18252872.	Only one subject with cognitive impairment.
Christian JC, Reed T, Carmelli D, Page WF, Norton JA Jr, Breitner JC. Self-reported alcohol intake and cognition in aging twins. *J Stud Alcohol.* 1995 Jul; 56(4): 414-416. PMID: 7674676.	Some subjects were diagnosed as alcoholics.

den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, van Duijn CM, Hofman A, Breteler MM. Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. *Am J Clin Nutr.* 2004 Oct; 80(4): 992-997. PMID: 15447910.	Cross-sectional study.
Espeland MA, Coker LH, Wallace R, Rapp SR, Resnick SM, Limacher M, Powell LH, Messina CR; Women's Health Initiative Study of Cognitive Aging. Association between alcohol intake and domain-specific cognitive function in older women. *Neuroepidemiology.* 2006; 27(1): 1-12. Epub 2006 May 24. PMID: 16717476.	Included in Peters et al, 2008 systematic review.
Espeland MA, Gu L, Masaki KH, Langer RD, Coker LH, Stefanick ML, Ockene J, Rapp SR. Association between reported alcohol intake and cognition: Results from the Women's Health Initiative Memory Study. *Am J Epidemiol.* 2005 Feb 1; 161(3): 228-238. PMID: 15671255.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Alcohol consumption and cognitive function in late life: A longitudinal community study. *Neurology.* 2005 Oct 25; 65(8): 1, 210-1, 217. PMID: 16247047.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
González-Muñoz MJ, Peña A, MeseguerI. Role of beer as a possible protective factor in preventing Alzheimer's disease. *Food Chem Toxicol.* 2008 Jan; 46(1): 49-56. Epub 2007 Jul 7. PMID: 17697731.	Cross-sectional study.
Huang W, Qiu C, Winblad B, Fratiglioni L. Alcohol consumption and incidence of dementia in a community sample aged 75 years and older. *J Clin Epidemiol*. 2002 Oct; 55(10): 959-964. PMID: 12464371.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Järvenpää T, Rinne JO, Koskenvuo M, Räihä I, Kaprio J. Binge drinking in midlife and dementia risk. *Epidemiology.* 2005 Nov; 16(6): 766-771. PMID: 16222166.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Kasahara H, Karasawa A, Ariyasu T, Thukahara T, Satou J, Ushijima S. Alcohol dementia and alcohol delirium in aged alcoholics. *Psychiatry Clin Neurosci.* 1996 Jun; 50(3): 115-123. PMID: 9201756.	Study population is alcoholics.

Leibovici D, Ritchie K, Ledésert B, Touchon J. The effects of wine and tobacco consumption on cognitive performance in the elderly: A longitudinal study of relative risk. *Int J Epidemiol.* 1999 Feb; 28(1): 77-81. PMID: 10195668.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Lemeshow S, Letenneur L, Dartigues JF, Lafont S, Orgogozo JM, Commenges D. Illustration of analysis taking into account complex survey considerations: the association between wine consumption and dementia in the PAQUID study. Personnes Ages Quid. *Am J Epidemiol.* 1998 Aug 1; 148(3): 298-306. PMID: 9690368.	Does not address the question. Looks at statistical software packages to best analyze data.
Leroi I, Sheppard JM, Lyketsos CG. Cognitive function after 11.5 years of alcohol use: relation to alcohol use. *Am J Epidemiol.* 2002 Oct 15; 156(8): 747-752. PMID: 12370163.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. *J Am Geriatr Soc.* 2004 Apr; 52(4): 540-546. PMID: 15066068.	Included in Peters et al, 2008 systematic review.
McDougall GJ Jr, Becker H, Areheart KL. Older males, cognitive function, and alcohol consumption. *Issues Ment Health Nurs.* 2006 May; 27(4): 337-353. PMID: 16546934; PMCID: PMC2535769.	Cross-sectional study.
Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA.* 2003 Mar 19; 289(11): 1, 405-1, 413. PMID: 12636463.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Müller-Thomsen T, Haasen C. Alcohol consumption in Alzheimer's disease. A case report. *Eur Addict Res.* 2003 Jan; 9(1): 51-52. PMID: 12566798.	Subjects diagnosed with Alzheimer’s disease.
Orgogozo JM, Dartigues JF, Lafont S, Letenneur L, Commenges D, Salamon R, Renaud S, Breteler MB. Wine consumption and dementia in the elderly: A prospective community study in the Bordeaux area. *Rev Neurol (Paris).* 1997 Apr; 153(3): 185-192. PMID: 9296132.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Panza F, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Santamato A, Ranieri M, Fiore P, Vendemiale G, Seripa D, Pilotto A, Capurso A, Solfrizzi V. Vascular risk factors, alcohol intake, and cognitive decline. *J Nutr Health Aging.* 2008 Jun-Jul; 12(6): 376-381. Review. PMID: 18548174.	Narrative review.

Piguet O, Cramsie J, Bennett HP, Kril JJ, Lye TC, Corbett AJ, Hayes M, Creasey H, Broe GA. Contributions of age and alcohol consumption to cerebellar integrity, gait and cognition in non-demented very old individuals. *Eur Arch Psychiatry Clin Neurosci.* 2006 Dec; 256(8): 504-511. Epub 2006 Aug 17. PMID: 16917683.	Cross-sectional study.
Red wine might prevent Alzheimer's disease. Moderate consumption could be a factor in reducing or slowing the incidence of AD. *Health News.* 2007 Jan; 13(1): 7-8. PMID: 17299887.	Not peered reviewed; article.
Reid MC, Maciejewski PK, Hawkins KA, Bogardus ST Jr. Relationship between alcohol consumption and Folstein mini-mental status examination scores among older cognitively impaired adults. *J Geriatr Psychiatry Neurol.* 2002 Spring; 15(1): 31-37. PMID: 11936241.	Subjects were cognitively-impaired adults.
Rozzini R, Trabucchi M. Re: "Association between reported alcohol intake and cognition: Results from the Women's Health Initiative Memory Study". *Am J Epidemiol.* 2005 Aug 1; 162(3): 294-295; author reply 295-296. Epub 2005 Jun 29. PMID: 15987726.	Letter to the editor.
Ruitenberg A, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, Breteler MM. Alcohol consumption and risk of dementia: The Rotterdam Study. *Lancet.* 2002 Jan 26; 359(9, 303): 281-286. PMID: 11830193.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. *N Engl J Med.* 2005 Jan 20; 352(3): 245-253. PMID: 15659724.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Truelsen T, Thudium D, Grønbaek M; Copenhagen City Heart Study. Amount and type of alcohol and risk of dementia: The Copenhagen City Heart Study. *Neurology.* 2002 Nov 12; 59(9): 1, 313-1, 319. PMID: 12427876.	Primary study cited under Peters et al, 2008 systematic review/meta-analysis.
Xu G, Liu X, Yin Q, Zhu W, Zhang R, Fan X. Alcohol consumption and transition of mild cognitive impairment to dementia. *Psychiatry Clin Neurosci.* 2009 Feb; 63(1): 43-49. PMID: 19154211.	Subjects studied had suspected cognitive impairment.

Zuccalà G, Onder G, Pedone C, Cesari M, Landi F, Bernabei R, Cocchi A; Gruppo Italiano di Farmacoepidemiologia nell'Anziano Investigators. Dose-related impact of alcohol consumption on cognitive function in advanced age. *Alcohol Clin Exp Res.* 2001 Dec; 25(12): 1, 743-1, 748. PMID: 11781507. Results of a multicenter survey.	Cross-sectional study.

CHAPTER 5. HEALTH-RELATED OUTCOMES – ALCOHOL INTAKE AND CORONARY HEART DISEASE

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL INTAKE AND CORONARY HEART DISEASE?

Conclusion statement

Strong evidence consistently demonstrates that compared to non-drinkers, individuals who drink moderately have lower risk of coronary heart disease (CHD).

Grade

Strong

Evidence summary overview

Related to the association between alcohol consumption and risk of coronary heart disease (CHD), six systematic reviews/meta-analyses were reviewed. This evidence included four methodologically strong meta-analyses (Bagnardi, 2008; Corrao, 2000; Di Castelnuovo, 2002; and Rimm, 1999); one methodologically neutral meta-analysis (Cleophas, 1999) and one systematic review that was methodologically neutral (Britton and McKee, 2000).

Overall, the evidence shows that compared to those who abstain from alcohol, regular light to moderate drinking can reduce the risk of CHD; whereas, heavy irregular or binge drinking increases risk of CHD. In a meta-analysis of 20 observational studies, Bagnardi et al, (2008) found significant differences in the alcohol intake dose response relationship to CHD risk in regular vs. irregular drinkers. These authors concluded that the consumption of alcohol on more than two days per week has a significant protective effect against CHD. Cleophas et al, (1999) found that alcohol consumption at one to four drinks per day reduced risk of mortality and CHD, while more than five drinks per day increased risk of mortality, and wine, beer and spirits were equally beneficial. Interestingly, a meta-analysis conducted by Corrao et al, (2000) of 43 cohort studies, found that in Mediterranean countries, protective effects were seen up to 145g per day, but in all other countries, the protective effects were only seen up to 80grams per day. Di Castelnuovo et al, (2000) compared wine and beer consumption in a meta-analysis of 26 international studies. The relative risks of cardiovascular disease (CVD) were 0.68 (95% CI: 0.59-0.77) and 0.78 (95% CI: 0.70-0.86) for consumption of wine and beer, respectively, relative to non-drinkers. Rimm (1999) concluded that based on a meta-analysis of 42 randomized controlled trials (RCTs), alcohol consumption per se, not other components of alcoholic beverages, was responsible for the lower risk of CHD among moderate drinkers. Furthermore, based on measures of high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fibrinogen, to the degree documented in the meta-analysis, consumption of two standard drinks per day would lower a person's risk of CHD by approximately 25%. According to Britton and Mckee (2000) a systematic review of international studies, not only alcohol quantity, but also drinking patterns such as binge drinking, influenced CVD risk.

Collectively, the research suggests that whereas binge drinking (more than three

alcoholic drinks every one to two hours) has harmful effects, light to moderate alcohol consumption spread over several days of the week has beneficial effects relative to CVD risk. Therefore, for a given volume of alcohol within a moderate drinking range, it is better to distribute this volume evenly over several days, rather than consuming it in two to three days.

Evidence summary paragraphs

Bagnardi et al, 2008 (positive quality) conducted a meta-analysis to evaluate whether drinking pattern, defined by the frequency of drinking days as well as drinking intensity per drinking occasion, modified the effect of alcohol intake on the risk of CHD. A Medline search for articles published between 1966 and 2006 was done using keywords related to disease (coronary heart disease, coronary death, myocardial infarction, ischemic heart disease), exposure (quantity or dose of alcohol intake and pattern of alcohol drinking) and frequency of alcohol drinking (regular, irregular, problem drinking, alcoholic intoxication, heavy episodic drinking, hangover). The final meta-analysis included six studies, four cohort studies and two case-control studies. Compared with those who abstained from alcohol, regular heavy drinkers had a reduced risk of CHD (RR 0.75; 95% CI: 0.64, 0.89) and heavy irregular or binge drinkers had an increased risk (RR 1.10; 95% CI: 1.03, 1.17). The dose-response relationship between the amount of alcohol consumed and CHD risk also differed between regular and irregular heavy drinkers (P<0.047). A J-shaped curve was seen for irregular drinkers: The nadir and the last protective dose of 28g per week (RR 0.59; 95% CI: 0.53 to 0.65) and 131g per week (RR 0.85; 95% CI: 0.72 to 0.99) were obtained included drinkers who consumed alcohol for two days a week or less. Conversely, in people who consumed alcohol for more than two days a week a significant protective effect was seen even when drinking high amounts of alcohol.

Britton and McKee, 2000 (neutral quality), presents the key findings of a comprehensive systematic review that examined the relationship between heavy drinking and irregular (binge) drinking and sudden cardiovascular mortality. Six prospective cohort studies, conducted in Europe and the US, were included, as well as a number of case-control studies. The prospective follow-up ranged from 6.7 to 40 years. The authors found considerable evidence that binge drinkers as are at greater risk of cardiac arrhythmias and sudden cardiac death. The evidence also supported a temporal and dose-response relationship for sudden cardiac death and for fatal myocardial infarction (MI). The authors concluded that physiological evidence indicates that a causal relationship is biologically plausible, and that the effects of binge drinking are quite different from those seen with regular moderate and even heavy drinking.

Cleophas, 1999 (neutral quality), a meta-analysis of 20 international studies, assessed the relationship between MI and consumption of different types of alcoholic beverages, both in low doses (one to four drinks per day) and high doses (more than four drinks per day). Eight cohort studies were included that reported on the association between alcohol consumption irrespective of the type of drink and cardiovascular death, as well as twelve prospective cohort studies that reported on the risk of MI and specific types of alcoholic drinks. Small doses of alcohol were associated with a reduced risk of mortality and CHD, while more than five drinks per day increased the risk of mortality; wine, beer and spirits were equally beneficial.

Corrao et al, 2000 (positive quality) conducted a meta-analysis to evaluate the relationship between alcohol consumption and risk of CHD. Searches were conducted using Medline, Current Content, EMBASE, CAB, and Core Biomedical Collection, and a hand search of general reviews and meta-analyses published on issue was performed. The search included studies published between 1966 and 1998, and used the keywords for disease (coronary heart disease, coronary artery disease, coronary event, coronary death, myocardial infarction, ischemic heart disease and angina pectoris) and alcohol consumption (alcohol or ethanol and consumption, intake and drinking). The final sample included 43 cohort studies, eight case-control studies. Results from all 51 studies showed that a protective effect was evident up to 90g per day (RR=0.94; 95%CI: 0.90, 1.00), with harmful effects evidence at 113g per day (RR=1.08; 95%CI: 1.00, 1.16). These effects were modified when only the high quality studies (N=28) were considered, such that a protective effect was evident up to 72g per day (RR=0.96; 95%CI: 0.92, 1.00), and harmful effects were evident at 89g per day (RR=1.05; 95%CI: 1.00, 1.11). When examining data from females only, a protective effect evident up to 31g per day (RR=0.93; 95%CI: 0.87, 1.00), and harmful effects were evident at 52g per day (RR=1.12; 95%CI: 1.00, 1.26); for males, a protective effect was evident up to 87g per day (RR=0.94; 95%CI: 0.88, 1.00), and harmful effects were evident at 114g per day (RR=1.09; 95%CI: 1.00, 1.19). When looking at Mediterranean countries, protective effects were seen up to 145g per day (RR=0.76; 95%CI: 0.61, 1.00), but in all other countries as a whole, protective effects were only seen up to 80g per day (RR=0.93; 95%CI: 0.87, 1.00).

Di Castelnuovo et al, 2002 (positive quality), a meta-analysis of 26 international studies, studied the relationship between wine or beer consumption and CVD. From 13 studies, the RR of vascular disease associated with wine intake was 0.68 (95% CI: 0.59-0.77) relative to non-drinkers, and 10 studies supported a J-shaped relationship between different amounts of wine intake and vascular risk. A statistically significant inverse relationship was found up to a daily intake of 150ml of wine. From 15 studies, the relative risk of vascular disease associated with moderate beer consumption was 0.78 (95% CI: 0.70-0.86). However, no significant (NS) relationship between different amounts of beer intake and vascular risk was found.

Rimm et al, 1999 (positive quality) a meta-analysis of 42 experimental trials quantitatively examined the association between moderate alcohol intake and CHD risk. All of these trials offered the advantage of being randomized design, but all we relatively small. Trials were weighted according to number of study participants. Consumption of 30g alcohol per day (approximately two standard drinks) increased HDL levels by 4.0mg/dL, which was associated with an adjusted 16.8% decrease in CHD risk. Fibrinogen concentration also decreased by 7.5mg/dL, but the decrease was NS. Conversely, TG levels increased by an estimated 5.7% resulting in a 4.6% increase in CHD risk, which slightly attenuated the alcohol benefit. Taken together, the estimated changes in HDL, TG and fibrinogen levels induced by consumption of 30g of alcohol result in a 24.7% reduction in the risk of CHD

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Significant Outcomes
Bagnardi V, Zatonski et al, 2008 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality	N=six studies (four cohort studies, two case-control studies).	Compared with those who abstained from alcohol, regular heavy drinkers had a ↓ risk of CHD (RR 0.75; 95% CI: 0.64, 0.89) and heavy irregular or binge drinkers had an ↑ risk (RR 1.10; 95% CI: 1.03, 1.17). Dose-response relationship between amount of alcohol consumed and CHD risk also differed between regular and irregular heavy drinkers (P<0.047). A J-shaped curve seen for irregular drinks: The nadir and the last protective dose of 28g per week (RR 0.59; 95% CI: 0.53 to 0.65) and 131g per week (RR 0.85; 95% CI: 0.72 to 0.99) were obtained included drinks who consumed alcohol for ≤two days a week. For people who consumed alcohol >two days a week, a significant protective effect was seen even when drinking ↑ amounts of alcohol.

Britton A and McKee M, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating: Neutral Quality	N=six prospective cohort studies with 6.7 to 40 years of follow-up; three selected case-control studies. Subjects were adult males. Location: Europe and the United States.	Considerable evidence from both cohort and case-control studies that binge drinkers are at ↑ risk of cardiac arrhythmias and sudden cardiac death. Physiological and case-control studies provide evidence of a temporal relationship between binge drinking and death. Consistent evidence of a dose-response relationship between binge drinking and sudden cardiac death and for fatal MI. A causal relationship is biologically plausible, and the effects of binge drinking are quite different from those seen with regular moderate, and even heavy drinking.
Cleophas TJ 1999 Study Design: Meta-analysis/Systematic Review Class: M Rating: Neutral Quality	N=20 international studies assessing the relationship between MI and consumption of different types of alcoholic beverages, both in low doses (one to four drinks per day) and high doses (>four drinks per day). Eight cohort studies reported on association between alcohol consumption irrespective of type of drink and cardiovascular death. 12 prospective cohort studies reported on risk of MI and specific types of alcoholic drinks.	Small doses of alcohol associated with ↓ risk of mortality and CHD, while >five drinks per day ↑ risk of mortality; wine, beer and spirits were equally beneficial.

Corrao G, Rubbiati L et al, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality	N=43 cohort studies, eight case-control studies.	Results from all 51 studies showed that a protective effect was evident up to 90g per day (RR=0.94; 95%CI: 0.90, 1.00), with harmful effects evidence at 113g per day (RR=1.08; 95%CI: 1.00, 1.16). Effects were modified when only the high quality studies (N=28) were considered, such that a protective effect was evident up to 72g per day (RR=0.96; 95%CI: 0.92, 1.00) and harmful effects were evident at 89g per day (RR=1.05; 95%CI: 1.00, 1.11). For females, protective effect evident up to 31g per day (RR=0.93; 95%CI: 0.87, 1.00) and harmful effects evident at 52g per day (RR=1.12; 95%CI: 1.00, 1.26). For males, protective effect evident up to 87g per day (RR=0.94; 95%CI: 0.88, 1.00) and harmful effects evident at 114g per day (RR=1.09; 95%CI: 1.00, 1.19).
Di Castelnuovo et al 2002 Study Design: Meta-analysis Class: M Rating: Positive Quality	N=26 international studies, studying relationship between wine or beer consumption and CVD.	From 13 studies, the RR of vascular disease associated with wine intake was 0.68 (95% CI: 0.59-0.77) relative to non-drinkers and 10 studies supported a J-shaped relationship between different amounts of wine intake and vascular risk. A statistically significant inverse relationship found up to a daily intake of 150ml of wine. From 15 studies, RR of vascular disease associated with moderate beer consumption was 0.78 (95% CI: 0.70-0.86). However, NS relationship between different amounts of beer intake and vascular risk.

Rimm EB, Williams P et al, 1999 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality	N=42 randomized trials.	RR for CHD with ethanol (30g per day): HDL: 0.69 (95% CI: 0.47-0.99) per 10mg/d^2. Fibrinogen: 1.34 (95% CI: 1.15-1.56) per 10mg/d^2. TG: 1.40 (1.10 to 1.77) per 10mg/d^2.

Search plan and results

Inclusion criteria

- January 1, 1995 through June 8, 2009
- Systematic reviews/meta-analyses only
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- Dropout rate: Less than 20%; preference for smaller dropout rates
- Ages: Adults of legal drinking age (21 years and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, hypertension, Type 2 diabetes, osteoporosis, osteopenia and obesity) and those with breast cancer, colon cancer and/or prostate cancer.

Exclusion criteria

- Medical treatment/therapy
- Diseased subjects (exceptions noted)
- Hospitalized patients
- Malnourished/third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)
- Cross-sectional study design.

Search terms and electronic databases used

- PubMed

  "Cardiovascular Diseases"[Mesh] OR “Heart Diseases"[Mesh] OR "Stroke"[Mesh] AND ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) "Stroke"[Mesh] AND ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh])

Date searched: 06/08/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 100
- Total articles identified to review from electronic databases: 23
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 0
- Number of Review Articles Identified: 6
- Total Number of Articles Identified: 6
- Number of Articles Reviewed but Excluded: 17

Included articles (References)

1. Bagnardi V, Zatonski W, Scotti L, La Vecchia C, Corrao G. Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. *J Epidemiol Community Health.* 2008 Jul; 62 (7): 615-619. PMID : 18559444.
2. Britton A, McKee M.The relation between alcohol and cardiovascular disease in Eastern Europe: Explaining the paradox. *J Epidemiol Community Health*. 2000 May; 54 (5): 328-332. Review. PMID : 10814651.
3. Cleophas TJ. Wine, beer and spirits and the risk of myocardial infarction: A systematic review. *Biomed Pharmacother*. 1999 Oct; 53 (9): 417-423. Review. PMID: 10554677.
4. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: A meta-analysis. *Addiction*. 2000 Oct; 95 (10): 1, 505-1, 523. PMID : 11070527.
5. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation*. 2002 Jun 18; 105 (24): 2, 836-2, 844. PMID : 12070110.
6. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: Meta-analysis of effects on lipids and haemostatic factors. *BMJ.* 1999 Dec 11; 319 (7224): 1, 523-1, 528. PMID : 10591709; PMCID: PMC 28294.

Excluded articles

Article	Reason for Exclusion
Barnett AG, Dobson AJ. Excess in cardiovascular events on Mondays: A meta-analysis and prospective study. *J Epidemiol Community Health.* 2005 Feb; 59 (2): 109-114. Review. PMID: 15650141; PMCID: PMC1733011.	Examines cardiovascular events on Mondays, not alcohol and incident CVD/CHD.

Chatfield J; Stroke Council of the American Heart Association. American Heart Association scientific statement on the primary prevention of ischemic stroke. *Am Fam Physician*. 2001 Aug 1; 64 (3): 513-514. PMID: 11515840.	Does not specifically answer question related to alcohol intake and CVD/CHD.
Chen L, Davey Smith G, Harbord RM, Lewis SJ. Alcohol intake and blood pressure: A systematic review implementing a Mendelian randomization approach. *PLoS Med*. 2008 Mar 4; 5 (3): e52. Review. PMID: 18318597; PMCID: PMC2265305.	Does not specifically answer question of CVD/CHD. Focus is blood pressure.
Daniel S, Bereczki D. Alcohol as a risk factor for hemorrhagic stroke. *Ideggyogy Sz*. 2004 Jul 20; 57 (7-8): 247-256. Review. PMID:15330400.	Does not directly answer question related to CVD/CHD. Focus is hemorrhagic stroke.
Djoussé L, Gaziano JM. Alcohol consumption and heart failure: A systematic review. *Curr Atheroscler* Rep. 2008 Apr; 10 (2): 117-120. Review. PMID: 18417065; PMCID: PMC2365733	Narrative review.
Hillbom M, Juvela S, Numminen H.Alcohol intake and the risk of stroke. *J Cardiovasc Risk*. 1999 Aug; 6 (4): 223-228. Review. PMID: 10501273.	Does not directly answer question related to CVD/CHD. Focus is stroke.
de Gaetano G, Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB. A meta-analysis of studies on wine and beer and cardiovascular disease. *Pathophysiol Haemost Thromb.* 2002 Sep-Dec; 32(5-6): 353-355. PMID: 13679674.	Reports on same meta-analysis as the included Di Castelnuovo, et al, 2002.
Grønbaek M.Type of alcohol and mortality from cardiovascular disease. *Food Chem Toxicol*. 1999 Sep-Oct; 37 (9-10): 921-924. PMID: 10541445.	Narrative review.
Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: A systematic review. *Ann Intern Med.* 2004 Feb 3; 140 (3): 211-219. PMID: 14757619.	Does not directly answer question related to CVD/CHD. The focus is diabetes.
Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Exploring the relationship between alcohol consumption and non-fatal or fatal stroke: A systematic review. *Diabetologia.* 2006 Apr; 49 (4): 648-652. Epub 2006 Feb 4. PMID: 16463045.	Does not directly answer question related to CVD/CHD. Focus is stroke.

Marmot MG.Alcohol and coronary heart disease. *Int J Epidemiol.* 2001 Aug; 30 (4): 724-729. PMID: 11511592.	Narrative review.
Mazzaglia G, Britton AR, Altmann DR, Chenet L.Exploring the relationship between alcohol consumption and non-fatal or fatal stroke: A systematic review. Dec; 96 (12): 1, 743-1, 756. Review. PMID: 11784467.	Does not directly answer question related to CVD/CHD. Focus is stroke.
Mukamal KJ, Rimm EB.Alcohol's effects on the risk for coronary heart disease. *Alcohol Res Health.* 2001; 25 (4): 255-261. Review. PMID: 11910702.	Narrative review.
Mukamal KJ. Alcohol use and prognosis in patients with coronary heart disease. *Prev Cardiol*. 2003 Spring; 6 (2): 93-98. Review. PMID: 12732795.	Met excluded criteria: Subjects diagnosed with CHD.
Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: A meta-analysis. *JAMA*. 2003 Feb 5; 289 (5): 579-588. Erratum in: *JAMA.* 2003 Jun 4; 289 (21): 2, 798. Lewis, Brian L [corrected to Lewis, Brian]. PMID: 12578491.	Does not directly answer question related to CVD/CHD. Focus is stroke.
Rotondo S, Di Castelnuovo A, de Gaetano G. The relationship between wine consumption and cardiovascular risk: From epidemiological evidence to biological plausibility. *Ital Heart J.* 2001 Jan; 2 (1): 1-8. Review. PMID: 11214695.	Narrative review.
Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of Alcohol Reduction on Blood Pressure: A meta-analysis of randomized controlled trials. *Hypertension*. 2001 Nov; 38 (5): 1, 112-1, 117.	Does not directly answer question related to CVD/CHD.

CHAPTER 6. HEALTH-RELATED OUTCOMES – ALCOHOL INTAKE PATTERNS AND CORONARY HEART DISEASE

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL INTAKE PATTERNS AND CORONARY HEART DISEASE?

Conclusion statement

Insufficient evidence was available to determine if drinking patterns were predictive of risk of CHD, although there was moderate evidence to suggest that heavy or binge drinking is detrimental.

Grade

Insufficient

Evidence summary overview

Related to the association between alcohol consumption and risk of coronary heart disease (CHD), six systematic reviews/meta-analyses were reviewed. This evidence included four methodologically strong meta-analyses (Bagnardi, 2008; Corrao, 2000; Di Castelnuovo, 2002; and Rimm, 1999); one methodologically neutral meta-analysis (Cleophas, 1999) and one systematic review that was methodologically neutral (Britton and McKee, 2000).

Overall, the evidence shows that compared to those who abstain from alcohol, regular light to moderate drinking can reduce the risk of CHD; whereas, heavy irregular or binge drinking increases risk of CHD. In a meta-analysis of 20 observational studies, Bagnardi et al, (2008) found significant differences in the alcohol intake dose response relationship to CHD risk in regular vs. irregular drinkers. These authors concluded that the consumption of alcohol on more than two days per week has a significant protective effect against CHD. Cleophas et al, (1999) found that alcohol consumption at one to four drinks per day reduced risk of mortality and CHD, while more than five drinks per day increased risk of mortality, and wine, beer and spirits were equally beneficial. Interestingly, a meta-analysis conducted by Corrao et al, (2000) of 43 cohort studies, found that in Mediterranean countries, protective effects were seen up to 145g per day, but in all other countries, the protective effects were only seen up to 80grams per day. Di Castelnuovo et al, (2000) compared wine and beer consumption in a meta-analysis of 26 international studies. The relative risks of cardiovascular disease (CVD) were 0.68 (95% CI: 0.59-0.77) and 0.78 (95% CI: 0.70-0.86) for consumption of wine and beer, respectively, relative to non-drinkers. Rimm (1999) concluded that based on a meta-analysis of 42 randomized controlled trials (RCTs), alcohol consumption per se, not other components of alcoholic beverages, was responsible for the lower risk of CHD among moderate drinkers. Furthermore, based on measures of high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fibrinogen, to the degree documented in the meta-analysis, consumption of two standard drinks per day would lower a person's risk of CHD by approximately 25%. According to Britton and Mckee (2000) a systematic review of international studies, not only alcohol quantity, but also drinking patterns such as binge drinking, influenced CVD risk.

Collectively, the research suggests that whereas binge drinking (more than three alcoholic drinks every one to two hours) has harmful effects, light to moderate alcohol consumption spread over several days of the week has beneficial effects relative to CVD risk. Therefore, for a given volume of alcohol within a moderate drinking range, it is better to distribute this volume evenly over several days, rather than consuming it in two to three days.

Evidence summary paragraphs

Bagnardi et al, 2008 (positive quality) conducted a meta-analysis to evaluate whether drinking pattern, defined by the frequency of drinking days as well as drinking intensity per drinking occasion, modified the effect of alcohol intake on the risk of CHD. A Medline search for articles published between 1966 and 2006 was done using keywords related to disease (coronary heart disease, coronary death, myocardial infarction, ischemic heart disease), exposure (quantity or dose of alcohol intake and pattern of alcohol drinking) and frequency of alcohol drinking (regular, irregular, problem drinking, alcoholic intoxication, heavy episodic drinking, hangover). The final meta-analysis included six studies, four cohort studies and two case-control studies. Compared with those who abstained from alcohol, regular heavy drinkers had a reduced risk of CHD (RR 0.75; 95% CI: 0.64, 0.89) and heavy irregular or binge drinkers had an increased risk (RR 1.10; 95% CI: 1.03, 1.17). The dose-response relationship between the amount of alcohol consumed and CHD risk also differed between regular and irregular heavy drinkers (P<0.047). A J-shaped curve was seen for irregular drinkers: The nadir and the last protective dose of 28g per week (RR 0.59; 95% CI: 0.53 to 0.65) and 131g per week (RR 0.85; 95% CI: 0.72 to 0.99) were obtained included drinkers who consumed alcohol for two days a week or less. Conversely, in people who consumed alcohol for more than two days a week a significant protective effect was seen even when drinking high amounts of alcohol.

Britton and McKee, 2000 (neutral quality), presents the key findings of a comprehensive systematic review that examined the relationship between heavy drinking and irregular (binge) drinking and sudden cardiovascular mortality. Six prospective cohort studies, conducted in Europe and the US, were included, as well as a number of case-control studies. The prospective follow-up ranged from 6.7 to 40 years. The authors found considerable evidence that binge drinkers as are at greater risk of cardiac arrhythmias and sudden cardiac death. The evidence also supported a temporal and dose-response relationship for sudden cardiac death and for fatal myocardial infarction (MI). The authors concluded that physiological evidence indicates that a causal relationship is biologically plausible, and that the effects of binge drinking are quite different from those seen with regular moderate and even heavy drinking.

Cleophas, 1999 (neutral quality), a meta-analysis of 20 international studies, assessed the relationship between MI and consumption of different types of alcoholic beverages, both in low doses (one to four drinks per day) and high doses (more than four drinks per day). Eight cohort studies were included that reported on the association between alcohol consumption irrespective of the type of drink and cardiovascular death, as well as twelve prospective cohort studies that reported on the risk of MI and specific types of alcoholic drinks. Small doses of alcohol were associated with a reduced risk of mortality and CHD, while more than five drinks per

day increased the risk of mortality; wine, beer and spirits were equally beneficial.

Corrao et al, 2000 (positive quality) conducted a meta-analysis to evaluate the relationship between alcohol consumption and risk of CHD. Searches were conducted using Medline, Current Content, EMBASE, CAB, and Core Biomedical Collection, and a hand search of general reviews and meta-analyses published on issue was performed. The search included studies published between 1966 and 1998, and used the keywords for disease (coronary heart disease, coronary artery disease, coronary event, coronary death, myocardial infarction, ischemic heart disease and angina pectoris) and alcohol consumption (alcohol or ethanol and consumption, intake and drinking). The final sample included 43 cohort studies, eight case-control studies. Results from all 51 studies showed that a protective effect was evident up to 90g per day (RR=0.94; 95%CI: 0.90, 1.00), with harmful effects evidence at 113g per day (RR=1.08; 95%CI: 1.00, 1.16). These effects were modified when only the high quality studies (N=28) were considered, such that a protective effect was evident up to 72g per day (RR=0.96; 95%CI: 0.92, 1.00), and harmful effects were evident at 89g per day (RR=1.05; 95%CI: 1.00, 1.11). When examining data from females only, a protective effect evident up to 31g per day (RR=0.93; 95%CI: 0.87, 1.00), and harmful effects were evident at 52g per day (RR=1.12; 95%CI: 1.00, 1.26); for males, a protective effect was evident up to 87g per day (RR=0.94; 95%CI: 0.88, 1.00), and harmful effects were evident at 114g per day (RR=1.09; 95%CI: 1.00, 1.19). When looking at Mediterranean countries, protective effects were seen up to 145g per day (RR=0.76; 95%CI: 0.61, 1.00), but in all other countries as a whole, protective effects were only seen up to 80g per day (RR=0.93; 95%CI: 0.87, 1.00).

Di Castelnuovo et al, 2002 (positive quality), a meta-analysis of 26 international studies, studied the relationship between wine or beer consumption and CVD. From 13 studies, the RR of vascular disease associated with wine intake was 0.68 (95% CI: 0.59-0.77) relative to non-drinkers, and 10 studies supported a J-shaped relationship between different amounts of wine intake and vascular risk. A statistically significant inverse relationship was found up to a daily intake of 150ml of wine. From 15 studies, the relative risk of vascular disease associated with moderate beer consumption was 0.78 (95% CI: 0.70-0.86). However, no significant (NS) relationship between different amounts of beer intake and vascular risk was found.

Rimm et al, 1999 (positive quality) a meta-analysis of 42 experimental trials quantitatively examined the association between moderate alcohol intake and CHD risk. All of these trials offered the advantage of being randomized design, but all we relatively small. Trials were weighted according to number of study participants. Consumption of 30g alcohol per day (approximately two standard drinks) increased HDL levels by 4.0mg/dL, which was associated with an adjusted 16.8% decrease in CHD risk. Fibrinogen concentration also decreased by 7.5mg/dL, but the decrease was NS. Conversely, TG levels increased by an estimated 5.7% resulting in a 4.6% increase in CHD risk, which slightly attenuated the alcohol benefit. Taken together, the estimated changes in HDL, TG and fibrinogen levels induced by consumption of 30g of alcohol result in a 24.7% reduction in the risk of CHD

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Significant Outcomes
Bagnardi V, Zatonski et al, 2008 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality	N=six studies (four cohort studies, two case-control studies).	Compared with those who abstained from alcohol, regular heavy drinkers had a ↓ risk of CHD (RR 0.75; 95% CI: 0.64, 0.89) and heavy irregular or binge drinkers had an ↑ risk (RR 1.10; 95% CI: 1.03, 1.17). Dose-response relationship between amount of alcohol consumed and CHD risk also differed between regular and irregular heavy drinkers (P<0.047). A J-shaped curve seen for irregular drinks: The nadir and the last protective dose of 28g per week (RR 0.59; 95% CI: 0.53 to 0.65) and 131g per week (RR 0.85; 95% CI: 0.72 to 0.99) were obtained included drinks who consumed alcohol for ≤two days a week. For people who consumed alcohol >two days a week, a significant protective effect was seen even when drinking ↑ amounts of alcohol.

Britton A and McKee M, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating: Neutral Quality	N=six prospective cohort studies with 6.7 to 40 years of follow-up; three selected case-control studies. Subjects were adult males. Location: Europe and the United States.	Considerable evidence from both cohort and case-control studies that binge drinkers are at ↑ risk of cardiac arrhythmias and sudden cardiac death. Physiological and case-control studies provide evidence of a temporal relationship between binge drinking and death. Consistent evidence of a dose-response relationship between binge drinking and sudden cardiac death and for fatal MI. A causal relationship is biologically plausible, and the effects of binge drinking are quite different from those seen with regular moderate, and even heavy drinking.
Cleophas TJ 1999 Study Design: Meta-analysis/Systematic Review Class: M Rating: Neutral Quality	N=20 international studies assessing the relationship between MI and consumption of different types of alcoholic beverages, both in low doses (one to four drinks per day) and high doses (>four drinks per day). Eight cohort studies reported on association between alcohol consumption irrespective of type of drink and cardiovascular death. 12 prospective cohort studies reported on risk of MI and specific types of alcoholic drinks.	Small doses of alcohol associated with ↓ risk of mortality and CHD, while >five drinks per day ↑ risk of mortality; wine, beer and spirits were equally beneficial.

Corrao G, Rubbiati L et al, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality	N=43 cohort studies, eight case-control studies.	Results from all 51 studies showed that a protective effect was evident up to 90g per day (RR=0.94; 95%CI: 0.90, 1.00), with harmful effects evidence at 113g per day (RR=1.08; 95%CI: 1.00, 1.16). Effects were modified when only the high quality studies (N=28) were considered, such that a protective effect was evident up to 72g per day (RR=0.96; 95%CI: 0.92, 1.00) and harmful effects were evident at 89g per day (RR=1.05; 95%CI: 1.00, 1.11). For females, protective effect evident up to 31g per day (RR=0.93; 95%CI: 0.87, 1.00) and harmful effects evident at 52g per day (RR=1.12; 95%CI: 1.00, 1.26). For males, protective effect evident up to 87g per day (RR=0.94; 95%CI: 0.88, 1.00) and harmful effects evident at 114g per day (RR=1.09; 95%CI: 1.00, 1.19).

Di Castelnuovo et al 2002 Study Design: Meta-analysis Class: M Rating: Positive Quality	N=26 international studies, studying relationship between wine or beer consumption and CVD.	From 13 studies, the RR of vascular disease associated with wine intake was 0.68 (95% CI: 0.59-0.77) relative to non-drinkers and 10 studies supported a J-shaped relationship between different amounts of wine intake and vascular risk. A statistically significant inverse relationship found up to a daily intake of 150ml of wine. From 15 studies, RR of vascular disease associated with moderate beer consumption was 0.78 (95% CI: 0.70-0.86). However, NS relationship between different amounts of beer intake and vascular risk.
Rimm EB, Williams P et al, 1999 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality	N=42 randomized trials.	RR for CHD with ethanol (30g per day): HDL: 0.69 (95% CI: 0.47-0.99) per 10mg/d^2. Fibrinogen: 1.34 (95% CI: 1.15-1.56) per 10mg/d^2. TG: 1.40 (1.10 to 1.77) per 10mg/d^2.

Search plan and results

Inclusion criteria

- January 1, 1995 through June 8, 2009
- Systematic reviews/meta-analyses only
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- Dropout rate: Less than 20%; preference for smaller dropout rates
- Ages: Adults of legal drinking age (21 years and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, hypertension, Type 2 diabetes, osteoporosis, osteopenia and obesity) and those with breast cancer, colon cancer and/or prostate cancer.

Exclusion criteria

- Medical treatment/therapy
- Diseased subjects (exceptions noted)
- Hospitalized patients
- Malnourished/third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)
- Cross-sectional study design.

Search terms and electronic databases used

- PubMed

  "Cardiovascular Diseases"[Mesh] OR “Heart Diseases"[Mesh] OR "Stroke"[Mesh] AND ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) "Stroke"[Mesh] AND ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh])

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5. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation*. 2002 Jun 18; 105 (24): 2, 836-2, 844. PMID : 12070110.
6. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: Meta-analysis of effects on lipids and haemostatic factors. *BMJ.* 1999 Dec 11; 319 (7224): 1, 523-1, 528. PMID : 10591709; PMCID: PMC 28294.

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Chatfield J; Stroke Council of the American Heart Association. American Heart Association scientific statement on the primary prevention of ischemic stroke. *Am Fam Physician*. 2001 Aug 1; 64 (3): 513-514. PMID: 11515840.	Does not specifically answer question related to alcohol intake and CVD/CHD.
Chen L, Davey Smith G, Harbord RM, Lewis SJ. Alcohol intake and blood pressure: A systematic review implementing a Mendelian randomization approach. *PLoS Med*. 2008 Mar 4; 5 (3): e52. Review. PMID: 18318597; PMCID: PMC2265305.	Does not specifically answer question of CVD/CHD. Focus is blood pressure.

Daniel S, Bereczki D. Alcohol as a risk factor for hemorrhagic stroke. *Ideggyogy Sz*. 2004 Jul 20; 57 (7-8): 247-256. Review. PMID:15330400.	Does not directly answer question related to CVD/CHD. Focus is hemorrhagic stroke.
Djoussé L, Gaziano JM. Alcohol consumption and heart failure: A systematic review. *Curr Atheroscler* Rep. 2008 Apr; 10 (2): 117-120. Review. PMID: 18417065; PMCID: PMC2365733	Narrative review.
Hillbom M, Juvela S, Numminen H.Alcohol intake and the risk of stroke. *J Cardiovasc Risk*. 1999 Aug; 6 (4): 223-228. Review. PMID: 10501273.	Does not directly answer question related to CVD/CHD. Focus is stroke.
de Gaetano G, Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB. A meta-analysis of studies on wine and beer and cardiovascular disease. *Pathophysiol Haemost Thromb.* 2002 Sep-Dec; 32(5-6): 353-355. PMID: 13679674.	Reports on same meta-analysis as the included Di Castelnuovo, et al, 2002.
Grønbaek M.Type of alcohol and mortality from cardiovascular disease. *Food Chem Toxicol*. 1999 Sep-Oct; 37 (9-10): 921-924. PMID: 10541445.	Narrative review.
Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: A systematic review. *Ann Intern Med.* 2004 Feb 3; 140 (3): 211-219. PMID: 14757619.	Does not directly answer question related to CVD/CHD. The focus is diabetes.
Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Exploring the relationship between alcohol consumption and non-fatal or fatal stroke: A systematic review. *Diabetologia.* 2006 Apr; 49 (4): 648-652. Epub 2006 Feb 4. PMID: 16463045.	Does not directly answer question related to CVD/CHD. Focus is stroke.
Marmot MG.Alcohol and coronary heart disease. *Int J Epidemiol.* 2001 Aug; 30 (4): 724-729. PMID: 11511592.	Narrative review.
Mazzaglia G, Britton AR, Altmann DR, Chenet L.Exploring the relationship between alcohol consumption and non-fatal or fatal stroke: A systematic review. Dec; 96 (12): 1, 743-1, 756. Review. PMID: 11784467.	Does not directly answer question related to CVD/CHD. Focus is stroke.

Mukamal KJ, Rimm EB.Alcohol's effects on the risk for coronary heart disease. *Alcohol Res Health.* 2001; 25 (4): 255-261. Review. PMID: 11910702.	Narrative review.
Mukamal KJ. Alcohol use and prognosis in patients with coronary heart disease. *Prev Cardiol*. 2003 Spring; 6 (2): 93-98. Review. PMID: 12732795.	Met excluded criteria: Subjects diagnosed with CHD.
Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: A meta-analysis. *JAMA*. 2003 Feb 5; 289 (5): 579-588. Erratum in: *JAMA.* 2003 Jun 4; 289 (21): 2, 798. Lewis, Brian L [corrected to Lewis, Brian]. PMID: 12578491.	Does not directly answer question related to CVD/CHD. Focus is stroke.
Rotondo S, Di Castelnuovo A, de Gaetano G. The relationship between wine consumption and cardiovascular risk: From epidemiological evidence to biological plausibility. *Ital Heart J.* 2001 Jan; 2 (1): 1-8. Review. PMID: 11214695.	Narrative review.
Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of Alcohol Reduction on Blood Pressure: A meta-analysis of randomized controlled trials. *Hypertension*. 2001 Nov; 38 (5): 1, 112-1, 117.	Does not directly answer question related to CVD/CHD.

CHAPTER 7. HEALTH-RELATED OUTCOMES – UNINTENTIONAL INJURY

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL INTAKE AND UNINTENTIONAL INJURY?

Conclusion statement

Strong evidence demonstrates that drinking in excess of current guidelines increases the risk of unintentional falls, motor vehicle crashes and drowning. When alcohol is consumed in moderation, the evidence for risk of unintentional injury is less well established for activities such as driving, swimming and athletic participation, but abstention from alcohol is the safest.

Grade

Strong

Evidence summary overview

This systematic review of 21 US and international studies dating back to 2004, included four systematic reviews (Cherpitel, 2007; Driscoll, Harrison, and Steenkamp, 2004; Gonzalez-Wilhelm, 2007; Kool, 2009), six cohort studies (Bedford, 2006; Driscoll, 2004; Hall, 2009; Hingson and Zha, 2009; Johnson, 2004; Mukamal, 2004;), five case-control studies (Kool, 2008; Kurzthaler, 2005; Sorock, 2006; Watt, 2004; Yoonhee, 2009), five cross-sectional studies (Hingson, 2009; Levy, 2004; McLean, 2009; Rehm, 2006; Watt, 2006) and one trend study (McDonald, 2004). Kool, 2009 and Watt, 2006 were deemed positive quality studies. Johnston and McGovern, 2004 was assessed as negative quality; all other studies were deemed to be neutral quality.

All of the studies found that alcohol consumption was positively associated with risk of unintentional injuries, and found associations with a wide range of different types of injuries. For example, many studies focused specifically on head injuries, spinal cord injuries and soft tissue injuries (Cherpitel, 2007; Hingson and Zha, 2009; Hingson, 2009; Johnston, 2004; Levy, 2004; McDonald, 2004; McLean, 2009; Norstrom, 2005; Rehm, 2006; Watt, 2006; Yoonhee, 2009) while others were related to fatal and non-fatal motor vehicle crashes (Bedford, 2006; Gonzalez-Wilhelm, 2007; Hingson and Zha, 2009; Hingson, 2009; Levy, 2004; Sorock, 2006), boating incidents (Driscoll, 2004) and all-terrain vehicle crashes (Hall, 2009).

Four studies found that even when consumed in moderation, alcohol consumption increases risk of falling (Kool, 2008; Kool, 2009; Kurzthaler, 2005; Mukamal, 2004; Sorock, 2006). Also, an association was shown between drinking alcohol and drowning (Driscoll, 2004; Driscoll, Harrison, and Steenkamp, 2004; Levy, 2004). Other areas of unintentional injury linked to alcohol consumption include suicide, fire-related injuries, and violence-related injury.

One study found evidence of a dose-response relationship between alcohol intake and injury (Kool, 2009), and several studies found that risk of unintentional injury tended to increase significantly after drinking two or more drinks per day (Kool, 2008; Mukamal, 2004; Watt, 2004).

Evidence summary paragraphs

Bedford et al, 2006 (neutral quality), a retrospective cohort study conducted in Ireland, identified the blood alcohol concentrations (BAC) in persons who died as a result of accidental death or suicide through the review of coroner's records from 2001 to 2002. There were 129 deaths eligible for inclusion, 98 (76%) were male and 113 (87.5%) were adults aged 18 years and over; BACs were available for 83% of the subjects. Of the 129 deaths, 55 (42.6%) were road traffic accidents, 31 (24.0%) were suicides, 12 (9.3%) were substance misuse, 11 (8.5%) were house fires, 7 (5.4%) were industrial and farming accidents and 13 (10.1%) were classified as other accidents. Of the 55 who died in road traffic accidents, 22 (40%) had positive BACs ranging from 16mg per 100ml to 325mg per 100ml. Of the 31 who died as a result of suicide, 16 (55.5%) had positive BACs ranging from 13mg per 100ml to 317mg per 100ml. Of the 11 who died in house fires, the mean BAC was 225.2mg per 100ml. None of those who died as a result of an industrial or farming accident had alcohol detected in their blood.

Cherpitel, 2007 (neutral quality), a systematic review of international studies including 56 references, reviewed emergency room studies on alcohol and injury, using representative probability samples of adult injury patients. Findings supported prior reviews: Injured patients were more likely to be positive for blood alcohol concentration and report drinking within six hours prior to injury than non-injured patients, and the magnitude of the association substantially increased for violence-related injuries compared to non-violence-related injuries. However, indicators of alcohol use disorders did not show a strong association with injury.

Driscoll et al, 2004 (neutral quality), a retrospective cohort study conducted in Australia, examined the contribution of alcohol to drowning deaths through the review of deaths in the National Coroners Information System (NCIS) from July 2000 to June 2001. There were 6,259 total deaths that were not classified as natural cause deaths and 289 drowning deaths were identified; valid blood alcohol measurements were available for 137 (58%) deaths. The level of blood alcohol ranged from 0g per 100ml in 47% of cases, to 0.10g per 100ml or greater in 12% of cases. Alcohol contributed to approximately 19% of these fatal drowning incidents (25% for recreational aquatic activity, 16% for incidental falls into water, and 12% for drowning due to suicide), with blood alcohol levels for these cases ranging from 0.020g per 100ml to 0.375g per 100ml. Using greater than 0.10g per 100ml as the cut-off, the estimated all-ages proportion of unintentional drowning attributed to alcohol was 17%.

Driscoll, Harrison and Steenkamp, 2004 (neutral quality), a systematic review of 65 international references, assessed the role of alcohol in drowning associated with recreational aquatic activity. Of the 65 references, 10 were studies regarding alcohol involvement in deaths arising from recreational swimming, 13 were studies regarding alcohol involvement in deaths arising from recreational boating, and five were published estimates of risk or relative risk (RR) of fatal injury in relation to recreational aquatic activity. Surveys have consistently stated that approximately 30% to 40% of people on boats drink alcohol while on board, that men tend to drink more and behave in higher-risk aquatic activities in association with drinking than women, and that boater training is inadequate. Drowning appears to be the overwhelming cause of death associated with recreational aquatic activity, with alcohol detected in the blood of

30% to 70% of persons; alcohol may contribute to 10% to 30% of all recreational drowning deaths. Studies suggest that persons with a blood alcohol level of 0.10g per 100ml have about 10 times the risk of death associated with recreational boating compared with persons who have not been drinking; the risk of drowning increases with increasing blood concentration of alcohol.

Gonzalez-Wilhelm, 2007 (neutral quality), a systematic review of 31 international studies, determined the reported prevalence of alcohol and illicit drugs in blood specimens from drivers involved in traffic law offenses. Of the 31 studies, 11 represented studies of fatally injured drivers, nine represented studies of drivers who survived road traffic accidents, two represented studies of drivers primarily suspected of driving under the influence of alcohol and nine represented studies of drivers primarily suspected of driving under the influence of drugs. Alcohol was the predominant substance, with a prevalence of 22.2% to 57.1% in studies of fatally injured drivers, 20.0% to 26.0% in studies of drivers who survived road traffic accidents, 88.1% to 95.5% in studies of drivers primarily suspected of driving under the influence of alcohol and 25.8% to 49.2% in studies of drivers primarily suspected of driving under the influence of drugs. However, in studies of drivers primarily suspected of driving under the influence of drugs, cannabinoids were more prevalent (26.1% to 59.3%).

Hall et al, 2009 (neutral quality), a retrospective cohort study conducted in the US, evaluated injury types and alcohol use in fatal all-terrain vehicle crashes. Cases were identified by searching the database of vital records at the Health Statistics Center of the West Virginia Department of Health and Human Resources for death certificates from 2004 to 2006. During that time, 112 fatal all-terrain vehicle crashes were identified; 101 (90.2%) were male, aged eight to 88 years (mean 35 years). Toxicologic testing was completed on 104 (92.9%) decedents, and 60 (57.7%) were positive for either alcohol or drugs of abuse, including opioid analgesics, diazepam, marijuana, cocaine and methamphetamine. Regardless of type of crash (traffic vs. non-traffic), 51 (49%) of decedents were positive for alcohol, and of those, 88% had blood alcohol concentrations higher than 0.08% (mean = 0.17%).

Hingson and Zha, 2009 (neutral quality), a prospective cohort study conducted in the US, explored whether early age of drinking onset is associated with respondents unintentionally injuring themselves and others when under the influence of alcohol. In-person interviews were conducted from 2001 to 2002 (wave one) in 43,093 adults aged 18 and older (mean age 45 years) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), and 34,653 adults were re-interviewed from 2004 to 2005 (wave two). Analyses revealed that the younger respondents were when they started drinking, the greater the likelihood that, between the waves, they experienced alcohol dependence/abuse, drank five drinks per occasion at least weekly, drove under the influence of alcohol and placed themselves in situations after drinking where they could be hurt. In addition, between the waves, respondents who began drinking at earlier ages remained more likely to have unintentionally injured themselves and someone else when under the influence of alcohol. When respondents were under the influence of alcohol, 20% of those injured were other people, with more than one-third in traffic crashes.

Hingson et al, 2009 (neutral quality), a cross-sectional study conducted in the US,

explored whether early drinkers take more risks even when sober by comparing potential associations between age of drinking onset and these outcomes after drinking relative to when respondents have not been drinking. Out of 5,778 current or former drinkers aged 18 to 39 from a national sample responding to a screening e-mail, 4,021 completed the survey (3,409 completed the survey online, 612 completed the survey by telephone). Of the 4,021 completing the survey, 1,225 were aged 18 to 25 years, 1,793 were aged 26 to 35 years and 787 were aged 36 to 39 years. Among all respondents, 38% had been a driver in a motor vehicle crash and 14% of those drivers were in accidents that occurred after they had been drinking; 34% reported being in a physical fight and 64% of them were in fights that occurred after drinking and 27% had been accidentally injured, with 50% of them injured after drinking. Compared with persons who waited until age 21 or older to start drinking, those who started drinking at age 14 years had 6.3 (95% CI: 2.6, 15.3) greater odds of having been in a motor vehicle crash after drinking, 4.6 (95% CI: 2.4, 8.7) greater odds of having been in a physical fight after drinking, and 5.2 (95% CI: 2.7, 10.2) greater odds of having been accidentally injured after drinking.

Johnston and McGovern, 2004 (negative quality), a prospective cohort study conducted in Ireland, compared the pattern and severity of fall-related injuries in patients with or without alcohol exposure. A total of 351 healthy adults presenting to the Ulster Hospital between November 2001 and July 2002 with fall injuries were included in the analysis; 113 had consumed alcohol and 238 had not, based on appearance, and blood alcohol concentrations were measured for 47 patients giving consent. There was a significant difference in the pattern of injury between those who had consumed alcohol and those who had not ($P<0.001$) and there was a significant difference between groups in the Injury Severity Scores ($Z=-2.5$, $P<0.001$). For those who consumed alcohol, severity and pattern correlated with alcohol concentration at the time of injury; patients with an alcohol concentration less than 2g per L had mostly soft tissue limb injuries (58%), 2g to 2.5g per L had mostly significant limb fractures (55%) and more than 2.5g per L had mostly significant head injuries (90%).

Kool et al, 2008 (neutral quality), a population-based case-control study conducted in New Zealand, examined the contribution of alcohol to fatal and hospitalized injuries due to unintentional falls at home among working-aged adults. Cases were identified through each of the three trauma admitting hospitals for the region and the Coroner's office, and controls comprised a random sample of people from the General and Maori electoral rolls in the region. Interviews were conducted by telephone or face-to-face, and proxy interviews with next-of-kin or close friends were undertaken for cases who had died or who were too unwell to be interviewed. A total of 335 cases (180 females, 155 males, mean age 45.9 years) and 352 controls (208 females, 144 males, mean age 44.6 years) were interviewed; blood alcohol measurements were only available for cases. The consumption of two or more standard alcoholic drinks in the preceding six hours relative to none was associated with a significantly increased risk of fall-related injury [for two standard drinks: OR=3.7 (95% CI: 1.2 to 10.9), for three or more drinks: OR=12.9 (95% CI: 5.2 to 31.9)]. Approximately 20% of unintentional falls at home may be attributable to the consumption of two or more drinks in the preceding six hours.

Kool et al, 2009 (positive quality), a systematic review of eight studies published in the US, Finland, Sweden and Canada, appraised the published epidemiological evidence quantifying the risk of falls associated with acute and usual alcohol consumption

among young and middle-aged adults. Of the eight studies, four were case-control studies, three were cohort studies and one was a case-crossover study. The proportion of fall subjects who had been drinking within six hours of the event ranged from 14% to 53%; acute alcohol use accounted for at least a three-fold increase in unintentional fall risk. Modest evidence of a dose-response relationship with acute alcohol use was observed; however, the association between usual alcohol use and fall risk was inconclusive.

Kurzthaler et al, 2005 (neutral quality), a case-control study conducted in Austria, obtained an epidemiologic measure of the relationship between fall-related accidents and alcohol consumption and benzodiazepine use in patients. Cases were patients admitted to the emergency room injured by falls over a 12-month period, and controls were patients admitted for accidents of other causes. A total of 615 cases (44.1% male, 55.9% female; mean age 64.8±20.8 years) and 996 controls (74.1% male, 25.9% female; mean age 40.5±16.2 years) were included in the analysis. Of the 615 cases, 22% tested positive for alcohol, 55% tested positive for benzodiazepines, and 1.5% tested positive for both substances. A significant number of males tested positive for alcohol than females (40.2% vs. 7.6%). The percentage of both male and female patients who had consumed alcohol at the time of the accident decreased significantly with age, across all age groups ($P<0.001$). In persons up to 70 years of age, the consumption of alcohol in males and females was substantially higher in patients hurt by a sudden fall (males = 49.7%, females = 18.9%) than in an age-matched sample of patients involved in accidents of other causes (males = 20.6%, females = 3.1%, $P<0.001$).

Levy et al, 2004 (neutral quality), a cross-sectional study conducted in the US, examined the relationship between alcohol involvement and outcome of injury (both fatal or non-fatal) by sex, age, race, time and the cause of injury using multiple years of data on fire and scald burns, submersions, spinal cord injuries and traumatic brain injuries. Data between 1988 and 1992 were obtained from a statewide, population-based injury surveillance system in Oklahoma. Alcohol involvement was defined as the percentage of people who imbibed alcohol on an average day. A total of 11,376 injured persons were studied and alcohol was known for 8,346 persons (73%), with 86% of fatalities and 69% of non-fatal cases. Total alcohol involvement ranged from 3.8% in scald burns to 34.2% for spinal cord injuries. In fire burns, mean alcohol involvement was significantly higher among persons killed than among survivors (30.7% vs. 11.0%, $\chi2=101.1$, $P<0.001$). A greater percentage of fatal non-work-related unintentional cases (32.5%) than non-fatal cases (11.7%) were alcohol involved ($\chi2=88.8$, $P<0.001$). Among non-fatal cases, a greater percentage of non-work-related unintentional injuries (11.7%) than work-related unintentional injuries (3.1%) were alcohol involved ($\chi2=14.8$, $P<0.001$). In scalds and other burns, mean alcohol involvement was similar among persons killed and among survivors (5.6% vs. 3.8%, $\chi2=0.2$, NS). Because of the small sample size of fatal non-work-related scald victims, comparisons were not made between fatal and non-fatal cases. In submersions, total alcohol involvement was similar for unintentional (23.9%) and intentional (17.4%) cases ($\chi2=0.5$, NS). Fatal cases were significantly more likely to be alcohol involved (31.0%) than non-fatal cases (6.2%) ($\chi2=43.0$, $P<0.001$). Alcohol-involved submersion cases were more than two times more likely to be fatal than non-alcohol-involved cases ($P=0.08$), even when controlling for victim age. Spinal cord injuries: Alcohol involvement between fatal and

non-fatal cases (33.3% vs. 34.1%, $\chi 2=0.1$) was not significant (NS). Among SCI cases associated with motor vehicle crashes, total alcohol involvement was slightly higher among non-fatal cases (42.3%) than among fatal cases (34.2%) ($\chi 2=2.4$, ns). Among non-fatal SCI cases, alcohol involvement was nearly twice as high in intentional (48.4%) than in unintentional (25.8%) injuries ($\chi 2=12.4$. $P<0.001$). In traumatic brain injury, of cases with known alcohol involvement, 38.5% of fatal and 42.3% of non-fatal cases involved alcohol ($\chi 2=4.8$, $P<0.05$). Alcohol involvement was higher among males (45% of cases) than females (27% of cases) ($\chi 2=117.2$, $P<0.001$). Nighttime and alcohol-involved injuries were slightly less likely to be fatal ($P<0.001$).

McDonald et al, 2004 (neutral quality), a trend analysis conducted in the US, examined the alcohol-related emergency department visits through the review of data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1992 through 2000. During these nine years, there were an estimated 68.6 million (95% CI: 65.6 to 71.7 million) emergency department visits attributable to alcohol, a rate of 28.7 (95% CI: 27.1 to 30.3) per 1,000 US population; the number of alcohol-related visits increased 18% during this period. Emergency department visit rates for diagnoses with alcohol-attributable fractions of one were highest for those who were aged 30 to 49 years, male and black.

McLean et al, 2009 (neutral quality), a cross-sectional study conducted in New Zealand, examined information regarding alcohol use and drinking location in order to better inform planning for local strategies to reduce alcohol-related harm in the future. Data was collected from first-presentation injury consultations for patients 16 years and older at three primary care facilities over a two-month period. A total of 317 eligible survey responses were obtained. The overall response rate was 71%. The age range of respondents was 16 to 84 years, with a mean age of 32 years and median age of 26; 37% of respondents were female. The anonymous survey provided information about the nature of the injury, alcohol use in the six hours prior to injury and identification of the location where the last drink was consumed. The results showed that 17% of respondents had had an alcoholic drink in the six hours prior to injury. Of this group, 36% had had moderate intake of alcohol and 64% a hazardous intake according to the Alcohol Advisory Council of New Zealand criteria for the maximum number of standard drinks on one drinking occasion of four for women and six for men. The mean number of standard drinks recalled by drinkers in the survey was nine. When comparing drinkers with non-drinkers (those who had not had a drink in the previous six hours), a greater proportion of women likely to be drinkers than men ($P=0.005$). Tertiary students were significantly more likely to have be drinkers ($P<0.001$). The mean age of drinkers was 21 years (95% CI: 19.6 to 22.8 years), and of non-drinkers 35 years (95% CI: 32.8 to 36.6 years). There was a statistically significant difference between the groups ($P<0.0001$) with respect to age. The mean number of standard drinks was 8.9 (median 7.7, SD 6.7). There was a significant association between hazardous intake and attributing one's injury to alcohol with those with hazardous intake more likely to attribute their injury to their drinking ($P=0.002$). The majority of drinkers (62%) had their last drink at a house or flat.

Mukamal et al, 2004 (neutral quality), a prospective and cross-sectional observational study conducted in the US, examined the relationship between alcohol consumption and risk of falls in 5,841 older adults (men and women aged older than 65 years) enrolled in the Cardiovascular Health Study. Self-reported alcohol intake was recorded

at baseline and included the number of drinks and frequency of consumption of beer, wine and spirits. Subjects were asked whether they changed their pattern of consumption during the previous five years and whether they ever regularly consumed five or more drinks daily. Data on self-reported falls was taken at baseline and every six months for four years. Cross-sectional analysis showed that before and after adjustment, prevalence of frequent falls was highest in abstainers and lowest in subjects who consumed 14 or more drinks per week (P=0.06). Longitudinal analysis results in no difference between abstainers and light to moderate drinkers in their risk of falls during follow-up. Subjects that consumed 14 or more drinks per week had a significantly higher risk of falls than abstainers in adjusted analyses (OR=1.25, 95% CI: 1.03 to 1.52, P=0.07). The HR for incident falls associated with consumption of 14 or more drinks per week was 1.20 (95% CI: 0.97 to 1.47) for white subjects and 1.51 (95% CI: 0.78 to 2.91) for black subjects. No interactions were found in subjects younger or older than 75, men or women or subjects who reported physical activity or gait speed were above or below the median level (P>0.2) for all.

Rehm et al, 2006 (neutral quality), a cross-sectional study examined the proportion of deaths "caused" or "prevented" by alcohol and premature deaths in Canada for 2001. Randomly drawn sample (initial N=13,090; final N=47% response rate; age greater than 15 years) from data taken from the Canadian Addiction Survey collected between 2003 and 2004. Subjects were interviewed by phone and completed a questionnaire that included seven-day self-reported alcohol intake. The analyses adjusted for drinking category, age and sex. Men consumed on average more than women and alcohol consumption decreased with age. The overall average age for an alcohol-attributable death was 45.9 years for men and 58.8 years for women. 3,892 alcohol-attributable deaths were estimated, accounting for 3,313 deaths among men and 579 among women. Among deaths caused by alcohol, the three biggest contributors were unintentional injuries, malignant neoplasms and digestive diseases.

Sorock et al, 2006 (neutral quality), a case-control study conducted in the US, determined the associations between drinking history and fatal injuries in the elderly, mainly from falls, motor vehicle crashes and suicides. A total of 1,735 cases (389 males, 339 females, aged 55 years and older) were selected from the 1993 National Mortality Follow-Back Survey, which provided national estimates of alcohol usage and demographic information among people who died from injuries and 13,381 controls (5,065 males, 8,316 females, aged 55 years and older) were selected from the 1992 National Longitudinal Alcohol Epidemiologic Survey, which provided national estimates of alcohol usage for the general public. Analysis indicated that 36% of cases and 29% of controls consumed 12 or more drinks in the prior 12 months. The unadjusted relative odds for drinkers vs. non-drinkers for falls was 1.7, for motor vehicle crashes was 1.7, and for suicides was 1.6. Drinking increased the risk of suicide more for women than for men; the adjusted odds ratio of suicide for women drinkers vs. non-drinkers was 2.5 (95% CI: 1.67 to 3.68), while for men drinkers vs. non-drinkers was 1.3 (95% CI: 1.00 to 1.65).

Watt et al, 2004 (neutral quality), a case-control study conducted in Australia, quantified the relationship between acute alcohol consumption and risk of injury, in the context of other potential confounding factors, such as substance use and risk-taking behavior. Of 727 patients aged 15 years and over that were treated at the emergency department for an injury, 543 were interviewed and 488 (311 males, 177 females)

were included in the analysis, as well as 488 population controls matched for gender, age group, neighborhood, day and time of injury. After controlling for demographic and situational variables, consuming any alcohol in the six hours prior to injury significantly increased risk of injury [OR=2.13 (95% CI: 1.3 to 3.9)], and drinking at levels above low-risk guidelines (higher than 40g alcohol per occasion for females, higher than 60g alcohol per occasion for males) increased injury risk by a factor of approximately 2.5 [OR=2.41 (95% CI: 1.1 to 5.2)]. In addition, drinking beer [OR=1.86 (95% CI: 0.9 to 3.9)], spirits [OR=3.05 (95% CI: 1.1 to 8.2)] or a combination of beverages [OR=3.16 (95% CI: 1.1 to 8.8)] increased risk of injury. When usual alcohol consumption patterns, risk-taking behavior and substance use were considered, changes in the effect of alcohol on injury risk were observed, demonstrating that the relationship between alcohol and injury appears confounded by these variables.

Watt et al, 2006 (positive quality), a cross-sectional study conducted in Australia, determined whether injury mechanism among injured patients is differentially distributed as a function of acute alcohol consumption. Every injured patient who presented to the Gold Coast Hospital Emergency Department for treatment of an injury sustained less than 24 hours prior to presentation was approached for an interview; 1,205 patients were approached, 789 were eligible and 593 injured patients (377 males, 216 females) were included in the final analysis (aged over 15 years). After adjustment for confounding variables, neither quantity nor type of alcohol was associated with injury mechanism; however, drinking setting was significantly associated with odds of sustaining an intentional vs. unintentional injury [OR=2.79 (95% CI: 1.4 to 5.6)], injury through being hit by or against something vs. other injury types [OR=2.59 (95% CI: 1.4 to 4.9)] and reduced odds of sustaining an injury through road traffic crashes vs. non-road traffic crashes [OR=0.02 (95% CI: 0.004 to 0.9)], compared with not drinking alcohol prior to injury.

Yoonhee et al, 2009 (neutral quality), a case-control study conducted in South Korea, evaluated the effects of alcohol consumption on injury type and severity in emergency department trauma patients. Of 1,188 patients requiring admission, the majority did not provide consent; of 407 patients, there were 123 cases in the intoxicated group (male:female ratio = 7.1:1, mean age 39±13.7 years) and 284 non-intoxicated controls (male:female ratio = 2.1:1, mean age 45.6±19.0 years). Head Abbreviated Injury Scale (AIS) score was significantly higher in intoxicated patients compared to non-intoxicated controls (1.1±1.7 vs. 0.6±1.2, P=0.008) and mortality was significantly higher in intoxicated patients than non-intoxicated controls (5.7% vs. 2.0%, P=0.003). There was a significantly higher number of intoxicated patients with severe injuries than non-intoxicated controls (21% vs. 11.7%, P=0.023) and specifically with head injuries (25.7% vs. 13.3%, P=0.004). There was NS difference found in the total length of hospitalization. However, the length of the intensive care unit admission was significantly longer in the intoxicated patients than in the non-intoxicated controls (1.9±4.6 days vs. 0.7±2.6 days, P<0.05).

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Significant Outcomes
Bedford, O'Farrell and Howell 2006 Study Design: Retrospective Cohort Study Class: B Rating: Neutral Quality	Reviewed coroner's records from 2001 to 2002. N=129 deaths eligible for inclusion, 98 (76%) male and 113 (87.5%) adults aged ≥18 years; blood alcohol concentrations (BAC) available for 83%. Location: Ireland.	Of the 129 deaths, 55 (42.6%) were road traffic accidents, 31 (24.0%) suicides, 12 (9.3%) substance misuse, 11 (8.5%) house fires, 7 (5.4%) industrial and farming accidents and 13 (10.1%) classified as other accidents. Of the 55 who died in road traffic accidents, 22 (40%) had positive BACs ranging from 16mg per 100ml to 325mg per 100 ml. Of the 31 who died as a result of suicide, 16 (55.5%) had positive BACs ranging from 13mg to 100ml to 317mg per 100 ml. Of the 11 who died in house fires, the mean BAC was 225.2mg per 100ml. None who died as a result of an industrial or farming accident had alcohol detected in their blood.
Cherpitel CJ 2007 Study Design: Systematic Review Class: M Rating: Neutral Quality	N=56 international references reviewing emergency room studies on alcohol and injury, using representative probability samples of adult injury patients.	Findings supported prior reviews: Injured patients more likely to be positive for BAC and report drinking within six hours prior to injury than non-injured patients, and the magnitude of the association substantially ↑ for violence-related injuries compared to non-violence-related injuries. However, indicators of alcohol use disorders did not show a strong association with injury.

Driscoll et al 2004 Study Design: Retrospective Cohort Study Class: B Rating: Neutral Quality	Review of deaths in the National Coroners Information System (NCIS) from July 2000 to June 2001. N=6,259 total deaths that were not classified as natural cause deaths and 289 drowning deaths were identified; valid blood alcohol measurements were available for 137 (58%) deaths. Location: Australia.	Level of blood alcohol ranged from 0g per 100ml in 47% of cases to 0.10g per ≥100ml in 12% of cases. Alcohol contributed to ~19% of these fatal drowning incidents (25% for recreational aquatic activity, 16% for incidental falls into water and 12% for drowning due to suicide), with blood alcohol levels for these cases ranging from 0.020g per 100ml to 0.375g per 100ml. Using >0.10g per 100ml as the cut-off, the estimated all-ages proportion of unintentional drowning attributed to alcohol was 17%.
Driscoll, Harrison and Steenkamp 2004 Study Design: Systematic Review Class: M Rating: Neutral Quality	N=65 international references assessing the role of alcohol in drowning associated with recreational aquatic activity. Of the 65 references, 10 were studies regarding alcohol involvement in deaths arising from recreational swimming, 13 were studies regarding alcohol involvement in deaths arising from recreational boating and five were published estimates of risk or RR of fatal injury in relation to recreational aquatic activity.	Surveys have consistently stated that ~30% to 40% of people on boats drink alcohol while on board, that men tend to drink more and behave in higher-risk aquatic activities in association with drinking than women and that boater training is inadequate. Drowning appears to be the overwhelming cause of death associated with recreational aquatic activity with alcohol detected in the blood of 30% to 70% of persons; alcohol may contribute to 10% to 30% of all recreational drowning deaths. Studies suggest that persons with a blood alcohol level of 0.10g per 100ml have about 10 times the risk of death associated with recreational boating compared with persons who have not been drinking; the risk of drowning ↑ with ↑ blood concentration of alcohol.

Gonzalez-Wilhelm 2007 Study Design: Systematic Review Class: M Rating: Neutral Quality	N=31 international studies. Of the 31 studies, 11 represented studies of fatally injured drivers, nine represented studies of drivers who survived road traffic accidents, two represented studies of drivers primarily suspected of driving under influence of alcohol and nine represented studies of drivers primarily suspected of driving under influence of drugs.	Alcohol was the predominant substance, with prevalence of 22.2% to 57.1% in studies of fatally injured drivers, 20.0% to 26.0% in studies of drivers who survived road traffic accidents, 88.1% to 95.5% in studies of drivers primarily suspected of driving under influence of alcohol and 25.8% to 49.2% in studies of drivers primarily suspected of driving under influence of drugs. However, in studies of drivers primarily suspected of driving under influence of drugs, cannabinoids were more prevalent (26.1% to 59.3%).
Hall et al 2009 Study Design: Retrospective Cohort Study Class: B Rating: Neutral Quality	Cases identified by searching the database of vital records at the Health Statistics Center of the West Virginia Department of Health and Human Resources for death certificates from 2004 to 2006. During that time, 112 fatal all-terrain vehicle crashes identified; 101 (90.2%) were male, aged eight to 88 years (mean 35 years). Toxicologic testing completed on 104 (92.9%) decedents. Location: United States.	Of 104 (92.9%) decedents with toxicologic testing, 60 (57.7%) were positive for either alcohol or drugs of abuse, including opioid analgesics, diazepam, marijuana, cocaine and methamphetamine. Regardless of type of crash (traffic vs. non-traffic), 51 (49%) of decedents were positive for alcohol, and of those, 88% had BACs >0.08% (mean = 0.17%).

Hingson and Zha 2009 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	Interviews were conducted from 2001 to 2002 (wave one) in 43,093 adults aged ≥18 years (mean 45 years) from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). N=34,653 adults re-interviewed from 2004 to 2005 (wave two). Location: United States.	Analyses revealed that the younger the respondents were when they started drinking, the ↑ likelihood that, between the waves, they experienced alcohol dependence/abuse, drank five drinks per occasion at least weekly, drove under influence of alcohol and placed themselves in situations after drinking where they could be hurt. In addition, between waves, respondents who began drinking at earlier ages remained more likely to have unintentionally injured themselves and someone else when under influence of alcohol. When respondents were under the influence of alcohol, 20% of those injured were other people, with >one-third in traffic crashes.
Hingson et al 2009 Study Design: Cross-sectional Study Class: D Rating: Neutral Quality	Out of 5,778 current or former drinkers aged 18 to 39 from national sample responding to a screening e-mail, 4,021 completed the survey (3,409 completed the survey online, 612 completed the survey by telephone). Of the 4,021 completing the survey, 1,225 were aged 18 to 25 years, 1,793 were aged 26 to 35 years and 787 were aged 36 to 39 years. Location: United States.	Among all respondents, 38% had been a driver in a motor vehicle crash and 14% of those drivers were in accidents that occurred after they had been drinking; 34% reported being in a physical fight and 64% of them were in fights that occurred after drinking, and 27% had been accidentally injured, with 50% of them injured after drinking. Compared with persons who waited until age ≥21 years to start drinking, those who started drinking at age 14 years had 6.3 (95% CI: 2.6, 15.3) greater odds of having been in a motor vehicle crash after drinking, 4.6 (95% CI: 2.4, 8.7) greater odds of having been in a physical fight after drinking, and 5.2 (95% CI: 2.7, 10.2) greater odds of having been accidentally injured after drinking.

Johnston and McGovern 2004 Study Design: Prospective Cohort Study Class: B Rating: Negative Quality	Total of 351 healthy adults presenting to the Ulster Hospital between November 2001 and July 2002 with fall injuries were included in the analysis N=113 had consumed alcohol and 238 had not, based on appearance and BACs were measured for 47 patients giving consent. Location: Ireland.	Significant difference in pattern of injury between those who had consumed alcohol and those who had not (P<0.001) and significant difference between groups in the Injury Severity Scores (Z=-2.5, P<0.001). For those who consumed alcohol, severity and pattern correlated with alcohol concentration at the time of injury: Patients with alcohol concentration <2g per L had mostly soft tissue limb injuries (58%), 2g to 2.5g per L had mostly significant limb fractures (55%) and >2.5g per L had mostly significant head injuries (90%).
Kool et al 2008 Study Design: Population-based Case-Control Study Class: C Rating: Neutral Quality	Cases identified through each of three trauma admitting hospitals for region and Coroner's office, and controls comprised random sample of people from General and Maori electoral rolls in the region. Interviews conducted by telephone or face-to-face and proxy interviews with next-of-kin or close friends undertaken for cases who had died or who were too unwell to be interviewed. Total of 335 cases (180 females, 155 males, mean age 45.9 years) and 352 controls (208 females, 144 males, mean age 44.6 years) interviewed; blood alcohol measurements only available for cases. Location: New Zealand.	Consumption of ≥two standard alcoholic drinks in preceding six hours relative to none was associated with significantly ↑ risk of fall-related injury [for two standard drinks: OR=3.7 (95% CI: 1.2 to 10.9), for ≥three drinks: OR=12.9 (95% CI: 5.2 to 31.9)]. ~20% of unintentional falls at home may be attributable to consumption of ≥two drinks in preceding six hours.

Kool et al 2009 Study Design: Systematic Review Class: M Rating: Positive Quality	Eight studies published in United States, Finland, Sweden and Canada appraised the published epidemiological evidence quantifying the risk of falls associated with acute and usual alcohol consumption among young and middle-aged adults. Of the eight studies: Four case-control studies Three cohort studies One case-crossover study.	Proportion of fall subjects who had been drinking within six hours of event ranged from 14% to 53%; acute alcohol use accounted for at least a three-fold ↑ in unintentional fall risk. Modest evidence of a dose-response relationship with acute alcohol use was observed; however, association between usual alcohol use and fall risk was inconclusive.
Kurzthaler et al 2005 Study Design: Case-Control Study Class: C Rating: Neutral Quality	Cases were patients admitted to the emergency room injured by falls over a 12-month period, and controls were patients admitted for accidents of other causes. Total of 615 cases (44.1% male, 55.9% female, mean age 64.8±20.8 years) and 996 controls (74.1% male, 25.9% female, mean age 40.5±16.2 years) included. Location: Austria.	Of the 615 cases, 22% tested positive for alcohol, 55% tested positive for benzodiazepines and 1.5% tested positive for both substances. Significant number of males tested positive for alcohol than females (40.2% vs. 7.6%). Percentage of both male and female patients who had consumed alcohol at the time of accident ↓ significantly with age, across all age groups (P<0.001). In persons up to 70 years of age, consumption of alcohol in males and females substantially ↑ in patients hurt by sudden fall (males 49.7%, females 18.9%), than in age-matched sample of patients involved in accidents of other causes (males 20.6%, females 3.1%, P<0.001).

Levy DT, Mallonee S et al, 2004 Study Design: Cross-Sectional Study Class: D Rating: Neutral Quality	Data from 1988 to 1992 on 11,376 persons were obtained from a statewide, population-based injury surveillance system in Oklahoma. Alcohol involvement and outcome of injury (both fatal or non-fatal) by sex, age, race, time and cause of injury using multiple years of data on fire and scald burns, submersions, spinal cord injuries and traumatic brain injuries. Location: United States.	Fire burns: Mean alcohol involvement significantly ↑ among persons killed than among survivors (30.7% vs. 11.0%, $\chi 2=101.1$, $P<0.001$). Among persons intentionally burned by fires/flames, alcohol involvement was similar for fatal (28.2%) and non-fatal (32.6%) cases ($\chi 2=0.2$, NS). ↑ percentage of fatal non-work-related unintentional cases (32.5%) than non-fatal cases (11.7%) were alcohol involved ($\chi 2=88.8$, $P<0.001$). Among non-fatal cases, ↑ percentage of non-work-related unintentional injuries (11.7%) than work-related unintentional injuries (3.1%) were alcohol involved ($\chi 2=14.8$, $P<0.001$). Alcohol involvement in non-work-related fire burns lowest among victims aged zero to 14 for both fatalities and injuries. Fire burns: Excluding work-related fire burn cases, alcohol-involved burn victim was >five times as likely to die as a non-alcohol-involved fire burn victim ($P<0.001$). Burns that occurred at nighttime ($P<0.001$) and to those >65 years ($P<0.01$) had the greatest likelihood of being fatal. Burns to those aged 15 to 24 years ($P<0.01$), male ($P<0.05$), and non-Caucasian ($P<0.05$) were the least likely to be fatal. Tobacco involvement also nearly doubled the risk of dying ($P<0.001$). Scalds and other burns: Mean alcohol involvement similar among persons killed and among survivors (5.6% vs. 3.8%, $\chi 2=0.2$, NS). All cases of intentional scald burns and unintentional work-related scald burns were non-fatal; alcohol involvement was 8.8% and 2.0%, respectively. Because of small sample size of fatal non-work-related scald victims, comparisons not made between fatal and non-fatal cases.

Continuation of: Levy DT, Mallonee S et al, 2004		Submersions: Total alcohol involvement similar for unintentional (23.9%) and intentional (17.4%) cases ($\chi2$=0.5, NS). Fatal cases significantly more likely to be alcohol involved (31.0%) than non-fatal cases (6.2%) ($\chi2$=43.0, P<0.001). Alcohol-involved submersion cases were >two times more likely to be fatal than non-alcohol-involved cases (P=0.08), even when controlling for victim age. Submersions that occurred at night (P<0.01) and in boating incidents (P=0.06) more likely to be fatal, and female victims were less likely to die. Victims age ≥15 years were six to 15 times more likely to be fatal cases than victims <age 15 (P<0.001). Spinal cord injuries: Alcohol involvement between fatal and non-fatal cases (33.3% vs. 34.1%, $\chi2$=0.1) NS. Among SCI cases associated with motor vehicle crashes, total alcohol involvement slightly ↑ among non-fatal cases (42.3%) than among fatal cases (34.2%) ($\chi2$=2.4, NS). Among non-fatal SCI cases, alcohol involvement nearly twice as ↑ in intentional (48.4%) than in unintentional (25.8%) injuries ($\chi2$=12.4, P<0.001). Victims ages 15 to 24 less likely to die (P<0.05) and victims ages ≥65 years were nearly four times more likely to die (P<0.01) than victims in other age groups. Traumatic brain injury: Of cases with known alcohol involvement, 38.5% of fatal and 42.3% of non-fatal cases were victim alcohol-involved ($\chi2$=4.8, P<0.05). Among intentional injuries, 37.9% of fatalities and 70.4% of survivors were alcohol involved ($\chi2$=119.0, P<0.001). Alcohol involvement was ↑ among males (45% of cases) than females (27% of cases) ($\chi2$=117.2, P<0.001). Nighttime and alcohol-involved injuries slightly less likely to be fatal (P<0.001), and cases aged ≥15 years and involving females more likely to be fatal compared to those <age 15 (P<0.001 for all four variables).

McDonald, Wang and Camargo 2004 Study Design: Trend Study Class: D Rating: Neutral Quality	Data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1992 through 2000. During these nine years, there were an estimated 68.6 million (95% CI: 65.6 to 71.7 million) emergency department visits attributable to alcohol, a rate of 28.7 (95% CI: 27.1 to 30.3) per 1,000 US population. Location: United States.	Number of alcohol-related visits ↑ 18% during the nine-year period. Emergency department visit rates for diagnoses with alcohol-attributable fractions of one were highest for those who were aged 30 to 49 years, male and black.
McLean R and Connor J 2009 Study Design: Cross-sectional Survey Class: D Rating: Neutral Quality	N=317 men and women, age 16 to 84 years who were admitted to three primary care facilities over a two-month period. Anonymous survey provided information about the nature of injury, alcohol use in the six hours prior to injury and identification of location where the 'last drink' was consumed. Location: New Zealand.	17% of people aged 16 years consumed an alcoholic drink in the six hours prior to injury. Of this group, 36% had had moderate intake of alcohol and 64% a hazardous intake (P=0.002). Mean number of standard drinks consumed was nine. Tertiary students and young people more likely to have been drinking than others (P<0.001). Greater proportion of women (24%) had been drinking prior to injury than men (11%) (P=0.005). Majority of drinkers (62%) had their last drink at a house or flat. Mean age of drinkers 21 years (95% CI: 19.6 to 22.8 years) and of non-drinkers 35 years (95% CI: 32.8 to 36.6 years). Statistically significant difference between the groups (P<0.0001) with respect to age.
Mukamal KJ, Mittleman MA et al, 2004 Study Design: Trend Study Class: B Rating: Neutral Quality	Initial N=5,888, final N=5,841 [5,201 participants from the Cardiovascular Health Study (original cohort) and 687 new, black participants (new cohort)]. Men and women were >65 years. Location: United States.	Cross-sectional analysis showed that before and after adjustment, prevalence of frequent falls highest in abstainers and lowest in subjects who consumed ≥14 drinks per week (P=0.06). Longitudinal analysis resulted in no difference between abstainers and light to moderate drinkers in their risk of falls during follow-up. Subjects that consumed ≥14 drinks per week had significantly ↑ risk of falls than abstainers in adjusted analyses (OR=1.25, 95% CI: 1.03 to 1.52, P=0.07). HR for incident falls associated with consumption of ≥14 drinks per week was 1.20 (95% CI: 0.97 to 1.47) for white subjects and 1.51 (95% CI: 0.78 to 2.91) for black subjects.

Rehm J, Patra J et al, 2006 Study Design: Cross-Sectional Study Class: D Rating: Neutral Quality	Initial N=13,090; final N=47% response rate. Age: ≥15 years. Randomly drawn sample from data taken from Canadian Addiction Survey collected between 2003 and 2004. Subjects completed questionnaire via telephone. Location: Canada.	Men consumed on average more than women and alcohol consumption ↓ with age. Oerall average age for an alcohol-attributable death was 45.9 years for men and 58.8 years for women. 3,892 alcohol-attributable deaths estimated accounting for 3,313 deaths among men and 579 among women. Numbers derived by multiplying Alcohol Attributable Fractions with number of deaths for each category. Among deaths caused by alcohol, the three biggest contributors were unintentional injuries, malignant neoplasms and digestive diseases. With respect to single disease categories, cirrhosis of the liver, motor vehicle accidents, suicides/self-inflicted injuries, oesophageal cancer and cardiac arrhythmias constituted the largest alcohol-attributable categories. Potential Years of Life Lost rate for Canada for deaths due to alcohol was 769 per 100,000 for men and 203 per 100,000 for women aged zero to 80+ years. For every 100,000 people in population, a potential loss of 769 years of life among men and 203 years of life among women as a result of premature death due to alcohol. A high PYLL rate for men observed, indicating ↑ levels of premature mortality among men compared to women.
Sorock et al 2006 Study Design: Case-Control Study Class: C Rating: Neutral Quality	Total of 1,735 cases (389 males, 339 females, aged ≥55 years) selected from 1993 National Mortality Follow-Back Survey, which provided national estimates of alcohol usage and demographic information among people who died from injuries. N=13,381 controls (5,065 males, 8,316 females, aged ≥55 years) selected from 1992 National Longitudinal Alcohol Epidemiologic Survey, which provided national estimates of alcohol usage for the general public. Location: United States.	Analysis indicated that 36% of cases and 29% of controls consumed ≥12 drinks in the prior 12 months. Unadjusted relative odds for drinkers vs. non-drinkers for falls was 1.7, for motor vehicle crashes was 1.7 and for suicides was 1.6. Drinking ↑ risk of suicide more for women than for men; the adjusted OR of suicide for women drinkers vs. non-drinkers was 2.5 (95% CI: 1.67 to 3.68), while for men drinkers vs. non-drinkers was 1.3 (95% CI: 1.00 to 1.65).

Watt et al 2004 Study Design: Case-Control Study Class: C Rating: Neutral Quality	Of 727 patients aged ≥15 years that were treated at emergency department for injury, 543 were interviewed and 488 (311 males, 177 females) were included in the analysis, as well as 488 population controls matched for gender, age group, neighborhood, day and time of injury. Location: Australia.	After controlling for demographic and situational variables, consuming any alcohol in the six hours prior to injury significantly ↑ risk of injury [OR=2.13 (95% CI: 1.3 to 3.9)], and drinking at levels above low-risk guidelines (>40g alcohol per occasion for females, >60g alcohol per occasion for males) ↑ injury risk by a factor of ~2.5 [OR=2.41 (95% CI: 1.1 to 5.2)]. In addition, drinking beer [OR=1.86 (95% CI: 0.9 to 3.9)], spirits [OR=3.05 (95% CI: 1.1 to 8.2)] or combination of beverages [OR=3.16 (95% CI: 1.1 to 8.8)] ↑ risk of injury. When usual alcohol consumption patterns, risk-taking behavior and substance use were considered, Δ in the effect of alcohol on injury risk observed, demonstrating that relationship between alcohol and injury appears confounded by these variables.
Watt et al 2006 Study Design: Cross-sectional Study Class: D Rating: Positive Quality	Every injured patient who presented to the Gold Coast Hospital Emergency Department for treatment of an injury sustained <24 hours prior to presentation was approached for an interview. N=1,205 patients approached, 789 were eligible and 593 injured patients (377 males, 216 females) included in the final analysis (aged >15 years). Location: Australia.	After adjustment for confounding variables, neither quantity nor type of alcohol was associated with injury mechanism; however, drinking setting significantly associated with odds of sustaining an intentional vs. unintentional injury [OR=2.79 (95% CI: 1.4 to 5.6)], injury through being hit by or against something vs. other injury types [OR=2.59 (95% CI: 1.4 to 4.9)]. ↓ odds of sustaining an injury through road traffic crashes vs. non-road traffic crashes [OR=0.02 (95% CI: 0.004 to 0.9)], compared with not drinking alcohol prior to injury.
Yoonhee C, Jung K et al 2009 Study Design: Case-Control Study Class: C Rating: Neutral Quality	Of 1,188 patients requiring admission, majority did not provide consent. O 407 patients, there were 123 cases in the intoxicated group (male:female ratio = 7.1:1, mean age 39±13.7 years) and 284 non-intoxicated controls (male:female ratio = 2.1:1, mean age 45.6±19.0 years). Location: South Korea.	Head Abbreviated Injury Scale (AIS) score significantly ↑ in intoxicated patients compared to non-intoxicated controls (1.1±1.7 vs. 0.6±1.2, P=0.008) and mortality significantly ↑ in intoxicated patients than non-intoxicated controls (5.7% vs. 2.0%, P=0.003). Significantly ↑ number of intoxicated patients with severe injuries than non-intoxicated controls (21% vs. 11.7%, P=0.023) and specifically with head injuries (25.7% vs. 13.3%, P=0.004). NS difference in total length of hospitalization, but length of the ICU admission significantly longer in intoxicated patients than in non-intoxicated controls (1.9±4.6 days vs. 0.7±2.6 days, P<0.05).

Research recommendations

1. Focus further research to avoid unintentional injury on effective communication policies that expand current messages on drinking and driving to inform individuals of other unintentional risk associated with alcohol consumption.
    - Rationale: The documented benefit of drunk driving campaigns is a public health success, yet alcohol-related injury is still substantial in other areas and should be addressed with the same vigilance and governmental support.

Search plan and results

Inclusion criteria

- January 1, 2004 to January 13, 2010
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- Dropout rate: Less than 20%; preference for smaller dropout rates
- Ages: Adults of legal drinking age (21 years and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, hypertension, type 2 diabetes, osteoporosis, osteopenia and obesity) and those with breast cancer, colon cancer or prostate cancer.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (exceptions noted)
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  (ethanol OR alcoholic OR alcohol's OR alcohol) AND ("unintentional injuries" OR "unintentional falls")

  ("Wounds and Injuries"[Mesh] OR "Accidents"[Mesh:NoExp] OR “Accidental Falls”[mh] OR “Accidents, Home”[mh]) AND ("Alcohol Drinking/adverse effects"[Mesh]

  ("Accidents"[majr:NoExp] OR “Accidental Falls”[majr] OR “Accidents, Home”[majr]) AND "Alcohol Drinking"[majr])

("Ethanol"[Mesh] OR "Alcoholic Beverages"[Mesh]) AND ("Accidents"[majr:NoExp] OR “Accidental Falls”[majr] OR “Accidents, Home”[majr])

("Ethanol"[majr] OR “Alcohol Drinking”[majr] OR "Alcoholic Beverages"[majr]) AND (drowning[mh] OR Accidents, Occupational"[majr])

Date searched: 01/13/2010

Summary of articles identified to review

- Total hits from all electronic database searches: 372
- Total articles identified to review from electronic databases: 30
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 19
- Number of Review Articles Identified: 2
- Total Number of Articles Identified: 21
- Number of Articles Reviewed but Excluded: 9

Included articles (References)

Reviews/Meta-analysis

1. Driscoll TR, Harrison JA, Steenkamp M. Review of the role of alcohol in drowning associated with recreational aquatic activity. Inj Prev. 2004 Apr; 10(2): 107-113. Review. PMID: 15066977; PMCID: PMC1730083.
2. González-Wilhelm L. Prevalence of alcohol and illicit drugs in blood specimens from drivers involved in traffic law offenses. Systematic review of cross-sectional studies. Traffic Inj Prev. 2007 Jun; 8(2): 189-198. Review. PMID: 17497523.

Primary Research

3. Bedford D, O'Farrell A, Howell F. Blood alcohol levels in persons who died from accidents and suicide. Ir Med J. 2006 Mar; 99(3): 80-83. PMID: 16700260.
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14. McDonald AJ 3rd, Wang N, Camargo CA Jr. US emergency department visits for alcohol-related diseases and injuries between 1992 and 2000. Arch Intern Med. 2004 Mar 8; 164(5): 531-537. PMID: 15006830.
15. McLean R, Connor J. Alcohol and injury: A survey in primary care settings. N Z Med J. 2009 Sep 25; 122(1, 303): 21-28. PMID: 19851417.
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Excluded articles

Article	Reason for Exclusion
Chen LH, Baker SP, Li G. Drinking history and risk of fatal injury: Comparison among specific injury causes. *Accid Anal Prev.* 2005 Mar; 37(2): 245-251. PMID: 15667810.	Study focused on fatal injury-mortality.

Elder RW, Shults RA, Swahn MH, Strife BJ, Ryan GW. Alcohol-related emergency department visits among people ages 13 to 25 years. *J Stud Alcohol.* 2004 May; 65(3): 297-300. PMID: 15222585.	Study looked at the prevalence of alcohol-related emergency department visits; no outcome measures were performed.
Fierro I, Yáñez JL, Alvarez FJ. Differences in alcohol-related mortality between foreign-born and native-born Spaniards. *Int J Drug Policy.* 2009 Sep 24. [Epub ahead of print] PubMed PMID: 19782553.	Study outcomes are related to mortality of foreign-born vs. native-born Spaniards.
Hosking J, Ameratunga S, Bullen C, Civil I, Ng A, Rodgers A. Screening and intervention for alcohol problems among patients admitted following unintentional injury: A missed opportunity? *N Z Med J.* 2007 Feb 16; 120(1, 249): U2, 417. PMID: 17308554.	Outcome focused on alcohol interventions and not incidence of unintentional injury.
Matzopoulos R, Peden M, Bradshaw D, Jordaan E. Alcohol as a risk factor for unintentional rail injury fatalities during daylight hours. *Int J Inj Contr Saf Promot.* 2006 Jun; 13(2): 81-88. PMID: 16707343.	Outcome focused on railway injuries based on day of week and time of day.
Miller JR, Pikora TJ. Alcohol consumption among recreational boaters: Factors for intervention. *Accid Anal Prev.* 2008 Mar; 40(2): 496-501. Epub 2007 Aug 31. PMID: 18329399.	Outcome explored educational intervention and not incidence of unintentional injury.
Moriya F, Hashimoto Y. Postmortem production of ethanol and n-propanol in the brain of drowned persons. *Am J Forensic Med Pathol.* 2004 Jun; 25(2): 131-133. PMID: 15166764.	Study looked at post-mortem production of ethanol.
Norström T, Ramstedt M. Mortality and population drinking: a review of the literature. *Drug Alcohol Rev.* 2005 Nov; 24(6): 537-547. Review. PMID: 16361210.	Narrative review.
Sindelar HA, Barnett NP, Spirito A. Adolescent alcohol use and injury. A summary and critical review of the literature. *Minerva Pediatr.* 2004 Jun; 56(3): 291-309. Review. PMID: 15252378.	Subjects aged 13 to 19.

CHAPTER 8. LACTATING WOMEN & OFFSPRING – POSTNATAL GROWTH PATTERNS, SLEEP PATTERNS AND/OR PSYCHOMOTOR PATTERNS OF THE OFFSPRING

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION AND POSTNATAL GROWTH PATTERNS, SLEEP PATTERNS AND/OR PSYCHOMOTOR PATTERNS OF THE OFFSPRING?

Conclusion statement

Limited evidence suggests that alcohol consumption during lactation was associated with altered postnatal growth, sleep patterns and/or psychomotor patterns of the offspring.

Grade

Limited

Evidence summary overview

This conclusion is based on the review of five studies examining the relation of mother's alcohol consumption during lactation on growth (Backstrand JR et al, 2004), psychomotor development (Little et al, 1989 and Little et al, 2002) and wake and sleep patterns (Mennella JA, Garcia PL, 2001 and Mennella JA, Gerrish CJ, 1998). Backstrand JR et al, 2004 evaluated the effects of pulque (a mildly alcoholic beverage) intake in a prospective cohort of 58 lactating women from rural Central Mexico and found heavier pulque intake during lactation was associated with slower postpartum growth from month one to 57 months (P=0.0054 for weight and P=0.0073 for length). Little et al, 1989 reported that infant motor development at age one, as measured by the Psychomotor Development Index (PDI), was significantly lower in infants exposed regularly to alcohol in breast milk (mother's alcohol intake of at least 0.5oz per day) with a dose response relation (P=0.006, for linear trend). There was no association found between maternal alcohol use and infant mental development, as measured by the Bayley Mental Development Index. These findings were not replicated by Little et al in 2002 in a sample of 915 18-month age toddlers from the United Kingdom, where infants with the highest alcohol exposure had the highest Griffiths scores in three of five scales, after adjustment for education and other associated factors. Mennella JA, Garcia PL, 2001 and Mennella JA, Gerrish CJ, 1998, using within-subject design studies, found short-term exposure to small amounts of alcohol in mothers' milk produces distinctive changes in the infants' sleep-wake patterning.

Evidence summary paragraphs

Growth

Backstrand JR et al, 2004 (positive quality), conducted a prospective cohort study to examine maternal intake of a mildly alcohol beverage (pulque) during pregnancy and lactation, and the potential effect on postpartum child growth and attained size. The study followed 58 mothers and their offspring (from birth to approximately 57 months of age), from rural Central Mexico. Dietary assessment was conducted for two days per

month during lactation. A total of 72% of mothers consumed pulque during lactation and the average ethanol intake was 113.8g per week. At month one, the children were relatively short in length, although of average weight-for-age; weight-for-length were well above the reference median. By 57 months, mean length-for-age and weight-for-age had declined substantially. At this age, 52.7% of the children were stunted and 24.1% were underweight. At 57 months, heavier pulque intake during lactation was associated with lower weight (P=0.0242) and length (P=0.0287). Heavier pulque intake during lactation was associated with slower postpartum growth from month one to 57 months (weight, P=0.0054 and length, P=0.0073). In general, the attained size measurements were associated with pulque intake during both pregnancy and lactation, while the child growth measurements were only associated with intake during lactation. In conclusion, pulque intake during lactation may adversely influenced postnatal growth in this population.

Psychomotor Development

Little et al, 1989 (positive quality), conducted a prospective study to investigate the relation of the mother's intake of alcohol during breastfeeding to the infant's mental and motor development. Four-hundred infants born to member of a health maintenance organization were evaluated at one year of age. Mental development, as measure by the Bayley Mental Development Index (MDI), was unrelated to maternal drinking during breastfeeding. However, motor development, as measured by the Psychomotor Development Index (PDI), was significantly lower in infants exposed regularly to alcohol in breast milk (after alcohol exposure during gestation was controlled for), with a dose response relation (P=0.006; for linear trend). The infants of breastfeeding mothers who had at least one drink daily (0.5 oz) had a mean PDI score of 98, whereas the infants exposed to less alcohol in breast milk had a mean PDI score of 103 (95% CI for the difference of the two means, 1.2 to 9.8). The effect was strong when mothers who supplemented breastfeeding with formula were excluded from the analysis. The regression analysis showed a predicted decreased of 5.4 points in the PDI for a breastfed infant with an AA score of 1.0, as compared with an infant with no alcohol exposure. In conclusion, ethanol ingested through breast milk has a significantly detrimental effect on motor development in breastfed infants.

Little et al, 2002 (positive quality), conducted a prospective cohort study to evaluate the influence of moderate alcohol use during lactation on the mental development of 915 randomly selected eighteen-month-old toddlers enrolled in a longitudinal population-based study in the United Kingdom. The study used the Griffiths Developmental Scale for the toddlers, and self-administered frequency questionnaires (FFQ) during and after pregnancy to assess alcohol intake. The dose or alcohol available to the lactating infant was obtained by multiplying the alcohol intake of the mother by the proportion of breast milk in the infant's diet. This dose was compared with the Griffiths Scale of Mental Development, taking into account potentially confounding variables. The Griffiths Scale includes the following measurements: Locomotor, hand and eye coordination, performance test and the General Intelligence Quotient (GQ). Only 5% of mothers had two or more drinks a day during the postpartum period; the average alcohol used was 1.0 or more. Binges in the postpartum period were reported by 37% of all women. For all scales, with the exception of hand-eye coordination and hearing and speech, infants with the highest alcohol exposure via breast milk had the highest Griffiths scores.

Sleep/Wake Patterns

Mennella JA, Garcia PL, 2001 (positive quality), conducted a within-subjects design study to test the hypothesis that infants would compensate less active sleep after exposure of alcohol in their mother's milk. Twenty-three breast-fed infants from three to five months of age and their mothers were tested on two days, separated by one week. A small, computerized movement detector, an actigraph, was placed on the infants' left ankles to monitor sleep and activity patterning after which they were bottle-fed mother's milk alone (control condition) on one test day and mother's milk containing 32mg of ethanol per 100ml on the other. The infants' behaviors were monitored for the next 24 hours; the first 3.5 hours of monitoring on each test day took place at the Monell Center. Infants exhibited significantly less active sleep during the 3.5 hours immediately after exposure to alcohol in mothers' milk compared with the control condition; the decrease in active sleep was observed in all but four of the infants tested. Compensatory increases in active sleep were then observed in the next 20.5 hours, when mothers refrained from drinking alcohol. These findings demonstrate that short-term exposure to small amounts of alcohol in mothers' milk produces distinctive changes in the infants' sleep-wake patterning.

Mennella JA, Gerrish CJ, 1998 (positive quality), conducted a randomized control trial (RCT) to test the hypothesis that exposure to alcohol in breast milk affects infants' sleep and activity levels in the short term. Thirteen lactating women and their infants were tested on two days, separated by an interval of one week. On each testing day, the mother expressed 100ml of milk, while a small, computerized movement detector called an actigraph was placed on the infant's left leg to monitor sleep and activity patterning. After the actigraph had been in place for 15 minutes, the infants ingested their mother's breast milk flavored with alcohol (32mg) on one testing day and breast milk alone on the other. The infants' behaviors were monitored for the next 3.5 hours. The infants spent significantly less time sleeping during the 3.5 hours after consuming the alcohol-flavored milk (78.2 minutes compared with 56.8 minutes after feeding alcohol in breast milk). This reduction was apparently attributable to a shortening in the longest sleeping bout (34.5 compared with 56.7 minutes for sleeping after breast milk alone) and the amount of time spent in active sleep (25.8 minutes compared with 44.2 minutes after breast milk alone); the decrease in active sleep was observed in all but two of the 13 infants tested.

Overview table

Author, Year, Study Design, Class, Rating	Study Subjects	Measurements	Treatment	Key Outcomes
Backstrand JR, Goodman AH et al, 2004 Study Design: A prospective cohort study Class: B Rating: Positve Quality	Data from the Mexico nutrition and CRSP and follow-up study (1984 to 1986 and 1992) in rural Central Mexico. N=58 mother-child pairs.	Two days per month, 24-hour recall. Weight. Length. Period: From birth to 57 months.	72.4% of mothers. Average ethanol intake: 113.8g per week (N=58).	Growth Stunting: Heavier pulque intake during lactation associated with slower postpartum growth from month one to 57 (weight; P=0.0054 and length; P=0.0073. At 57 months, heavier pulque intake during lactation associated with ↓ weight (P=0.0242) and length (0.0287). By 57 months, mean height-for-age and weight-for-age had ↓ substantially. More than half of children (52.7%) were stunted and nearly a quarter (24.1%) were underweight.

Little RE et al 1989 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	Data from the Group Health Cooperative of Puget Sound in Seattle (1982 to 1983). N=400 mothers and infants. Age: One year. "Long-term breast-feeders:" Infants from women who breastfed their infants for >three months. "Short-term breast-feeders:" Infants from women who breastfed them for <one month.	Absolute Alcohol (AA) consumed by mother ("maternal AA score") was an estimate of the average number of ounces of ethanol ingested daily, computed by determining amount of ethanol ingested in both usual and max quantities and weighting these values against frequency of consumption. Infants' development with Bayle Scales of Infant Development (both mental and psychomotor scales), Mental Development Index (MDI). Psychomotor Development Index (PDI) of breastfed infants (who obtained all or nearly all nourishment from breast milk, receiving more than 473ml (16oz) of formula per day. Mothers' ethanol intake, energy intake, protein and selected micronutrients by food consumption over a four-day period.	N=153 "Heavier" drinkers: Mothers with an AA score of ≥1.0, or a report of binge drinking [consumption on a single occasion of ≥74ml (2.5oz) of ethanol]. N=247 "Lighter" drinkers: All other mothers, including non-drinkers. Maternal AA score of 1.0=29.6ml (1oz) of ethanol daily intake (equivalent of two drinks). Infant AA score: estimated infant's exposure to ethanol in the postpartum period by weighting the mother's AA score.	Psychomotor Development and General Intelligent Quotient: No relation apparent between infants' exposure to ethanol and MDI. Strong linear relation between level of exposure to ethanol in breast milk and PDI (P=0.006 for linear trend), mean PDI scores for: Infants of breastfeeding mothers who had at least one drink daily = 98 (95% CI for the difference of the two means, 1.2 to 9.8). Regression analysis showed a predicted ↓ of 5.4 points in the PDI for breastfed infant with AA score of 1.0, as compared with infant with no alcohol exposure. Mean PDIs of the infants exposer only to small quantities of ethanol in breast milk (Infant AA score, <0.5) did not vary significantly between infants who had no exposure.

Little RE et al 2002 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) (1991-92). N=1,175; Final N=915. Age: 18-month-old toddlers.	Self-reported lactation history (at six months postpartum), alcohol consumption (at eight weeks after delivery) and FFQ. Griffiths Developmental Scale for toddlers at 18 months of age (10% were evaluated later). Partially breastfed: 55% breast milk and 45% formula.	Infant Alcohol exposure via breast milk (IAA): N=295; >zero to <0.1 N=257; 0.1 to 0.4 N=51; 0.5 to 0.9 N=17; 1.0. IAA: Dose or alcohol available to lactating infant = alcohol intake of mother x proportion of breast milk in infant's diet.	Psychomotor Development and General Intelligent Quotient: Only 5% of mothers had ≥two drinks a day during postpartum period; average alcohol used was ≥1.0. Binges in postpartum period reported by 37% of all women. For all scales with the exception of hand-eye coordination and hearing and speech, infants with the highest alcohol exposure via breast milk had highest Griffiths score.

Menella JA and Garcia PL, 2001 Study Design: Non-Randomized Controlled Trial Class: C Rating: Positive Quality	Subjects recruited from ads in local newspapers and from WIC centers in Philadelphia. N=23 (13 girls, 10 boys). Age: 3.1 to 5.1 months.	Infant sleep and activity rhythms with an actigraph.	Babies were fed with 100ml of breast milk. Control day: Milk alone. Test day: Milk containing 32mg of ethanol. Mean actually consumed = 30.5±0.3mg.	Changes in Sleep/wake Patterns: Significant interaction between time since exposure (zero to 3.5 vs. 3.5 to 24 hours) and experimental test day (i.e., control, alcohol) for the amount of time that infants spent in active sleep [F(1,21df) =14.1; P=0.001]. Infants spent ↓ time in active sleep [paired t (22df)=2.11; P=0.05] during the hours immediately after exposure to alcohol in mothers' milk. ↓ in active sleep observed in 19 of the 23 infants. Effects of alcohol exposure on active sleep were not immediate [F(1,22df)=8.68; P=0.007]. Infants spent significantly ↓ time in active sleep during the second half of the test session (i.e., 1.75 to 3.5 hours), in which they were fed alcohol in mothers' milk, compared with mothers' milk containing no alcohol [paired t (22df)=3.68; P=0.001]. Infants compensated for such ↓ when their mothers refrained from drinking alcohol [paired t(21df)=−2.73; P=0.01].

Menella JA and Gerrish CJ, 1998 Study Design: Non-Randomized Controlled Trial Class: C Rating: Positive Quality	Subjects recruited from ads in local newspapers and from WIC centers in Philadelphia. N=13 (nine girls, four boys). Age: 1.5 to 5.6 months.	Infant sleep and activity rhythms with an actigraph.	Babies were fed with 100ml of breast milk. Control day: Milk alone. Test day: Milk containing 40uL (32mg) of ethanol. Mean actually consumed = 31.3±0.6mg.	Changes in Sleep/wake Patterns: Infants spent significantly ↓ time in active sleep during second half of testing session (i.e., 1.75 to 3.5 hours) after exposure to alcohol in breast milk, compared with breast milk alone (control vs. alcohol, 25.2 to 5.5 vs. 8.6 to 2.6 minutes; paired T-test (12df) = 3.14; P=0.009).

Search plan and results

Inclusion criteria

- Subjects/Population: Human subjects.
- Age: Children, men and women of all ages.
- Setting: International.
- Health Status: Healthy and those with elevated chronic disease risk (CHD/CVD, Type 2 diabetes, metabolic syndrome and obesity).
- Nutrition Related Problem/Condition: None.
- Search Criteria
    - Study Design Preferences: Randomized controlled trial (RCT) or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis.
    - Size of Study Groups: The sample size must equal 10 adults for each study group. For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group.
    - Study Dropout Rate: Less than 20%; preference for smaller dropout rates.
    - Year Range: No date range.
    - Authorship: If an author is included on more than one review article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected.
    - Languages: Limited to articles in English.
    - Other: Article must be published in peer-reviewed journal.

Exclusion criteria

- Subjects/Population
    - Animal and in vitro studies
    - Malnourished/third-world populations or disease incidence not relative to US population (e.g., malaria).
- Age: Not applicable.
- Setting: Hospitalized patients.

- Health Status: Medical treatment/therapy and diseased subjects.
- Nutrition Related Problem/Condition: All conditions.
- Search Criteria
    - Study Design Preferences: Not applicable.
    - Size of Study Groups: Sample sizes <10.
    - Study Dropout Rate: If the dropout rate in a study is 20% or greater, the study will be rejected.
    - Year Range: Not applicable.
    - Authorship: Studies by same author similar in content.
    - Languages: Articles not in English.
    - Other: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  No date range ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND ((breast milk) OR "Milk, Human"[Mesh]) ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND (postnatal OR "Postpartum Period"[Mesh] OR postpartum OR "Breast Feeding"[Mesh] OR lactation[mh])

Date searched: 12/03/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 160
- Total articles identified to review from electronic databases: 44
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 5
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 5
- Number of Articles Reviewed but Excluded: 39

Included articles (References)

1. Backstrand JR, Goodman AH, Allen LH, Pelto GH. Pulque intake during pregnancy and lactation in rural Mexico: Alcohol and child growth from one to 57 months. Eur J Clin Nutr. 2004 Dec; 58 (12): 1, 626-1, 634. PMID: 15280906.
2. Little RE, Anderson KW, Ervin CH, Worthington-Roberts B, Clarren SK. Maternal alcohol use during breast-feeding and infant mental and motor development at one year. N Engl J Med. 1989 Aug 17; 321 (7): 425-430. PMID: 2761576.
3. Little RE, Northstone K, Golding J; ALSPAC Study Team. Alcohol, breastfeeding and development at 18 months. Pediatrics. 2002 May; 109 (5): E72-2. PMID: 11986478.
4. Mennella JA, Garcia-Gomez PL. Sleep disturbances after acute exposure to alcohol in mothers' milk. Alcohol. 2001 Nov; 25 (3): 153-158. PMID: 11839458.
5. Mennella JA, Gerrish CJ. Effects of exposure to alcohol in mother's milk on infant sleep. Pediatrics. 1998 May; 101 (5):E2. PMID: 9565435.

Excluded articles

Excluded Articles	Reason for Exclusion
Alvik A, Haldorsen T, Lindemann R. Alcohol consumption, smoking and breastfeeding in the first six months after delivery. *Acta Paediatr*. 2006 Jun; 95 (6): 686-693. PMID: 16754549.	Does not answer the question. About drinking levels during lactation.
Alvik A, Haldorsen T, Lindemann R. Alcohol consumption, smoking and breastfeeding in the first six months after delivery. *Acta Paediatr.* 2006 Jun; 95 (6): 686-693.PMID: 16754549.	Report about alcohol consumption.
Anderson PO. Alcohol and breastfeeding. *J Hum Lact.* 1995 Dec; 11 (4): 321-323. No abstract available. PMID: 8634110.	Comment.
Binkiewicz A, Robinson MJ, Senior B. Pseudo-Cushing syndrome caused by alcohol in breast milk. *J Pediatr*. 1978 Dec; 93 (6): 965-967. No abstract available. PMID: 722441.	Does not answer the question. About Cushing syndrome.
Chaves RG, Lamounier JA, César CC. Factors associated with duration of breastfeeding. *J Pediatr* (Rio J). 2007 May-Jun; 83 (3): 241-246. Epub 2007 Apr 20. PMID: 17486198.	Does not answer the question. About factors associated with breastfeeding.
Chien YC, Huang YJ, Hsu CS, Chao JC, Liu JF. Maternal lactation characteristics after consumption of an alcoholic soup during the postpartum 'doing-the-month' ritual. *Public Health Nutr.* 2009 Mar; 12 (3): 382-388. Epub 2008 Apr 22. PMID: 18426631.	Does not answer the question. About alcohol consumption and lactation performance.
Chien YC, Liu JF, Huang YJ, Hsu CS, Chao JC. Alcohol levels in Chinese lactating mothers after consumption of alcoholic diet during postpartum "doing-the-month" ritual. *Alcohol.* 2005 Nov; 37 (3): 143-150. PMID: 16713502.	Does not answer the question. About OH blood levels.
Cobo E. Effect of different doses of ethanol on the milk-ejecting reflex in lactating women. *Am J Obstet Gynecol.* 1973 Mar 15; 115 (6): 817-821. PMID: 4688584.	Does not answer the question. Consider in previous question.

Dewailly E, Ayotte P, Laliberté C, Weber JP, Gingras S, Nantel AJ. Polychlorinated biphenyl (PCB) and dichlorodiphenyl dichloroethylene (DDE) concentrations in the breast milk of women in Quebec. *Am J Public Health*. 1996 Sep; 86 (9): 1, 241-1, 246. PMID: 1380586.	Does not answer the question. About chemicals in breast-milk.
Flores-Huerta S, Hernández-Montes H, Argote RM, Villalpando S. Effects of ethanol consumption during pregnancy and lactation on the outcome and postnatal growth of the offspring. *Ann Nutr Metab.* 1992; 36 (3): 121-128. PMID: 1530279.	Does not answer the question.
Giglia RC, Binns CW. Alcohol and breastfeeding: What do Australian mothers know? *Asia Pac J Clin Nutr.* 2007; 16 Suppl 1:473-7.PMID: 17392153.	Does not answer the question. About levels of knowledge of the danger of drinking OH during breastfeeding by Australian mothers.
Giglia RC, Binns CW. Alcohol, pregnancy and breastfeeding: A comparison of the 1995 and 2001 National Health Survey data. Breastfeed Rev. 2008 Mar; 16 (1): 17-24. PMID: 18546573.	Does not answer the question. About patterns of alcohol intake.
Giglia RC, Binns CW, Alfonso HS, Scott JA, Oddy WH. The effect of alcohol intake on breastfeeding duration in Australian women. *Acta Paediatr*. 2008 May; 97 (5): 624-629. PMID: 18394108.	Does not answer the question. About breastfeeding duration and OH intake.
Gottesfeld Z, Abel EL. Maternal and paternal alcohol use: effects on the immune system of the offspring. *Life Sci.* 1991; 48 (1): 1-8. Review. PMID: 1986181.	Does not answer the question. About immune system.
Ho E, Collantes A, Kapur BM, Moretti M, Koren G. Alcohol and breast feeding: Calculation of time to zero level in milk. *Biol Neonate.* 2001; 80 (3): 219-222. PMID: 11585986.	No intervention. Modeled time to alcohol clearance in breast milk.
Howard CR, Lawrence RA. Breast-feeding and drug exposure. *Obstet Gynecol Clin North Am.* 1998 Mar; 25 (1): 195-217. Review. PMID: 9547767.	Does not answer the question. About drug exposure.

Kacew S. Adverse effects of drugs and chemicals in breast milk on the nursing infant. *J Clin Pharmacol.* 1993 Mar; 33 (3): 213-221. Review. PMID: 8463434.	Does not answer the question. About drugs and chemicals in breast-milk.
Kochenour NK, Emery MG. Drugs in lactating women. *Obstet Gynecol Annu.* 1981; 10: 107-126. Review. No abstract available. PMID: 7024869.	Does not answer the question. About drugs.
Koletzko B, Lehner F. Beer and breastfeeding. Adv *Exp Med Biol.* 2000; 478: 23-28. Review. PMID: 11065057.	Publication.
Koren G. Drinking alcohol while breastfeeding. Will it harm my baby? *Can Fam Physician.* 2002 Jan; 48: 39-41.PMID: 11852608.	Commentary.
Lawton ME. Alcohol in breast milk. *Aust N Z J Obstet Gynaecol.* 1985 Feb; 25 (1): 71-73. PMID: 3862407.	Sample size (N=80), less than inclusion criterion.
Little RE, Lambert MD, Worthington-Roberts B. Drinking and smoking at three months postpartum by lactation history. *Paediatr Perinat Epidemiol.* 1990 Jul; 4 (3): 290-302. PMID: 2374748.	Does not answer the question. About behavior in postpartum drinking.
Liston J. Breastfeeding and the use of recreational drugs-alcohol, caffeine, nicotine and marijuana. *Breastfeed Rev.* 1998 Aug; 6 (2): 27-30. PMID: 9849117.	Does not answer the question. About drugs.
Ludvigsson JF, Ludvigsson J. Socio-economic determinants, maternal smoking and coffee consumption and exclusive breastfeeding in 10205 children. *Acta Paediatr*. 2005 Sep; 94 (9): 1, 310-1, 319. PMID: 16278998.	Does not answer the question. About socio-economic determinants of breastfeeding.
Matheson I, Kristensen K, Lunde PK. Drug utilization in breast-feeding women. A survey in Oslo. *Eur J Clin Pharmacol*. 1990; 38 (5): 453-459. PMID: 1974205.	Does not answer the question. About drug utilization in breastfeeding women.
Mennella J. Alcohol's effect on lactation. *Alcohol Res Health*. 2001; 25 (3): 230-234. Review.PMID: 11810962.	NI AAA Publication

Mennella JA. Infants' suckling responses to the flavor of alcohol in mothers' milk. *Alcohol Clin Exp Res.* 1997 Jun; 21 (4): 581-585. PMID: 9194908.	Does not answer the question. About flavor of alcohol in mothers' milk.
Mennella JA. Regulation of milk intake after exposure to alcohol in mothers' milk. *Alcohol Clin Exp Res.* 2001 Apr; 25 (4): 590-593. PMID: 11329500.	Does not answer the question. About alcohol consumption and lactation performance.
Mennella JA. Short-term effects of maternal alcohol consumption on lactational performance. *Alcohol Clin Exp Res*. 1998 Oct; 22 (7): 1, 389-1, 392. PMID: 9802517.	Does not answer the question. About alcohol consumption and lactation performance.
Mennella JA, Beauchamp GK. Beer, breast feeding and folklore. *Dev Psychobiol*. 1993 Dec; 26 (8): 459-466. PMID: 8293892.	Does not answer the question. About alcohol consumption and lactation performance.
Mennella JA, Beauchamp GK. The transfer of alcohol to human milk. Effects on flavor and the infant's behavior. *N Engl J Med*. 1991 Oct 3; 325 (14): 981-985. PMID: 1886634.	Does not answer the question. About alcohol consumption and effects on flavor.
Na HR, Daniels LC, Seelig LL Jr. Preliminary study of how alcohol consumption during pregnancy affects immune components in breast milk and blood of postpartum women. *Alcohol Alcohol*. 1997 Sep-Oct; 32 (5): 581-589. PMID: 9373700.	Does not answer the question. About influence of pregnancy OH intake on breast-milk.
Pepino MY, Mennella JA. Effects of breast pumping on the pharmacokinetics and pharmacodynamics of ethanol during lactation. *Clin Pharmacol Ther.* 2008 Dec; 84 (6): 710-714. Epub 2008 Jul 2. PMID: 18596681.	Does not answer the question. About breast pumping and ethanol.
Rayburn WF. Adverse reproductive effects of beer drinking. *Reprod Toxicol.* 2007 Jul; 24 (1): 126-130. Epub 2007 May 3. PMID: 17544619.	Does not answer the question.

Schimmel MS, Eidelman AI, Wilschanski MA, Shaw D Jr, Ogilvie RJ, Koren G. Toxic effects of atenolol consumed during breast feeding. *J Pediatr.* 1989 Mar; 114 (3): 476-478. No abstract available. Erratum in: *J Pediatr* 1990 Jan; 116 (1): 158. Schmimmel, MS [corrected to Schimmel, MS]; Eidelman, AJ [corrected to Eidelman, AI]. PMID: 2921694.	Does not answer the question. About atenolol effects during breastfeeding.
Schulte P. Minimizing alcohol exposure of the breastfeeding infant. *J Hum Lact*. 1995 Dec; 11 (4): 317-319. PMID: 8634109.	Comment.
Somogyi A, Beck H. Nurturing and breast-feeding: exposure to chemicals in breast milk. *Environ Health Perspect*. 1993 Jul; 101 Suppl 2: 45-52. Review. PMID: 8243405.	Does not answer the question. Chemicals in breast-milk.
Villalpando S, Flores-Huerta S, Fajardo A, Hernandez-Beltran MJ. Ethanol consumption during pregnancy and lactation.Changes in the nutritional status of predominantly breastfeeding mothers. *Arch Med Res*. 1993 Winter; 24 (4): 333-338. PMID: 8118156.	Does not answer the question. About mothers' health and OH consumption.
Wolin MJ, Yerry S, Miller TL, Zhang Y, Bank S. Changes in production of ethanol, acids and H2 from glucose by the fecal flora of a 16- to 158-day-old breast-fed infant. *J Nutr*. 1998 Jan; 128 (1): 85-90. PMID: 9430607.	About ethanol changes in the breast-feeding infant.

CHAPTER 9. LACTATING WOMEN & OFFSPRING – QUALITY & QUANTITY OF BREAST MILK AVAILABLE FOR OFFSPRING

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION DURING LACTATION AND THE QUALITY AND QUANTITY OF BREAST MILK AVAILABLE FOR THE OFFSPRING?

Conclusion statement

Moderate, consistent evidence shows that when a lactating mother consumes alcohol, alcohol enters the breast milk and the quantity of milk produced is reduced, leading to reduced milk consumption by the infant.

Grade

Moderate

Evidence summary overview

This conclusion is based upon the review of thirteen small studies examining the influence of alcohol consumption during lactation on the quality and quantity of milk available for the offspring. Six studies examined the effect of alcohol ingestion during lactation on quality (impact on physical properties or chemical composition) of breast milk produced. Seven within-subject design studies addressed the impact of alcohol consumption during lactation on quantity of breast milk produced or consumed.

Influence on quality of breast milk:

- Four studies evaluated alcohol pharmacokinetics in lactating women using a dose of 0.4g per kg and one study used a dose of 0.3g per kg alcohol. A prospective cohort study (N=23 Chinese women) (Chien et al, 2005) predicted time required for milk alcohol level to return to zero level was 175 minutes following consumption of approximately 0.3g per kg alcohol in a chicken soup flavored with sesame oil and rice wine. Pepino et al, 2007 found that blood alcohol concentration was significantly lower in lactating women when compared with non-lactating women. Mennella and Pepino, 2010 evaluated Breath Alcohol Concentration (BrAC) before and after pumping, and found that levels of BrAC were significantly lower during than after pumping. Pepino and Mennella, 2008 found that pumping before drinking significantly decreased blood ethanol concentration ($P<0.05$) and ethanol bioavailability ($P=0.05$)
- Two studies (Mennella JA, 1997; Mennella JA and Beauchamp GK, 1991) evaluated the influence of potential alterations in breast milk flavor and odor caused by alcohol consumption during lactation on infant breast milk intake. Results showed that short-term alcohol consumption by lactating women significantly increased the perceived intensity of the odor of their milk. One study found no suppression of sucking or intake in response to the ethanol-flavored milk. Rather, the infants consumed significantly more milk [Paired T (39df)=2.78; $P<0.008$] and sucked more [paired T (38df)=2.45; $P<0.019$] frequently when drinking the alcohol-flavored milk compared with the unaltered milk. The second study found that infants sucked more frequently during the first minute of feedings after alcohol consumption by their mothers (67.0±6.5

sucks, as compared with 58.4±5.9 sucks for feeding after the consumption of the non-alcoholic beverage; P<0.05), but they consumed significantly less milk (120.4±9.5ml vs. 156.4±8.2ml P<0.001) during the testing sessions in which mothers drank the alcohol beverage.

Influence on quantity of breast milk:

- Two within-subjects design studies evaluated milk ejection response before and after administration of different doses of alcohol. Chien YC et al, 2008 (neutral quality) reported significant inhibited milk-ejecting response in 23 Chinese women following consumption of a soup prepared with alcohol (average dose of 0.3g per kg body weight. Similarly, Cobo et al, 1973, evaluated 22 lactating women, finding that 1-2g per kg intake of alcohol significantly reduce milk ejection.
- Three within-subjects design studies evaluated breast milk intake of infants after their mother ingested alcoholic beverages. Menella, 2001 and Menella and Beauchamp, 1993 found that infants consumed approximately 20-22% less milk after their mother had ingested 0.3g per kg dose of alcohol. With a similar dose of maternal alcohol intake Menella, 1998 found that the amount of milk produced by the lactating mother was significantly reduced (9.3% ±4.1).
- Two studies evaluated the effects of alcohol on hormonal responses and milk yield over time. Menella and Pepino, 2008 found that alcohol consumption increased basal PRL levels (P<0.0001) and modified the PRL response to pumping (P<0.0001), but the directionality of the response depended on when pumping occurred along the blood alcohol concentration (BAC) curve. Menella et al, 2005 found that oxytocin levels significantly decreased, whereas prolactin levels and measures of sedation, dysphoria, and drunkenness significantly increased, during the immediate hours after alcohol consumption. In the short term, mothers may be more relaxed, but the hormonal milieu underlying lactation performance is disrupted, and in turn, the infant's milk supply is diminished.

Evidence summary paragraphs

Influence on Quality

Pharmacokinetics

Chien et al, 2005 (positive quality), conducted a non-randomized trial to investigate the pharmacokinetics of alcohol in 23 Chinese lactating mothers after they consumed chicken soup flavored with sesame oil and rice wine (CSSR). Experimental findings were employed to estimate the potential ethanol dose to neonates and determine associated health risks. The target alcohol dosage was 0.3g per kg. Milk and blood samples were collected at fixed time intervals from each subject following exposure to CSSR, and alcohol levels were determined. Blood alcohol level peaked at 20 minutes after exposure to CSSR and decreased almost linearly thereafter. Alcohol in milk reached a plateau roughly at 20-40 minutes after exposure to CSSR and then decreased. Alcohol pharmacokinetics among subjects varied widely. The coefficients of variation in subject alcohol concentrations were 16.5-46.2% (mean=30.0%) for blood and 32.8-57.6% (mean=44.4%) for milk. Mean maximal alcohol concentration in blood (30.2±5.0mg/dL) was achieved at 23.5±7.6 minutes and in milk

(31.6±10.3mg/dL) at 31.7±12.7 minutes. Potential infant doses were 3.0-58.8mg (mean=13.4mg), and the predicted time required for milk alcohol level to return to zero level was 175 minutes. The acute health risks for infants exposed to alcohol through their mothers' milk under the current exposure scenario are low (hazard index<0.2).

Pepino et al, 2007 (positive quality), conducted a within-subjects design study to test the hypothesis that lactation alters alcohol pharmacokinetics. Subjects included 20 lactating women who were exclusively breastfeeding a two- to five-month-old infant and two control groups of non-lactating women. The first control group consisted of nine women who were exclusively formula-feeding similarly aged infants, whereas the other consisted of 15 women who had never given birth. Women drank a 0.4g/kg dose of alcohol following a 12-hour overnight fast during one test session (fasted condition) or 60 minutes after consuming a standard breakfast during the other (fed condition). Blood alcohol concentration (BAC) levels and mood states were obtained at fixed intervals before and after alcohol consumption. Under both conditions, the resultant BAC levels at each time point were significantly lower and the area under the blood alcohol time curve were significantly smaller in lactating women when compared with the two groups of non-lactating women. There were no significant differences among the three groups of women in the stimulant effects of alcohol. However, lactating women did differ in the sedative effects of alcohol when compared with nulliparous but not formula-feeding mothers. That is, both groups of parous women felt sedated for shorter periods of time when compared with nulliparous women. The authors concluded that the systemic availability of alcohol was diminished during lactation. However, the reduced availability of alcohol in lactating women did not result in corresponding changes in the subjective effects of alcohol.

Mennella JA and Pepino MY, 2010 (positive quality), conducted a randomized control trial (RCT) to determine whether breast pumping works independently of the physiological and metabolic changes that accompany lactation. Twelve women were tested during two reproductive stages: When they were exclusively breastfeeding three- to five-month-old infants and then again several months after lactation had ceased. Subjects were randomly assigned to one of two groups that differed in the timing of breast pumping relative to drinking a 0.4g/kg dose of alcohol: One group breast pumped 0.6 hours after drinking (PA) and the other pumped one hour before drinking (PB). For each reproductive stage, subjects were tested on two separate days, consuming a standardized meal one hour before drinking during test day and remaining fasted during the other. Breath alcohol concentrations (BrAC) and temperature readings were obtained before and at fixed intervals after drinking. Pumping before drinking significantly decreased BrAC during both reproductive stages, whereas pumping after drinking resulted in different BrAC time curves during lactation when compared with after lactation. Levels of BrAC were significantly lower during the descending phase of the time curve during than after lactation. The interactions between pumping and reproductive stage were most apparent during fed condition.

Pepino MY and Mennella JA, 2008 (positive quality), conducted a randomized, within-subject design study to evaluate two hypotheses. First, that breast pumping contributes to the previously observed decrease in ethanol bioavailability in lactating women. Second, that the effects of breast pumping are more pronounced when ethanol is consumed after a meal. The within-subject factor was test condition (fed or

fasted) and the between-subject factor was experimental group (pumped before, PB; pumped after, PA). Those randomly assigned to the PB group (N=8) breast pumped one hour before drinking, whereas those assigned to the PA group (N=8) breast pumped 0.6 hour after drinking. Pumping before drinking significantly decreased blood ethanol concentration (P<0.05) and ethanol bioavailability (P=0.05). The effects were more pronounced when ethanol was consumed after a meal.

Influence on Breast Milk Flavor or Odor

Mennella JA, 1997 (positive quality), conducted an RCT to determine whether diminished milk intake by infants of lactating women who consumed alcohol was due to infants responding to the altered flavor of the milk. Forty women and their infants were recruited from the Women, Infant and Children program in Philadelphia. Mothers expressed approximately 130ml of milk (mean=127.2±4.9), and divided into two equal aliquots. One aliguot remained unaltered and the other was flavored with 32mg ethanol/dL-the average concentration detected in human milk approximately one hour after lactating women drank an acute does (0.3g per kg) of alcohol. The evaluation consisted of a two-bottle test preference composed of four, 60 seconds. trials in which the mother's milk flavored with alcohol was alternated with the control in an ABBA or BAAB design (data were obtained for the first two trials for only nine of the 40 infants because there was not enough milk remaining in the bottles to complete the session). Attached to the nipple of each bottle was a transducer that responded to pressure changes produced by the infant's suckling. There was not suppression of sucking or intake in response to the ethanol-flavored milk. Rather, the infants consumed significantly more [Paired T(39df)=2.78; P<0.008] and sucked more [paired T(38df)=2.45; P<0.019] frequently when drinking the alcohol-flavored milk compared with the unaltered milk. These findings indicate that infants can readily detect the flavor of alcohol in mother's milk but that the decreased in consumption is apparently not due to the infants rejecting the flavor of alcohol on their mothers' milk.

Mennella JA and Beauchamp GK, 1991 (positive quality), conducted a randomized crossover study to investigate whether the ingestion of alcohol by lactating women altered the odor of their milk and whether exposure to a small amount of alcohol on the mother's milk had immediate effects on the behavior of the infant. Twelve lactating women and their infants were tested on two days separated by an interval of one week. On each testing day, the mother drank either orange juice or orange juice containing a small quantity of ethanol (0.3g per kg of body weight). Ethanol content of milk was analyzed in additional samples and a panel of adults determined whether the difference in the odor of the milk was detectable after alcohol consumption. The infants were weighed before and after nursing to assess the amount of milk they ingested, and their behavior during breastfeeding was monitored by videotape. Results showed that short-term alcohol consumption by lactating women significantly increased the perceived intensity of the odor of their milk, peaked 30 minutes to one hour after consumption and decreased thereafter. Alteration in the milk's odor closely paralleled the changes in ethanol concentration (mean range, 0 to 6.9mmol per liter). The infants sucked more frequently during the first minute of feedings after alcohol consumption by their mothers (67.0±6.5 sucks, as compared with 58.4±5.9 sucks for feeding after the consumption of the non-alcohol beverage; P<0.05), but they consumed significantly less milk (120.4±9.5ml vs. 156.4±8.2ml P<0.001) during the testing sessions in which mothers drank the alcohol beverage.

Influence on Quantity

Changes in Milk Yield/Infant Intake

Chien YC et al, 2009 (positive quality), conducted a within-subjects design study to examine whether ethanol exposure influences selected constituents in a maternal blood and milk, as well as lactation performance. Twenty-three lactating Chinese mothers were examined on two occasions, separated by a week. The target alcohol dosage was 0.3g per kg body weight. Milk and blood samples were collected prior to consumption of a traditional soup containing alcohol [chicken flavored soup with sesame oil and rice wine (CSSR)], and at 120 and 150 minutes, respectively, after consumption. Differences in concentrations of triacylglycerol (TAG) insulin, and lactate levels in maternal blood were statistically significant ($P<0.05$; paired T test) between CSSR and control groups, 150 minutes after soup consumption. Alcohol also affected milk composition and its nutritional status, particularly total protein, TAG, fatty acid, β-hydroxybutyrate, and lactate levels. The CSSR intake significantly affected TAG and lactate levels in milk ($P<0.05$; paired T test) at the end of the experiment. The time for the first milk droplet to be ejected was significantly longer in the CSSR group ($P<0.05$), indicating that the milk-ejecting reflex is inhibited. Comparing both groups, differences in milk volume was not statistically significant (NS).

Cobo et al, 1973 (neutral quality), conducted a non-randomized, within-subjects design study to evaluate milk-ejection response before and after administration of different doses of ethanol in 38 lactating women from the US. The magnitude of the milk-ejection response was estimated by measuring planimetrically the area under the pressure tracings during each suckling period, before and after ethanol intake. Ethanol in doses of 1g per kg did NS reduce the response, but after administration of 1-2g per kg of ethanol a significant reduction of the milk-ejecting response was observed. This inhibition appeared to be dose dependent.

Mennella JA, 2001 (positive quality), conducted a non-randomized, within-subjects design study (controlling for time of day) to test the hypothesis that infants would compensate for the diminished milk intake if their mothers then refrained from drinking alcohol. Twelve exclusively breastfed infants and their mothers in the US were tested on two days separated by one week. Each woman drank a 0.3g per kg dose of alcohol in orange juice on one testing day and orange juice alone on the other. The infants' behaviors were monitored for the next 16 hours, the first four hours of monitoring on each test day occurred at the Monell Center. Infants consumed approximately 20% less breast milk (paired T [11df]=2.35; P=0.04), but breastfed similar number of times (paired T [11df]= -0.00; P=1.00] during the first four hours after exposure to alcohol, compared with the control condition. They then compensated for diminished intake during the eight- to 12-hour exposure (paired T [11df]= -2.13; P=0.05]. This compensation appears to be due, in part, to the increased numbers of breastfeeding that occurred during the eight-to 12-hour post-exposure (paired T [11df]= -2.24; P=0.04.

Mennella JA and Beauchamp GK, 1993 (positive quality), conducted a within-subjects design study to examine if beer consumption by 12 US nursing women altered the sensory qualities of their milk and the behavior of their infants during breast-feeding in the short term. Women had 0.3g per kg of body weight dose of alcohol during the testing day and non-alcoholic beer during the control day. All of

them were used as their own control (tested on two days, separated by a week). The infants consumed significantly less milk during the four-hour testing sessions in which their mothers drank alcoholic beer compared to when the mothers drank non-alcoholic beer, 149.5±13.1ml, compared to the session in which she drank the non-alcoholic beer, 193.1±18.4ml, paired T (10df)= -2.47; P=0.03. This decrease in milk intake was not due to a decrease in the number of times babies fed. Although the infants consumed less of the alcohol-flavored milk, the mothers believed their infants had ingested enough milk. The amount of milk expressed by each mother did not differ on the two testing days (non-alcoholic vs. alcoholic beer: 47.4±3.1ml vs. 50.0±4.2ml, paired T [10df]; P NS).

Mennella JA, 1998 (positive quality), conducted a non-randomized, within-subjects design to test the hypothesis that maternal alcohol consumption decreases the amount of milk available to the infant and alters milk composition in the short term. Timeline follow-back questionnaire for the mothers to record number, types, and frequency of alcohol consumption. To this end 22 US lactating women were tested on two days separated by one week (±2 days), and they expressed milk from both breasts simultaneously by using an electrical breast pump. The entire collecting procedure was repeated two hours later (baseline), after which the mother drank either a 0.3g per kg dose of alcohol in orange juice or an equal volume of orange juice alone within a 15-minute period. There was NS difference in the amount of milk pumped at baseline [paired T(21df)= -1.06; P=0.30], but mothers pumped significantly less milk two hours after consumption of the alcoholic beverage when compared with the amount pumped two hours after consuming the control beverage {paired T(21df)=2.45; P=0.02]. Although there was no difference in the energy content of the milk, maternal alcohol consumption significantly reduced the amount of milk produced by the lactating mother (9.3% (±4.1) less milk). This decrease in milk production tended to be apparent during the first five minutes of pumping during the two-hours post-consumption collection period [control vs. alcohol: 53.6±5.2 vs. 50.1±ml; paired T(21df)=1.54; P=0.13)].

Mennella JA and Pepino MY, 2008 (positive quality), conducted a 2x2 within-subject design, double-blind, four-session study to test effects of alcohol on prolactin (PRL) responses and milk yield over time. In 13 lactating mothers, the two within-subject factors were beverage condition (control or 0.4g per kg dose of alcohol) and pumping condition (pumping occurred at fixed intervals once or twice during the 5.3-hour session. Plasma PRL, blood alcohol concentrations (BAC) and milk yield were measured. Alcohol consumption increased basal PRL levels (P<0.0001) and modified the PRL response to pumping (P<0.0001), but the directionality of the response depended on when pumping occurred along the BAC curve. Pumping enhanced PRL response when it occurred during the ascending BAC limb but blunted the response when it occurred during the descending limb, providing evidence that the effects were transient and of a biphasic nature. The slower alcohol was metabolized, the greater the relative PRL response to breast pumping (P<0.05). The dynamics of the PRL response between pumping sessions were also altered if women drank. If women pumped within an hour after drinking alcohol, the PRL response during the next pumping some 1.5 hours later was delayed by a few minutes. BAC levels ascended during the first hour, reaching peak levels of 0.60±0.03g per L at around 42 minutes post-consumption during the two sessions in which women drank alcohol. For the next 2.6 hours, BAC levels steadily descended reaching levels of 0.15±0.02g per L at the

time the sessions ended. On average, the alcohol disappearance rate was 0.14±0.01g per L per hour. There were NS differences in the BAC time curve during the two test session in which subjects drank alcohol. Milk yield was significantly lower after drinking alcohol but such deficits were NS related to PRL or the speed at which alcohol was eliminated. Effects of alcohol on suckling-induced PRL were biphasic in nature, but could not explain the deficits in lactational performance. Such findings provide further evidence that the dynamic changes in neuroendocrine state are integrally involved in alcohol's effects over time and underscore the complexity of lactation.

Mennella et al, 2005 (positive quality), conducted a randomized, within-subjects design study to test the hypothesis that alcohol consumption affects hormonal response in lactating women (N=17). Women consumed a 0.4g per kg dose of alcohol in orange juice during one test session and an equal volume of orange juice during the other. Changes in plasma prolactin, oxytocin, and cortisol levels during and after breast stimulation, lactational performance and mood states were compared under the two experimental conditions. Oxytocin levels significantly decreased, whereas prolactin levels and measures of sedation, dysphoria, and drunkenness significantly increased, during the immediate hours after alcohol consumption. Changes in oxytocin were related to measures of lactational performance such as milk yield and ejection latencies, whereas changes in prolactin were related to self-reported measures of drunkenness. Although alcohol consumption resulted in significantly higher cortisol when compared with the control condition, cortisol levels were NS correlated with any of the indices of lactational performance or self-reported drug effects. In conclusion, recommending alcohol as an aid to lactation may be counterproductive. In the short term, mothers may be more relaxed, but the hormonal milieu underlying lactational performance is disrupted, and, in turn, the infant's milk supply is diminished.

Overview table

Author, Year, Study Design, Class, Rating	Study Subjects	Measurements	Treatment	Key Outcomes
Chien YC et al 2009 Study Design: Non-Randomized Crossover Trial Class: C Rating: Positive Quality	Subjects recruited from gynecology and obstetrics clinics at Taipei Medical University Wan-Fang Hospital. N=23. Each subject tested on two occasions separated by a week.	Breast milk alcohol analysis within the mid-point (135 minutes). Breast milk composition. Time for ejection of the first milk droplet. Total milk volume.	Target alcohol dosage of 0.30g per kg body weight achieved by administering ~8 ml of traditional soup (CSSR) per kg of body weight. Control: Non-alcoholic soup. Compliance measure by three-day dietary records.	150 minutes after soup consumption, concentrations of TAG, insulin and lactate levels in maternal blood were statistically significant (P<0.05; paired T test) between CSSR and control groups. CSSR intake affected milk. Composition and its nutritional status, particularly total PRO, fatty acid, β-hydroxybutyrate and lactate levels. CSSR intake significantly affected TAG and lactate levels in milk (P<0.05; paired T test) at end of experiment. Time for the first milk droplet to be ejected was significantly longer in CSSR group (P<0.05). Comparing both groups, milk volume was NS.

Chien YC, Liu JF et al, 2005 Study Design: Non-randomized trial Class: C Rating: Positive Quality	N=23 Chinese women. Subjects recruited from gynecology and obstetrics clinics at Taipei Medical University Wan-Fang Hospital. Age: 24.5±3.4 years. Height: 158.8±6.5cm. Weight: 62.5±9.6kg.	Alcohol levels in milk and blood at 10, 20, 30, 40, 60 and 90 minutes. Milk volume at 120 minutes post-exposure to "chicken soup flavored with sesame oil and rice wine" (CSSR). Mean time required for milk alcohol levels to return to zero level (defined as half the analytical detection limit) using the equation: Milk alcohol level= -0.193 x time+35.1 (r^2=0.999, P<0.05). Mean blood ethanol disappearance rate using the equation: Blood alcohol level= -0.15 x time+31.9 (r^2=0.994, P<0.05). Infant risk associated with alcohol exposure through breast milk, using hazard index (estimated worst-case infant dose divided by a reference dose).	CSSR alcohol level varies, for this study it was determined to be 40.6±1.8mg per ml. Target alcohol dosage of 0.3g per kg of body weight achieved by administering ~8 ml of soup for each kg of subject body weight.	Mother's blood alcohol levels peaked at 20 minutes after ingestion of CSSR and ↓ almost linearly to zero level after roughly three hours. Milk alcohol levels peaked at around 20-40 minutes and ↓ linearly thereafter. At 135 minutes post-CSSR consumption, alcohol concentrations in milk were 9.0±5.2mg per dL, significantly ↑ than the pre-CSSR consumption level. Mean time required for milk alcohol levels to return to zero level was estimated at ~175 minutes. Mean blood ethanol disappearance rate was 90mg per L per hour. Average peak time for milk alcohol was 31.7±12.7 minutes post-exposure. Average peak time for blood alcohol was 23.5±7.6 minutes, occurring statistically faster than in milk, P<0.05. Mean maximal milk alcohol concentration in this study was 31.6±10.3mg per dL, and NS different from the mean maximal BAC (30.2±5.0mg per dL). Correlation coefficients between blood and milk alcohol levels varied for each individual: (range, 20.96 to 0.99; median, 0.79; mean, 0.62). Six of the correlation coefficients (subjects one, four, 13, 14, 16, 22) reached significant levels. Correlation coefficient between blood and milk alcohol levels based on pooled data from all subjects was 0.769.

Cobo E, 1973 Study Design: Non-randomized trial Class: C Rating: Neutral Quality	Study from the Unit of Physiology of Reproduction, Division of Health, del Valle University, Colombia. N=38. All subjects used as their own control.	Mammary response to milk ejection by measuring planimetrically the area under pressure tracing during each suckling period, before and after ethanol intake.	Ethyl alcohol doses expressed in weight per volume. Doses divided into four groups (per kg): 0.1-0.49 0.5-0.99 1.0-1.49 1.5-1.99g. Two subjects received 2.0g per kg.	Results by doses of ethanol: 0.147-0.450g per kg did not produce inhibition of the milk-ejecting reflex 0.521-1.464g per kg ↓, but not statistically difference 1.583-1.924g per kg ↓, statistically different.
Menella JA and Pepino MY, 2008 Study Design: Randomized control trial. 2x2 within-subject quasi-randomized trial Class: A Rating: Positive Quality	N=16. Study based on Pepino et al, 2007. Subjects recruited from the Philadelphia area.	Blood ethanol concentrations (BECs). N=9; five in group PA (pumped after) and four in group PB (pumped before) were exclusively breastfeeding. N=7; three in group PA and four in group PB supplemented breastfeeding with formula or baby foods no more than once a day.	Subjects drank 0.4g per kg dose of OH mixed with a non-caloric juice.	Significant Δ in BECs over time ($P<0.001$) and significantly dependent on timing of breast pumping (main effect of group: $P<0.05$;) and on whether ethanol was consumed before or after a meal (main effect of condition: $P<0.001$). During the fed condition, BEC levels significantly ↓ ($P<0.001$) and tended to peak later ($P=0.06$). Women who pumped before drinking (group PB) had lower peak BECs ($P=0.01$) and ↓ systemic availability of ethanol. Those who did not breast pump until 0.6 hours after drinking (group PA) eliminated ethanol faster.

Menella JA and Pepino MY, 2010 Study Design: Randomized Controlled Trial Class: A Rating: Positive Quality	Lactating women. N=12 (Six Caucasian, four African American, and two other/mixed race/ethnic groups). Age: 33.0±1.2 years.	Each woman was tested during two reproductive stages: 1) Exclusively breastfeeding (durin g lactation) 2) After lactation had ceased (after lactation), on two days separated by one week. Groups evaluated: 1) Pumping Before lactation (PB) breast pumped an hour before drinking 2) Pumping After lactation (PA) begin pumping 0.6 hour after alcohol consumption. Conditions evaluated: 1) Fed condition 2) Fasted condition one hour later of drinking a 0.4g per kg dose of alcohol 3) BrAC (Breath Alcohol Concentration) 4) Alcohol elimination rate (R), expressed as amount of alcohol eliminated per kg per hour calculated as R=β60/body weight.	Alcohol dose=0.4g per kg.	Elimination rates were faster during fed (0.12±0.01) than fasted (0.09±0.01, F[1, 7]=100.8, P<0.001) condition. Significant interactions: Reproductive stage by time (F[14,140]=3.67, P<0.0001) and condition by time (F[14,140]=21.95, P<0.0001), and three-way interactions: Food condition by group and time (F[14, 140]=2.10, P=0.015) and reproductive stage by group and time (F[14,140]=7.67, P<0.0001) for the BrAC time curve. Fed and fasted conditions, in both reproductive stages significantly interacted with group and time (fed condition: F[14, 140]=2.86, P<0.001; fasted condition: F14,140]=5.93, P<0.0001). No differences observed between during and after lactation staged for group PB. Group PA had ↑ BrAC levels at time 25-35 minutes and ↓ BrAC levels at time 65, 85, and 105 minutes. Differences in BrAC between PA and PB groups were only observed in one time-point. PA BrAC levels were ↓ at 45 minutes during lactation, and ↑ at 25 minutes after lactation when compared with PB.

Mennella JA and Beauchamp GK, 1991 Study Design: Randomized Controlled Trial Class: A Rating: Positive Quality	Subjects recruited from University of Pennsylvania area and from local La Leche groups. N=12. Age: 21 to 38 years (median 30 years). Infants: Eight girls, four boys Age: 25 to 216 days (median 120 days) All participants were used as their own control.	Babies' weight before and after breastfeeding. Volume (ml) of milk consumed estimated by dividing the weight of milk consumed by 1.031. Babies videotaped after breastfeeding. Odor of the milk by a sensory panel of 17 adults.	Testing day: 0.3g per kg of body weight dose of alcohol in orange juice. Control day: Orange juice alone.	Estimated dose of alcohol ingested by infants, taking into account the body weight of each infant, was 1.6 to 9.9mg per kg (mean 5.1±0.8 (3.3% of the maternal dose). Infants consumed significantly ↓ milk during the three-hours testing session in which their mothers drank alcohol (120.4±9.5ml vs. 156.4±8.2ml, paired T(11df)= -4.69, P<0.001). NS difference in number of feedings (control vs. alcohol: 2.5±0.2 vs. 2.2±0.2, paired T[11df]=1.91, P=NS). NS difference in total length of time during which infant was attached to the nipple (control vs. alcohol: 28.6±7.7 vs. 28.2±7.3 minutes, paired T [11df]=0.15, P=NS). Infants sucked significantly more frequently during first few minutes of feedings on the day their mothers consumed the alcohol [F(8,1 df)=12.11, P<0.008]; the videotapes of three infants were not clear to detect frequency of sucking. However, NS difference in total number of sucks on the two days of testing [control vs. alcohol: 856.7±103.4 vs. 877.2±102.3, T (8df)=0.23, P=NS] NS difference in total amount of time infants slept during the three hours testing sessions (control vs. alcohol: 65.10±10.96 vs. 62.97±12.04 minutes, paired T [11df]=0.15, P=NS) or for remainder of the day until child awoke the next morning (14.45 ±1.71 vs. 13.47±1.76 hours, paired T [11df]=1.18, P=NS). Number of times infants slept ↑ on days when mothers consumed alcohol (6.6 ±0.7 vs. 7.8±0.9, paired T [11df]= -2.31, P<0.05).

Mennella JA, 1997 Study Design: Randomized trial Class: A Rating: Positive Quality	Subjects recruited from ads in local newspapers and from WIC Centers (Philadelphia). N=40.	Sucking responses recorded and measured using a device and computer software (Maone and colleagues 1992). Timeline follow-back questionnaire for mothers (to record number, types and frequency of alcohol consumption).	Evaluation consisted of a two-bottle test preference composed of four, 60-second trials in which mother's milk flavored with alcohol [with 32mg ethanol per dL; the average concentration detected in human milk ~one hour after lactating women drank an acute dose (0.3g per kg) of alcohol] was alternated with the control in an ABBA or BAAB design.	Infants consumed ~20% ↓ breast milk (paired T [11df]=2.35; P=0.04), but breastfed similar number of times [paired T (11df)= -0.00; P=1.00] during the first four hours after exposure to alcohol, compared with control condition.
Mennella JA, 1998 Study Design: Non-randomized crossover trial Class: C Rating: Positive Quality	Subjects recruited from ads in local newspapers and from WIC Centers in Philadelphia. N=22. Subjects used as their own control.	At baseline and post-consumption collection periods: Latency to eject (amount of time for first droplet of milk to be ejected) Milk yield or volume of milk expressed for each breast within each five-minute period Timeline follow-back questionnaire for mothers (to record number, types and frequency of alcohol consumption) Caloric and fat content of the milk.	Testing day: 0.3g per kg of body weight dose of alcohol in orange juice. Control day: Orange juice alone.	Mothers pumped significantly ↓ milk two hours after consumption of alcoholic beverage when compared with amount pumped two hours after consuming control beverage [paired T(21df)=2.45; P=0.02.

Mennella JA, 2001 Study Design: Non-randomized crossover trial Class: C Rating: Positive Quality	Subjects recruited from ads in local newspapers and from WIC Centers (Philadelphia). N=12. Subjects used as their own control.	Babies' weight after breastfeeding Babies videotaped after breastfeeding Volume (milliliters) of milk consumed estimated by dividing the weight of milk consumed by 1.031.	Testing day: 0.3g per kg of body weight dose of alcohol in orange juice. Control day: Orange juice alone.	Infants consumed ~20% ↓ breast milk (paired T [11df]=2.35; P=0.04), but breastfed similar number of times [paired T (11df)= -0.00; P=1.00] during first four hours after exposure to alcohol, compared with control condition.
Mennella JA, Beauchamp GK, 1993 Study Design: Randomized crossover study Class: A Rating: Positive Quality	Subjects recruited from the Philadelphia area. N=12. All subjects used as their own control (tested on two days, separated by a week).	Babies' weight after breastfeeding. Babies videotaped after breastfeeding. Volume (ml) of milk consumed estimated by dividing the weight of the milk consumed by 1.031.	Testing day: 0.3g per kg of body weight dose of alcohol. Control day: Equal volume of non-alcoholic beer. Half of women drank alcoholic beer during first session and non-alcoholic during second session. Estimated alcohol ingested by infant: 18.6-66.7mg (mean 43.1±5.2) or 2.3-8.4mg per kg or 0.8-2.8 % of the maternal dose (300mg per kg).	Infants consumed significantly ↓ milk during the four-hour testing sessions in which their mothers drank alcoholic beer compared to when mothers drank non-alcoholic beer, 149.5±13.1ml, compared to the session in which she drank nonalcoholic beer, 193.1±18.4ml, paired T (10df)= -2.47, P=0.03. Amount of milk expressed by each mother did not differ on the two testing days (non-alcoholic vs. alcoholic beer: 47.4±3.1ml vs. 50.0±4.2ml, paired T [10df]; P=NS).

Mennella JA, Pepino MY & Teff K 2005 Study Design: randomized crossover trial Class: A Rating: Positive Quality	Subjects recruited from the Philadelphia area. N=17. Subjects used as their own control.	Plasma prolactin, oxytocin and cortisol levels during and after breast stimulation, lactational performance and mood states. Blood alcohol concentrations (BAC) by having subject breath into an Alco-Sensor III.	Treatment: 0.4g per kg dose of alcohol. Control: No alcohol intake.	Significant interaction between condition and time on oxytocin levels (F[15,240df]=1.83; P=0.03). Significant interaction between condition and time on prolactin plasma levels (F[15,240df] =3.31; P=0.001). Significant effects of condition (F[1,16df]=5.91; P=0.03) and time (F[15,240df]=4.39; P=0.001). BAC peaked ~43-51 minutes after alcohol consumption and ↓ thereafter.
Pepino MY and Mennella JA, 2008 Study Design: Randomized Controlled Trial Class: A Rating: Positive Quality	Subjects recruited from the Philadelphia area. N=13. 2x2 within-subject design, double-blind.	Blood alcohol concentration (BAC). Beverage condition (control or 0.4g per kg dose of alcohol). Pumping condition (pumping occurred at fixed intervals once or twice during the 5.3-hour session).	Treatment: 0.4g per kg dose of alcohol. Control: No alcohol intake.	BAC levels ↑ during first hour, reaching peak levels of 0.60±0.03g per L at around 42 minutes post-consumption. On average, alcohol disappearance rate was 0.14±0.01g per L per hour. Significant effect of beverage condition on lactational performance (F1,11df)=8.74; P=0.01). Women expressed significantly ↓ milk during sessions in which they drank the alcoholic beverage. NS differences in fat content of milk expressed (F[1,11]=0.40; P=0.54).

Pepino MY, Steinmeyer AL et al, 2007 Study Design: Non-randomized trial with concurrent controls Class: C Rating: Positive Quality	Subjects recruited from the Philadelphia area. Three groups of women were compared: Lactating (N=20) Formula-feeding (N=9) Nulliparous (N=15).	BAC by breathing into a fuel-cell sensor analyzer. Using Mumenthaler et al, 1999: Time-to-peak BAC Peak BAC disappearance rate (β60) Total amount of OH eliminated per hour (b60) was calculated by: b60=β60xTBW/Bw (equation not validated in lactating women) Alcohol eliminated rate (R)=β60/body weight.	Subjects drank 0.4g per kg dose of OH mixed with a non-caloric juice.	BAC time curves in lactating, formula-feeding and nulliparous women under the fed and fasted conditions showed significant main effects of reproductive state on BAC levels [F(2, 41)=4.98; P<0.025], peak BAC [F(2, 41)=4.8; P<0.025] and blood alcohol time curve (AUC) [F(2,41]=5.3; P<0.01). NS differences between groups in time to reach peak alcohol levels (P=0.25), BAC levels, and peak BAC levels significantly ↓ and AUCs significantly smaller in lactating women, when compared with both groups of non-lactating women. NS differences in β60, b60 or R among the groups (all P>0.50).

Search plan and results

Inclusion criteria

- Subjects/Population: Human subjects
- Age: Children, men and women of all ages
- Setting: International
- Health Status: Healthy and those with elevated chronic disease risk (CHD/CVD, Type 2 diabetes, metabolic syndrome and obesity)
- Nutrition Related Problem/Condition: None.
- Search Criteria
    - Study design preferences: RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis
    - Size of study groups: The sample size must equal 10 adults for each study group. For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group
    - Study dropout rate: Less than 20%; preference for smaller dropout rates
    - Year range: No date range
    - Authorship: If an author is included on more than one review article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected
    - Languages: Limited to articles in English
    - Other: Article must be published in peer-reviewed journal.

Exclusion criteria

- Subjects/population:
    - Animal and in vitro studies

    - Malnourished/third-world populations or disease incidence not relative to US population (e.g., malaria)
- Setting: Hospitalized patients
- Health status: Medical treatment and therapy and diseased subjects
- Nutrition Related Problem/Condition: All conditions.
- Search Criteria
    - Size of study groups: Sample sizes less than 10
    - Study Dropout rate: If the dropout rate in a study is 20% or greater, the study will be rejected
    - Authorship: Studies by same author similar in content
    - Languages: Articles not in English
    - Other: Abstracts or presentations and articles not peer reviewed (Web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  Date 8/12/09 & 10/21/09: ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND (lactation[mh] OR breast feed* OR (breast fed*))

  Date: 12/3/09: No date range ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND ((breast milk) OR "Milk, Human"[Mesh])

  ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND (postnatal OR "Postpartum Period"[Mesh] OR postpartum OR "Breast Feeding"[Mesh] OR lactation[mh])

Date searched: 12/04/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 324
- Total articles identified to review from electronic databases: 46
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 11
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 13
- Number of Articles Reviewed but Excluded: 35

Included articles (References)

1. Chien YC, Huang YJ, Hsu CS, Chao JC, Liu JF. Maternal lactation characteristics after consumption of an alcoholic soup during the postpartum 'doing-the-month' ritual. Public Health Nutr. 2009 Mar; 12(3): 382-388. Epub 2008 Apr 22. PMID: 18426631.
2. Chien YC, Liu JF, Huang YJ, Hsu CS, Chao JC. Alcohol levels in Chinese lactating mothers after consumption of alcoholic diet during postpartum "doing-the-month" ritual. Alcohol. 2005 Nov; 37(3): 143-150. PMID: 16713502.
3. Cobo E. Effect of different doses of ethanol on the milk-ejecting reflex in

lactating women. Am J Obstet Gynecol. 1973 Mar 15; 115(6): 817-821. PMID: 4688584.
4. Mennella JA. Infants' suckling responses to the flavor of alcohol in mothers' milk. Alcohol Clin Exp Res. 1997 Jun; 21(4): 581-585. PMID: 9194908.
5. Mennella JA. Short-term effects of maternal alcohol consumption on lactational performance. Alcohol Clin Exp Res. 1998 Oct; 22(7): 1, 389-1, 392. PMID: 9802517.
6. Mennella JA. Regulation of milk intake after exposure to alcohol in mothers' milk. Alcohol Clin Exp Res. 2001 Apr; 25(4): 590-593. PMID: 11329500.
7. Mennella JA, Beauchamp GK. Beer, breast feeding, and folklore. Dev Psychobiol. 1993 Dec; 26(8): 459-466. PMID: 8293892.
8. Mennella JA, Beauchamp GK. The transfer of alcohol to human milk. Effects on flavor and the infant's behavior. N Engl J Med. 1991 Oct 3; 325(14): 981-985. PMID: 1886634.
9. Mennella JA, Pepino MY. Biphasic effects of moderate drinking on prolactin during lactation. Alcohol Clin Exp Res. 2008 Nov; 32(11): 1, 899-1, 908. Epub 2008 Aug 18. PMID: 18715274 (Hand search - 12-08-09).
10. Mennella JA, Pepino MY. Breast pumping and lactational state exert differential effects on ethanol pharmacokinetics. Monell Chemical Senses Center, Philadelphia, PA 19104, USA. Alcohol. 2010 Mar; 44(2): 141-148. Epub 2010 Jan 6. PMID: 20056373 (Hand search - 03-08-10).
11. Mennella JA, Pepino MY, Teff KL. Acute alcohol consumption disrupts the hormonal milieu of lactating women. J Clin Endocrinol Metab. 2005 Apr; 90(4): 1, 979-1, 985. Epub 2004 Dec 28. PMID: 15623810.
12. Pepino MY, Mennella JA. Effects of breast pumping on the pharmacokinetics and pharmacodynamics of ethanol during lactation. Clin Pharmacol Ther. 2008 Dec; 84(6): 710-714. Epub 2008 Jul 2. PMID: 18596681.
13. Pepino MY, Steinmeyer AL, Mennella JA. Lactational state modifies alcohol pharmacokinetics in women. Monell Chemical Senses Center, Philadelphia, Pennsylvania, USA. Alcohol Clin Exp Res. 2007 June; 31(6): 909-918.

Excluded articles

Article	Reason for Exclusion
Alvik A, Haldorsen T, Lindemann R. Alcohol consumption, smoking and breastfeeding in the first six months after delivery. A*cta Paediatr.* 2006 Jun; 95(6): 686-693. PMID: 16754549.	About drinking levels during lactation.
Anderson PO. Alcohol and breastfeeding. *J Hum Lact.* 1995 Dec; 11(4): 321-323. No abstract available. PMID: 8634110.	Comment.
Backstrand JR, Goodman AH, Allen LH, Pelto GH. Pulque intake during pregnancy and lactation in rural Mexico: Alcohol and child growth from 1 to 57 months. *Eur J Clin Nutr.* 2004 Dec; 58(12): 1, 626-1, 634. PMID: 15280906.	Does not answer the question; about lactation and health of the offspring.

Binkiewicz A, Robinson MJ, Senior B. Pseudo-Cushing syndrome caused by alcohol in breast milk. *J Pediatr.* 1978 Dec; 93(6): 965-967. No abstract available. PMID: 722441.	Does not answer the question; about Cushing syndrome.
Chaves RG, Lamounier JA, César CC. Factors associated with duration of breastfeeding. *J Pediatr (Rio J).* 2007 May-Jun; 83(3): 241-246. Epub 2007 Apr 20. PMID: 17486198.	Does not answer the question; about factors associated with breastfeeding.
Dewailly E, Ayotte P, Laliberté C, Weber JP, Gingras S, Nantel AJ. Polychlorinated biphenyl (PCB) and dichlorodiphenyl dichloroethylene (DDE) concentrations in the breast milk of women in Quebec. *Am J Public Health.* 1996 Sep; 86(9): 1, 241-1, 246. PMID: 1380586.	Does not answer the question; about chemicals in breast-milk.
Flores-Huerta S, Hernández-Montes H, Argote RM, Villalpando S. Effects of ethanol consumption during pregnancy and lactation on the outcome and postnatal growth of the offspring.	Does not answer the question; about lactation and health of the offspring.
Giglia RC, Binns CW. Alcohol and breastfeeding: What do Australian mothers know? *Asia Pac J Clin Nutr.* 2007; 16 Suppl 1: 473-477. PMID: 17392153.	Does not answer the question; about levels of knowledge of the danger of drinking OH during breastfeeding.
Giglia RC, Binns CW. Alcohol, pregnancy and breastfeeding: A comparison of the 1995 and 2001 National Health Survey data. *Breastfeed Rev.* 2008 Mar; 16(1): 17-24. PMID: 18546573.	Does not answer the question; about patterns of alcohol intake.
Giglia RC, Binns CW, Alfonso HS, Scott JA, Oddy WH. The effect of alcohol intake on breastfeeding duration in Australian women. *Acta Paediatr.* 2008 May; 97(5): 624-629. PMID: 18394108.	Does not answer the question; about breastfeeding duration and OH intake.
Gottesfeld Z, Abel EL. Maternal and paternal alcohol use: effects on the immune system of the offspring. *Life Sci.* 1991; 48(1): 1-8. Review. PMID: 1986181.	Does not answer the question; about lactation and health of the offspring.
Ho E, Collantes A, Kapur BM, Moretti M, Koren G. Alcohol and breast feeding: Calculation of time to zero level in milk. *Biol Neonate.* 2001; 80(3): 219-222. PMID: 11585986.	No intervention; modeled time to alcohol clearance in breast milk.

Howard CR, Lawrence RA. Breast-feeding and drug exposure. *Obstet Gynecol Clin North Am.* 1998 Mar; 25(1): 195-217. Review. PMID: 9547767.	Does not answer the question; about lactation and health of the offspring.
Kacew S. Adverse effects of drugs and chemicals in breast milk on the nursing infant. *J Clin Pharmacol.* 1993 Mar; 33(3): 213-221. Review. PMID: 8463434.	Does not answer the question; about drugs and chemicals in breast-milk.
Kochenour NK, Emery MG. Drugs in lactating women. *Obstet Gynecol Annu.* 1981; 10: 107-126. Review. No abstract available. PMID: 7024869.	Does not answer the question; about lactation and health of the offspring.
Koletzko B, Lehner F. Beer and breastfeeding. *Adv Exp Med Biol.* 2000; 478: 23-28. Review. PMID: 11065057.	Publication.
Koren G. Drinking alcohol while breastfeeding. Will it harm my baby? *Can Fam Physician.* 2002 Jan; 48: 39-41. PMID: 11852608.	Commentary.
Lawton ME. Alcohol in breast milk. *Aust N Z J Obstet Gynaecol.* 1985 Feb; 25(1): 71-73. PMID: 3862407.	Sample size (N=8), less than inclusion criterion.
Liston J. Breastfeeding and the use of recreational drugs: Alcohol, caffeine, nicotine and marijuana. *Breastfeed Rev.* 1998 Aug; 6(2): 27-30. PMID: 9849117.	Does not answer the question; about lactation and health of the offspring.
Little RE, Anderson KW, Ervin CH, Worthington-Roberts B, Clarren SK. Maternal alcohol use during breast-feeding and infant mental and motor development at one year. *N Engl J Med.* 1989 Aug 17; 321(7): 425-430. PMID: 2761576.	Does not answer the question; about lactation and health of the offspring.
Little RE, Lambert MD, Worthington-Roberts B. Drinking and smoking at 3 months postpartum by lactation history. *Paediatr Perinat Epidemiol.* 1990 Jul; 4(3): 290-302. PMID: 2374748.	Does not answer the question; about behavior in postpartum drinking.
Little RE, Northstone K, Golding J; ALSPAC Study Team. Alcohol, breastfeeding, and development at 18 months. *Pediatrics.* 2002 May; 109(5): E72-E72. PMID: 11986478.	Does not answer the question; about lactation and health of the offspring.
Ludvigsson JF, Ludvigsson J. Socio-economic determinants, maternal smoking and coffee consumption, and exclusive breastfeeding in 10205 children. *Acta Paediatr.* 2005 Sep; 94(9): 1, 310-1, 319. PMID: 16278998.	Does not answer the question; about socio-economic determinants of breastfeeding.

Matheson I, Kristensen K, Lunde PK. Drug utilization in breast-feeding women. A survey in Oslo. *Eur J Clin Pharmacol.* 1990; 38(5): 453-459. PMID: 1974205.	Does not answer the question; about drug utilization in breastfeeding women.
Mennella J. Alcohol's effect on lactation. *Alcohol Res Health.* 2001; 25(3): 230-234. Review. PMID: 11810962.	NI AAA publication.
Mennella JA, Garcia-Gomez PL. Sleep disturbances after acute exposure to alcohol in mothers' milk. *Alcohol.* 2001 Nov; 25(3): 153-158. PMID: 11839458.	Does not answer the question; about lactation and infant sleep disturbances.
Mennella JA, Gerrish CJ. Effects of exposure to alcohol in mother's milk on infant sleep. *Pediatrics.* 1998 May; 101(5): E2. PMID: 9565435.	Does not answer the question; about lactation and infant sleep disturbances
Na HR, Daniels LC, Seelig LL Jr. Preliminary study of how alcohol consumption during pregnancy affects immune components in breast milk and blood of postpartum women. *Alcohol Alcohol.* 1997 Sep-Oct; 32(5): 581-589. PMID: 9373700.	Does not answer the question; about influence of pregnancy OH intake on breast-milk.
Rayburn WF. Adverse reproductive effects of beer drinking. *Reprod Toxicol.* 2007 Jul; 24(1): 126-130. Epub 2007 May 3. PMID: 17544619.	Systematic review included studies tested animals.
Schimmel MS, Eidelman AI, Wilschanski MA, Shaw D Jr, Ogilvie RJ, Koren G. Toxic effects of atenolol consumed during breast feeding. *J Pediatr.* 1989 Mar; 114(3): 476-478. No abstract available. Erratum in: *J Pediatr.* 1990 Jan; 116(1): 158. Schmimmel, MS [corrected to Schimmel, MS]; Eidelman, AJ [corrected to Eidelman, AI]. PMID: 2921694.	Does not answer the question; about atenolol effects during breastfeeding.
Schulte P. Minimizing alcohol exposure of the breastfeeding infant. *J Hum Lact.* 1995 Dec; 1(4): 317-319. PMID: 8634109.	Comment.
Somogyi A, Beck H. Nurturing and breast-feeding: exposure to chemicals in breast milk. *Environ Health Perspect.* 1993 Jul; 101 Suppl 2: 45-52. Review. PMID: 8243405.	Descriptive; chemicals in breast-milk.

Villalpando S, Flores-Huerta S, Fajardo A, Hernandez-Beltran MJ. Ethanol consumption during pregnancy and lactation. Changes in the nutritional status of predominantly breastfeeding mothers. *Arch Med Res.* 1993 Winter; 24(4): 333-338. PMID: 8118156.	Does not answer the question; about mothers' health and OH consumption.
Wolin MJ, Yerry S, Miller TL, Zhang Y, Bank S. Changes in production of ethanol, acids and H_2 from glucose by the fecal flora of a 16- to 158-day-old breast-fed infant. *J Nutr.* 1998 Jan; 128(1): 85-90. PMID: 9430607.	Does not answer the question; about ethanol changes in the breast-feeding infant.

CHAPTER 10. WEIGHT GAIN

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL INTAKE AND WEIGHT GAIN?

Conclusion statement

Moderate evidence suggests that among free-living populations, moderate drinking is not associated with weight gain. However, heavier consumption over time is associated with weight gain.

Grade

Moderate

Evidence summary overview

Based on the literature dating back to November 1994, one randomized control trial (RCT) (Flechtner-Mors et al, 2004) and seven prospective observational studies directly addressed the question of alcohol consumption and weight gain. One RCT received a neutral rating. Of the seven prospective observational studies, three received positive ratings and four received neutral ratings. Flechtner-Mors 2004 concluded that an energy-restricted diet is effective in losing weight regardless if 10% of energy is derived from white wine or grape juice. Of the prospective studies, Liu et al, 1994 suggests that alcohol intake is not a risk factor for obesity. Drinkers were less likely to have either major weight gain or weight loss than non-drinkers. Sherwood et al, 2000 and Sammel et al, 2003 found similar results that indicated alcohol consumption was not associated with substantial weight gain. While light to moderate drinking appeared to show no significant (NS) increase in weight, heavy drinking was shown to increase weight (Wannamethee and Sharper 2003; Wannamethee et al, 2004). However, Wannameethee 2004 found that light drinking was associated with increased odds of weight gain in African American women. Two studies (Koh-Banerjee et al, 2003 and Tolstrup et al, 2008) looked at changes in waist circumference. Koh-Banerjee found no significant association in total alcohol consumption and nine-year waist gain while Tolstrup found drinking frequency inversely associated with major waist gain and unassociated with major waist loss.

Evidence summary paragraphs

Randomized Control Trial

Flechtner-Mors et al, 2004 (neutral quality). This study was an RCT conducted in Germany, as part of a three-month isocaloric weight loss trial, that examined whether daily consumption of 10% of energy from either white wine or grape juice influenced the effectiveness of an energy-restricted diet in overweight and obese subjects. Forty subjects, men and women older than 18 years with body mass index (BMI) between 25.0 and 40.0kg/m2, completed the study. They were recruited from an Obesity Center at an outpatient clinic of a University Hospital. The subjects regularly consumed 20 to 30g of alcohol per day. The subjects were randomly assigned to one of two dietary treatment groups, a white wine (WW) group (10% of total energy derived from white wine) and a grape juice (GJ) group (10% of total energy derived from grape juice). Participants consumed a 1,500kcal per day diet (15% protein, 30% to 35% fat and

50% to 55% carbohydrates or 45% to 50% carbohydrates and 10% of energy from white wine or grape juice). All subjects achieved significant body weight loss. Weight loss in the GJ group and WW group was 3.75+0.46 and 4.73+0.53kg, respectively, and the difference was NS. The authors concluded that a diet with 10% of energy from white wine is as effective as an isocaloric 1,500kcal diet with 10% of energy derived from grape juice in achieving weight loss in overweight and obese subjects.

Prospective Observational Studies

Koh-Banerjee et al, 2003 (positive quality). In this prospective cohort study conducted in the US, the authors examined the association of changes in dietary intake, physical activity, alcohol consumption and smoking in a nine-year gain in waist circumference (WC) among a cohort of 16,587 men aged 40 to 75 years at baseline in 1986. The participants were part of the Health Professionals Follow-up Study. In 1986, participants completed a questionnaire regarding medical history, diet and physical activity. They self-reported their age, height, weight, smoking status and history, marital status and family history of coronary heart disease (CHD) and cancer. Biennially, participants completed a new questionnaire updating their information. Body mass index was calculated at each follow-up interval using participants' self-reported height and weight. In 1987 and 1996, participants self-reported their waist and hip circumferences. Over the nine-year follow-up period, the mean (+SD) WC increased 3.3+6.2cm, from 93.8+8.5cm in 1987 to 97.2+9.9cm in 1996. Alcohol consumption remained fairly constant over time, at an overall average of approximately 11.5±14.9g per day. Authors found NS associations between changes in total alcohol consumption and nine-year waist gain.

Liu et al 1994 (neutral quality). This study was a prospective study conducted in the US to examine the relationship between alcohol intake and body weight in 7,320 adults aged 25 to 74 who participated in the First National Health and Nutrition Examination Survey (NHANES) (1971 to 1975) and who were reweighed 10 years later (1982 to 1984). Alcohol intake was assessed during baseline interviews. Information on alcohol consumption (drinks per day) was obtained by responses to quantity-frequency questions during the medical history interview. Participants were categorized into six groups: Non-drinkers (did not drink during the past year), infrequent drinkers (less than 12 drinks a year), very light drinkers (12 or more drinks a year, but less than one drink a week), light drinkers (one or more drinks per week, but less than one drink per day), moderate drinkers (one to 1.9 drinks per day) and heavy drinkers (more than two drinks per day). Analyses were adjusted for age, race, height, education, health status, smoking status, diet status, physical activity and total non-alcoholic caloric intake. Both men and women drinkers tended to gain less weight than did non-drinkers (P=0.006 for trend in women, P=0.11 for trend in men). Drinkers also had more stable weight over the 10-year follow-up period. Drinkers were less likely to have major weight gain or loss (gaining or losing more than 10kg) than were non-drinkers. Compared with non-drinkers, those who consumed one to 6.9 drinks per week, women had an odds ratio (OR) = 0.7 (95% CI: 0.5 to 0.9) for major weight gain and an OR=0.7 (95% CI: 0.5 to 1.1) for major weight loss, while men had an OR=1.0 (95% CI: 0.6 to 1.6) for major weight gain and an OR=0.7 (95% CI: 0.5 to 1.2) for major weight loss. For those who consumed more than two drinks per day, women had an OR=0.5 (95% CI: 0.3 to 1.0) for major weight gain and an OR=0.8 (95% CI: 0.4 to 1.6) for major weight loss, while men had an OR=0.9 (95% CI: 0.5 to 1.6) for major weight gain and an OR=1.0 (95%

CI: 0.6 to 1.7) for major weight loss. These results suggest that moderate alcohol intake is not a risk factor for obesity.

Sammel et al, 2003 (neutral quality). In a prospective study, 336 African American and Caucasian women were followed for four years regarding predictors of weight among women in their late reproductive years. Baseline measures included anthropometric variables, socio-demographic factors, measures of anxiety, depressed mood, quality of life and self-reported measures of diet, vigorous physical activity, alcohol consumption and cigarette smoking. Over 25% of the cohort gained ten or more pounds during the follow-up. Among the women who gained more than ten pounds over the four-year period, the average alcohol consumption at baseline was 7.3 (±15.2) drinks per week. Among the remaining women who were more weight stable, baseline alcohol consumption was 8.5 (±19.0) drinks per week. The difference was still not statistically significantly different after multivariate adjustment for the main predictors of weight in this cohort of women.

Sherwood et al, 2000 (positive quality). In this prospective study of community volunteers, 826 women and 218 men who were participants in the Pound of Prevention study were followed over three years. Participants reported their usual serving size and frequency of consumption over the last year for 60 separate food items at baseline. Analyses also included baseline demographic information, smoking, physical activity and a behavioral eating score. At baseline, the average age was 35 in both men and women and the baseline BMI was 28.0kg/m2 and 26.8kg/m2 respectively. During the three years of follow-up, the average weight gain was 1.69kg (±5.4kg) among men and 1.76kg (±6.7kg) among women. During the same time period the average caloric consumption decreased by 211kcal per day among men and 168kcal per day among women, with a corresponding increase in percent of calories from alcohol by 0.88% and 0.30%, respectively. In prospective analyses, change in energy from alcohol was not associated with weight change in the men or women. Among participants who were in one of three groups: 1) Lost weight; 2) Maintained weight; or 3) Gained weight over the three years, there was NS difference in their average change in alcohol consumption. Although other diet and energy expenditure measures were associated with weight change in this cohort, alcohol consumption at baseline or changes during follow-up were not associated with weight change.

Tolstrup et al, 2008, (neutral quality), conducted a prospective cohort study in Denmark to test the hypothesis that drinking frequency is associated with subsequent changes in WC and development of abdominal obesity. A total of 43,543 male and female participants from the Diet, Cancer and Health study were included in the analysis. Drinking frequency was not associated with major waist loss, but was inversely associated with major waist gain, suggesting that non-drinkers and the most rare drinker had the highest odds for major gain in WC. Odds ratios for major waist gain among men were 0.97 (95% CI: 0.73, 1.28) for never drinking, 0.95 (95% CI: 0.81, 1.12) for drinking on one day of the week, 0.88 (95% CI: 0.77, 0.99) for drinking on two to four days of the week, 0.82 (95% CI: 0.71, -0.95) for drinking on five to six days of the week, and 0.79 (95% CI: 0.69, 0.9) for drinking every day of the week, compared to men who drank alcohol on less than one day per week (P<0.0001). Results for women were similar, and adjustment for amount of alcohol intake or total energy intake did not affect results. The authors concluded that drinking frequency was inversely associated with major waist gain and was unassociated with major waist

loss.

Wannamethee and Shaper, 2003 (neutral quality), a prospective cohort study, examined the relationship between alcohol intake and body weight, and the association between changes in alcohol intake and body weight over five years of follow-up in 6,832 middle-aged male participants of the British Regional Heart Study. After adjustment for potential confounding variables, mean BMI and the prevalence of men with BMI higher than 28kg/m2 was not different between men who stayed as abstainers or light drinkers when compared with men who were moderate drinkers or those who became moderate drinkers. After five years of follow-up, stable heavy drinkers or men who became heavy drinkers (more than 30g per day of alcohol consumption) showed the greatest weight gain and had the highest prevalence rates of high BMI.

Wannamethee et al, 2004 (positive quality) conducted a prospective cohort study in the US to examine the relationship between alcohol and eight-year weight gain in 49,324 female registered nurses between the ages of 27 to 44 years from the Nurses' Health Study II. Women completed a validated 116-item food frequency questionnaire (FFQ) in 1991 and self-reported weights both in 1991 and 1999. A non-linear relationship was seen between alcohol and weight gain of 5kg or more. Compared with non-drinkers, the adjusted relative odds of weight gain according to grams per day were 0.94 (95% CI: 0.89, 0.99) for those consuming 0.1 to 4.9g per day, 0.92 (95% CI: 0.85, 0.99) for those consuming five to 14.9g per day, 0.86 (95% CI: 0.76, 0.78) for those consuming 15 to 29.9g per day and 1.07 (95% CI: 0.89, 1.28) for those consuming 30g or more per day (P<0.0001). The increased odds of weight gain associated with heavy drinking (30+ grams per day) were most marked in women under age 35 (OR=1.64; 95% CI: 1.03, 2.61). However, in the less than 3% of women who were African-American, light drinking was associated with increased odds of weight gain (OR=2.43, 95% CI: 1.22, 4.82).

Overview table

Author, Year, Study Design, Class, Rating	Populations/Subjects	Significant Outcomes
Flechtner-Mors M, Biesalski HK et al, 2004 Study Design: Randomized Controlled Trial Class: A Rating: Neutral Quality	N=40 overweight or obese middle-aged men and women. Three-month 1,500kcal weight loss intervention with daily self-monitoring. Mean age: 48.1±11.4 years. Mean BMI: 34.2±6.4kg/m^2. Location: Germany.	All subjects achieved significant body weight loss. Weight loss in the GJ group and WW group was 3.75±0.46 and 4.73±0.53kg, respectively, but the difference NS.

Koh-Banerjee P, Chu NF et al, 2003 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	N=16,587 healthy male health professionals without CVD, cancer or diabetes. Age: 40 to 75 years. Follow-up rate: 65%. Nine-year follow-up. Location: United States.	Alcohol consumption remained fairly constant over time, at an overall average of ~11.5+14.9g per day. NS associations observed between Δ in total alcohol consumption and nine-year waist gain. Alcohol and WC were self-reported.
Liu S, Serdula MK et al, 1994 Study Design: Cross-Sectional Study Class: D Rating: Neutral Quality	N=7,320 adults who participated in the First NHANES. Reweighed in 10-year follow-up. Location: United States.	Little relation observed between body weight and alcohol intake among men. Both men and women drinkers tended to gain less weight than did non-drinkers. Drinkers also had more stable weight over the 10-year follow-up period. Drinkers less likely to have major weight gain or loss (gaining or losing >10kg) than were non-drinkers. Compared with non-drinkers, those who consumed one to 6.9 drinks per week, women had an OR = 0.7 for major weight gain and an OR=0.7 for major weight loss, while men had an OR=1.0 for major weight gain and an OR=0.7 for major weight loss. For those who consumed >two drinks per day, women had an OR=0.5 for major weight gain and an OR=0.8 for major weight loss, while men had an OR=0.9 (for major weight gain) and an OR=1.0 for major weight loss. Results suggest that alcohol intake is not a risk factor for obesity. Drinkers less likely to have either major weight gain or weight loss than non-drinkers.

Sammel MD, Grisso JA et al, 2003 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=336 African American and Caucasian American women who participated in the Penn Study of Ovarian Aging over a four-year period. Location: United States.	Alcohol consumption among subjects did not affect risk of substantial weight gain. Subjects who gained ≥10 lbs drank an average of 7.3 drinks per week SD±15.2. Those who did not gain ≥10 lbs drank an average of 8.5 drinks per week SD±19.0. P=0.784.
Sherwood NE, Jeffery RW et al, 2000 Study Design: Prospective study Class: B Rating: Positive Quality	N=826 women and 218 men taking part in a weight gain prevention project over a three-year period. Location: United States.	No statistically significant findings between alcohol consumption and weight gain. Multivariate associations between weight and exercise and dietary intake patterns over three years in men (m) and women (w): Energy from alcohol (%): Coefficient 0.088 (m), 0.011 (w); standard error 0.056 (m), 0.034 (w); P value 0.116 (m), 0.734 (w). Mean (standard error) Δ in dietary intake and physical activity between baseline and year three by weight gain status in men (m) and women (w): Energy from alcohol (%): By weight losers +0.1 (0.8) (m), +0.1 (0.3) (w) By weight maintainers +1.4 (0.5) (m), +0.1 (0.2) (w) By weight gainers +0.5 (0.4) (m), +0.4 (0.2) (w). P-value for men was 0.218 and 0.367 for women.

Tolstrup et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N=43,543 male and female participants from the Diet, Cancer and Health Study. Baseline alcohol intake related to five-year waist Δ. Location: Denmark.	Results do not imply that regular alcohol intake is involved in development of abdominal obesity. Observed that drinking frequency was inversely associated with waist gain, suggesting that the most frequent drinkers had lowest odds for a positive change in WC during the follow-up period of ~five years. Finding independent of smoking status, absolute value of WC at baseline, preferred beverage type and amount of alcohol intake. Drinking frequency inversely associated with Δ in WC in women (P for linear trend <0.0001) and was unassociated with Δ in WC in men (P for linear trend = 0.15). Drinking frequency unassociated with major waist loss, but was inversely associated with major waist gain: OR among men were (drinking days per week) compared with men who drank alcohol 0.97 (95% CI: 0.73 to 1.28) never drinking 0.95 (95% CI: 0.81 to 1.12) one day 0.88 (95% CI: 0.77 to 0.99) two to four days 0.82 (95% CI: 0.71 to -0.95) five to six days 0.79 (95% CI: 0.69 to 0.9) seven days. Results for women were similar (P<0.0001).

Wannamethee and Shaper 2003 Study Design: Prospective Cohort Study Class: B Rating: Neutral Quality	N-6,832 middle-aged male participants of the British Regional Heart Study. Five-year follow-up. Location: United Kingdom.	After adjustment for potential confounding variables, mean BMI and prevalence of men with BMI >28kg/m^2 ↑ significantly from light-moderate to very heavy alcohol intake group. Similar patterns seen for all types and combinations of alcohol. After five years, stable and new heavy drinkers (>30g per day of alcohol consumption) showed greatest weight gain and had highest prevalence rates of ↑ BMI.
Wannamethee et al 2004 Study Design: Prospective cohort study Class: B Rating: Positive Quality	N=49,324 female RNs from the Nurses' Health Study II who reported weight in 1991 and 1999. No history of CVD, cancer, diabetes or recent pregnancy. Mean age: ~38 years. Eight-year follow-up. Location: United States.	A non-linear relationship seen between alcohol and weight gain of >5kg in all women. Compared with non-drinkers, adjusted relative odds of weight gain according to g per day consumption were: 0.94 (95% CI: 0.89, 0.99) for 0.1 to 4.9g 0.92 (95% CI: 0.85, 0.99) for five to 14.9g 0.86 (95% CI: 0.76, 0.78) for 15 to 29.9g 1.07 (95% CI: 0.89, 1.28) for ≥30g (P< 0.0001). ↑ odds of weight gain associated with heavy drinking (≥30g per day) most marked in women <35 years of age (OR=1.64; 95% CI: 1.03, 2.61). However, in African-American women, light drinking associated with ↑ odds of weight gain (OR=2.43, 95% CI: 1.22, 4.82).

Research recommendations

1. Conduct a comprehensive set of studies in a controlled setting to assess the influences that alcohol may have on factors that affect energy intake and expenditure.
    - Rationale: The effects of energy from alcohol on body weight are complex and not completely understood. These studies will clarify whether the lack of association between moderate alcohol consumption and weight gain is due

to biological compensation or changes in other behaviors (e.g., diet or physical activity).

Search plan and results

Inclusion criteria

- November 1, 1994 to May 11, 2009
- Human subjects
- English language
- International
- Sample size: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- Dropout rate: Less than 20%; preference for smaller dropout rates
- Ages: Adults of legal drinking age (21 years and older)
- Populations: Healthy, those with elevated chronic disease risk, those diagnosed with the highly prevalent chronic diseases (CHD/CVD, hypertension, type 2 diabetes, osteoporosis, osteopenia and obesity) and those with breast cancer, colon cancer or prostate cancer.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (exceptions noted)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)
- Cross-sectional study design.

Search terms and electronic databases used

- PubMed

  ("Ethanol"[Mesh] OR “Alcohol Drinking”[mesh] OR "Alcoholic Beverages"[Mesh]) AND ("Body Mass Index"[Mesh] OR "Waist-Hip Ratio"[Mesh] OR "Body Fat Distribution"[Mesh] OR Obesity[mesh] OR overweight[mesh] OR "Weight Gain"[Mesh] OR lipogenesis[mesh]) AND "english and humans"[Filter] AND "Cohort Studies"[Mesh]

Date searched: 05/11/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 518
- Total articles identified to review from electronic databases: 54
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 8
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 8

- Number of Articles Reviewed but Excluded: 46

Included articles (References)

1. Flechtner-Mors M, Biesalski HK, Jenkinson CP, Adler G, Ditschuneit HH. Effects of moderate consumption of white wine on weight loss in overweight and obese subjects. Int J Obes Relat Metab Disord. 2004 Nov; 28(11): 1, 420-1, 426. PMID: 15356671.
2. Koh-Banerjee P, Chu NF, Spiegelman D, Rosner B, Colditz G, Willett W, Rimm E. Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with a nine-year gain in waist circumference among 16, 587 US men. Am J Clin Nutr. 2003 Oct; 78(4): 719-727. PMID:14522729.
3. Liu S, Serdula MK, Williamson DF, Mokdad AH, Byers T. A prospective study of alcohol intake and change in body weight among US adults. Am J Epidemiol. 1994 Nov 15; 140(10): 912-920. PMID: 7977278.
4. Sammel MD, Grisso JA, Freeman EW, Hollander L, Liu L, Liu S, Nelson DB, Battistini M. Weight gain among women in the late reproductive years. Fam Pract. 2003 Aug; 20(4): 401-409. PMID: 12876110.
5. Sherwood NE, Jeffery RW, French SA, Hannan PJ, Murray DM. Predictors of weight gain in the Pound of Prevention study. Int J Obes Relat Metab Disord. 2000 Apr; 24(4): 395-403. PMID: 10805494.
6. Tolstrup JS, Halkjaer J, Heitmann BL, Tjønneland AM, Overvad K, Sørensen TI, Grønbaek MN. Alcohol drinking frequency in relation to subsequent changes in waist circumference. Am J Clin Nutr. 2008 Apr; 87(4): 957-963. PMID: 18400719.
7. Wannamethee SG, Field AE, Colditz GA, Rimm EB. Alcohol intake and eight-year weight gain in women: A prospective study. Obes Res. 2004 Sep; 12(9): 1, 386-1, 396. PMID: 15483203.
8. Wannamethee SG, Shaper AG. Alcohol, body weight, and weight gain in middle-aged men. Am J Clin Nutr. 2003 May; 77(5): 1, 312-1, 317. PMID: 12716687.

Excluded articles

Article	Reason for Exclusion
Alatalo PI, Koivisto HM, Hietala JP, Puukka KS, Bloigu R, Niemelä OJ. Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 097-1, 103. PMID: 18842799.	Study focused on effect of alcohol on liver enzymes; does not address the question.

Arif AA, Rohrer JE. Patterns of alcohol drinking and its association with obesity: Data from the Third National Healthand Nutrition Examination Survey, 1988-1994. *BMC Public Health.* 2005 Dec 5; 5: 126. PMID: 16329757; PMCID: PMC1318457.	Cross-sectional study.
Barry D, Petry NM. Associations between body mass index and substance use disorders differ by gender: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addict Behav.* 2009 Jan; 34(1): 51-60. Epub 2008 Aug 27. PMID: 18819756; PMCID: PMC2645714.	Study focused on substance use disorders by gender and body mass index; does not answer the question.
Berkey CS, Rockett HR, Colditz GA. Weight gain in older adolescent females: The Internet, sleep, coffee, and alcohol. *J Pediatr.* 2008 Nov; 153(5): 9, 635e-9, 639.e1. Epub 2008 Jul 9. PMID: 18614178; PMCID: PMC2631208.	Population studied age 14 to 21 years.
Beulens JW, de Zoete EC, Kok FJ, Schaafsma G, Hendriks HF. Effect of moderate alcohol consumption on adipokines and insulin sensitivity in lean and overweight men: A diet intervention study. *Eur J Clin Nutr.* 2008 Sep; 62(9): 1, 098-1, 105. Epub 2007 Jun 6. PMID: 17554246.	One sample group had less than 10 subjects; does not answer the question.
Beulens JW, van Beers RM, Stolk RP, Schaafsma G, Hendriks HF. The effect of moderate alcohol consumption on fat distribution and adipocytokines. *Obesity (Silver Spring).* 2006 Jan; 14(1): 60-66. PMID: 16493123.	Study focused on effect of alcohol on fat distribution; does not answer the question.
Bobak M, Skodova Z, Marmot M. Beer and obesity: a cross-sectional study. *Eur J Clin Nutr.* 2003 Oct; 57(10): 1, 250-1, 253. PMID: 14506485.	Cross-sectional study.
Breslow RA, Smothers BA. Drinking patterns and body mass index in never smokers: National Health Interview Survey, 1997-2001. *Am J Epidemiol.* 2005 Feb 15; 161(4): 368-376. PMID: 15692081.	Cross-sectional data.
Carels RA, Young KM, Coit C, Clayton AM, Spencer A, Wagner M. Skipping meals and alcohol consumption. The regulation of energy intake and expenditure among weight loss participants. *Appetite.* 2008 Nov; 51(3): 538-545. Epub 2008 Apr 15. PMID: 18511146.	Study focused on meal skipping; does not answer the question.

Chaix B, Chauvin P. Tobacco and alcohol consumption, sedentary lifestyle and overweightness in France: A multilevel analysis of individual and area-level determinants. *Eur J Epidemiol.* 2003; 18(6): 531-538. PMID: 12908718.	Study focused on tobacco consumption; does not answer the question.
Chyou PH, Burchfiel CM, Yano K, Sharp DS, Rodriguez BL, Curb JD, Nomura AM. Obesity, alcohol consumption, smoking, and mortality. *Ann Epidemiol.* 1997 May; 7(4): 311-317. PMID: 9177115.	Study outcome related to mortality; does not address the question.
Croezen S, Visscher TL, Ter Bogt NC, Veling ML, Haveman-Nies A. Skipping breakfast, alcohol consumption and physical inactivity as risk factors for overweight and obesity in adolescents: Results of the E-MOVO project. *Eur J Clin Nutr.* 2009 Mar; 63(3): 405-412. Epub 2007 Nov 28. PMID: 18043703.	Population studied age 13 to 16 years.
Dall TM, Zhang Y, Chen YJ, Wagner RC, Hogan PF, Fagan NK, Olaiya ST, Tornberg DN. Cost associated with being overweight and with obesity, high alcohol consumption, and tobacco use within the military health system's TRICARE prime-enrolled population. *Am J Health Promot.* 2007 Nov-Dec; 22(2): 120-139. PMID: 18019889.	Study addressed cost; does not answer the question.
Dixon JB, Dixon ME, O'Brien PE. Alcohol consumption in the severely obese: Relationship with the metabolic syndrome. *Obes Res.* 2002 Apr; 10(4): 245-252. PMID: 11943832.	Cross-sectional study.
Dorn JM, Hovey K, Muti P, Freudenheim JL, Russell M, Nochajski TH, Trevisan M. Alcohol drinking patterns differentially affect central adiposity as measured by abdominal height in women and men. *J Nutr.* 2003 Aug; 133(8): 2, 655-2, 662. PMID: 12888654.	Study focused on coronary heart disease; does not answer the question.
Duncan AE, Grant JD, Bucholz KK, Madden PA, Heath AC. Relationship between body mass index, alcohol use, and alcohol misuse in a young adult female twin sample. *J Stud Alcohol Drugs.* 2009 May; 70(3): 458-466. PMID: 19371498; PMCID: PMC2670751.	Study focused on alcohol misuse; does not answer the question.

Fueki Y, Miida T, Wardaningsih E, Ito M, Nakamura A, Takahashi A, Hanyu O, Tsuda A, Saito H, Hama H, Okada M. Regular alcohol consumption improves insulin resistance in healthy Japanese men independent of obesity. *Clin Chim Acta.* 2007 Jul; 382(1-2): 71-76. Epub 2007 Apr 13. PMID: 17482151.	Study focused on insulin resistance; does not answer the question.
Greenfield JR, Samaras K, Jenkins AB, Kelly PJ, Spector TD, Campbell LV. Moderate alcohol consumption, dietary fat composition, and abdominal obesity in women: Evidence for gene-environment interaction. *J Clin Endocrinol Metab.* 2003 Nov; 88(11): 5, 381-5, 386. PMID: 14602777.	Study focused on gene-environment interaction; does not answer the question.
Gutiérrez-Fisac JL, Rodríguez-Artalejo F, Rodríguez-Blas C, del Rey-Calero J. Alcohol consumption and obesity in the adult population of Spain. J Epidemiol Community Health. 1995 Feb; 49(1): 108-109. PMID: 7706996; PMCID: PMC1060086.	Cross-sectional study.
Haenle MM, Brockmann SO, Kron M, Bertling U, Mason RA, Steinbach G, Boehm BO, Koenig W, Kern P, Piechotowski I, Kratzer W; EMIL-Study group. Overweight, physical activity, tobacco and alcohol consumption in a cross-sectional random sample of German adults. *BMC Public Health.* 2006 Sep 18; 6: 233. PMID:16981990; PMCID: PMC1586017.	Cross-sectional study.
Hill SY, Shen S, Locke Wellman J, Rickin E, Lowers L. Offspring from families at high risk for alcohol dependence: increased body mass index in association with prenatal exposure to cigarettes but not alcohol. *Psychiatry Res.* 2005 Jun 30; 135(3): 203-216. PMID: 16000226.	Study focused on offspring from high risk families; does not answer the question.
Hong J, Smith RR, Harvey AE, Núñez NP. Alcohol consumption promotes insulin sensitivity without affecting body fat levels. *Int J Obes (Lond).* 2009 Feb; 33(2): 197-203. Epub 2009 Jan 6. PMID: 19125162.	Study focused on insulin sensitivity; does not answer the question.
Kageyama T, Nishikido N, Honda Y, Kurokawa Y, Imai H, Kobayashi T, Kaneko T, Kabuto M. Effects of obesity, current smoking status, and alcohol consumption on heart rate variability in male white-collar workers. *Int Arch Occup Environ Health.* 1997; 69(6): 447-454. PMID: 9215932.	Study focused on heart rate variability; does not answer the question.

Katsika D, Tuvblad C, Einarsson C, Lichtenstein P, Marschall HU. Body mass index, alcohol, tobacco and symptomatic gallstone disease: A Swedish twin study. *J Intern Med.* 2007 Nov; 262(5): 581-587. Epub 2007 Oct 1. PMID: 17908165.	Study focused on gallstone disease; does not answer the question.
Kleiner KD, Gold MS, Frost-Pineda K, Lenz-Brunsman B, Perri MG, Jacobs WS. Body mass index and alcohol use. *J Addict Dis.* 2004; 23(3): 105-118. PMID: 15256347.	Cross-sectional study.
Lee DH, Ha MH, Christiani DC. Body weight, alcohol consumption and liver enzyme activity: A four-year follow-up study. *Int J Epidemiol.* 2001 Aug; 30(4): 766-770. PMID: 11511600.	Study focused on liver enzyme activity; does not answer the question.
Li Y, Wang JG, Gao PJ, Wang GL, Qian YS, Zhu DL, Staessen JA. Interaction between body mass index and alcohol intake in relation to blood pressure in HAN and SHE Chinese. *Am J Hypertens.* 2006 May; 19(5): 448-453. PMID: 16647612.	Study focused on blood pressure; does not answer the question.
Lukasiewicz E, Mennen LI, Bertrais S, Arnault N, Preziosi P, Galan P, Hercberg S. Alcohol intake in relation to body mass index and waist-to-hip ratio: the importance of type of alcoholic beverage. *Public Health Nutr.* 2005 May; 8(3): 315-320. PMID: 15918929.	Cross-sectional study.
Männistö S, Uusitalo K, Roos E, Fogelholm M, Pietinen P. Alcohol beverage drinking, diet and body mass index in a cross-sectional survey. *Eur J Clin Nutr.* 1997 May; 51(5): 326-332. PMID: 9152684.	Cross-sectional study.
Männistö S, Pietinen P, Haukka J, Ovaskainen ML, Albanes D, Virtamo J. Reported alcohol intake, diet and body mass index in male smokers. *Eur J Clin Nutr.* 1996 Apr; 50(4): 239-245. PMID: 8730611.	Cross-sectional study.
Oh HS, Seo WS. The compound relationship of smoking and alcohol consumption with obesity. *Yonsei Med J.* 2001 Oct; 42(5): 480-487. PMID: 11675675.	Cross-sectional data.
Powers JR, Young AF. Longitudinal analysis of alcohol consumption and health of middle-aged women in Australia. *Addiction.* 2008 Mar; 103(3): 424-432. PMID: 18269363.	Study focused on self-rated health; does not answer the question.

Risérus U, Ingelsson E. Alcohol intake, insulin resistance, and abdominal obesity in elderly men. *Obesity (Silver Spring).* 2007 Jul;15(7):1766-73. PubMed PMID: 17636095.	Study focused on insulin resistance; does not answer the question
Rosenberg M, Knaan T, Cohen D. Association among bad breath, body mass index, and alcohol intake. *J Dent Res.* 2007 Oct; 86(10): 997-1, 000. PMID: 17890678.	Study focused on effect of bad breath on body mass index and alcohol intake; does not answer the question.
Sakurai Y, Umeda T, Shinchi K, Honjo S, Wakabayashi K, Todoroki I, Nishikawa H, Ogawa S, Katsurada M. Relation of total and beverage-specific alcohol intake to body mass index and waist-to-hip ratio: A study of self-defense officials in Japan. *Eur J Epidemiol.* 1997 Dec; 13(8): 893-898. PMID: 9476818.	Cross-sectional study.
Sasaki A, Kurisu A, Ohno M, Ikeda Y. Overweight/obesity, smoking, and heavy alcohol consumption are important determinants of plasma PAI-1 levels in healthy men. *Am J Med Sci.* 2001 Jul; 322(1): 19-23. PMID: 11465242.	Study focused on plasma PAI-1 levels; does not answer the question.
Sasaki A, Kurisu A, Ohno M, Ikeda Y. Overweight/obesity, smoking, and heavy alcohol consumption are important determinants of plasma PAI-1 levels in healthy men. *Am J Med Sci.* 2001 Jul; 322(1): 19-23. PMID: 11465242.	Cross-sectional study.
Schröder H, Morales-Molina JA, Bermejo S, Barral D, Mándoli ES, Grau M, Guxens M, de Jaime Gil E, Alvarez MD, Marrugat J. Relationship of abdominal obesity with alcohol consumption at population scale. *Eur J Nutr.* 2007 Oct; 46(7): 369-376. Epub 2007 Sep 20. PMID: 17885722.	Cross-sectional study.
Skrzypczak M, Szwed A, Pawlinska-Chmara R, Skrzypulec V. Body mass index, waist to hip ratio and waist/height in adult Polish women in relation to their education, place of residence, smoking and alcohol consumption. *Homo.* 2008; 59(4): 329-342. Epub 2008 Aug 3. PMID: 18675976.	Cross-sectional study.
Stamler J, Caggiula AW, Grandits GA. Relation of body mass and alcohol, nutrient, fiber, and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr.* 1997 Jan; 65(1 Suppl): 338S-365S. PMID: 8988947.	Study focused on blood pressure; does not answer the question.

Suter PM. Is alcohol consumption a risk factor for weight gain and obesity? *Crit Rev Clin Lab Sci.* 2005; 42(3): 197-227. Review. PMID: 16047538.	Narrative review.
Suter PM, Häsler E, Vetter W. Effects of alcohol on energy metabolism and body weight regulation: Is alcohol a risk factor for obesity? *Nutr Rev.* 1997 May; 55(5): 157-171. Review. PMID: 9212692.	Narrative review.
Tolstrup JS, Heitmann BL, Tjønneland AM, Overvad OK, Sørensen TI, GrønbaekMN. The relation between drinking pattern and body mass index and waist and hip circumference. *Int J Obes (Lond).* 2005 May; 29(5): 490-497. PMID: 15672114.	Cross-sectional study.
Tremblay A, Buemann B, Thériault G, Bouchard C. Body fatness in active individuals reporting low lipid and alcohol intake. *Eur J Clin Nutr.* 1995 Nov; 49(11): 824-831. PMID: 8557020.	Study focused on effect of low lipid and alcohol intake related to body fatness; does not answer the question.
Wannamethee SG, Shaper AG, Whincup PH. Alcohol and adiposity: Effects of quantity and type of drink and time relation with meals. *Int J Obes (Lond).* 2005 Dec; 29(12): 1, 436-1, 444. PMID: 16077718.	Cross-sectional study.
Watanabe M, Barzi F, Neal B, Ueshima H, Miyoshi Y, Okayama A, Choudhury SR. Alcohol consumption and the risk of diabetes by body mass index levels in a cohort of 5, 636 Japanese. *Diabetes Res Clin Pract.* 2002 Sep; 57(3): 191-197. PMID: 12126769.	Study focused on diabetes; does not answer the question.
Williams PT, Krauss RM. Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. *Arterioscler Thromb Vasc Biol.* 1997 Jun; 17(6): 1, 082-1, 090. PMID: 9194758.	Study does not answer the question.