

DRAFT

Effect of Alcohol Consumption and Drug Abuse on Diabetes Mellitus: A Systematic Review

Andrea A. Howard^{1,2,3}

Julia H. Arnsten^{1,3,4}

Marc N. Gourevitch^{1,3,4}

¹AIDS Research Program, Department of Epidemiology and Social Medicine,

²Division of Infectious Diseases, ³Department of Medicine, ⁴Division of

Substance Abuse, Department of Psychiatry and Behavioral Sciences,

Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New

York

ABSTRACT

Purpose: To conduct a systematic review assessing the impact of alcohol, heroin, and cocaine use on the incidence, management, and complications of diabetes mellitus in adults.

Data Sources: All relevant English-language studies in humans aged 19 or older identified in searches of the MEDLINE (1966 to July 2002) database, and reference lists of key articles.

Study Selection: All experimental, cohort and case-control studies that assessed the effect of alcohol, heroin, or cocaine use on pre-defined diabetes-related outcomes. Two independent assessors reviewed the 960 retrieved citations.

Data Extraction: Two reviewers extracted data independently. Reviewers evaluated study quality on the basis of established criteria.

Data Synthesis: 32 studies that met inclusion criteria were reviewed. Moderate alcohol consumption (1-3 drinks/day) was associated with a decreased risk of diabetes and diabetes-related coronary heart disease, and did not acutely affect glycemic control. Heavy alcohol consumption (≥ 4 drinks/day) was associated with an increased risk of diabetes.

Conclusions: Moderate alcohol consumption does not increase diabetes risk, and decreases the risk of heart disease in diabetics. Heavy alcohol consumption may represent a potentially modifiable risk factor for type 2 diabetes. Studies that assess the long-term effects of alcohol consumption on glycemic control and non-cardiac complications in diabetics are warranted. Further research is

needed to assess the effects of heroin and cocaine use on diabetes-related outcomes.

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases in the United States, affecting 7.8% of adults 20 years of age or older [1]. The acute, microvascular, and macrovascular complications of diabetes make it the sixth leading cause of death and a leading cause of blindness in the United States [2]. Successful long-term control of hyperglycemia decreases the risk for diabetic complications [3]. Although a family history of diabetes is an established risk factor for type 2 diabetes, lifestyle factors also play an important role in its etiology [4]. For example, diabetes incidence has been associated with physical inactivity and obesity, both of which can be modified to decrease the risk of diabetes [5].

Alcohol consumption and drug abuse are also prevalent in the United States, and may affect the incidence, management, and complications of diabetes through physiologic interactions, impact on medication adherence, and interaction with diabetic medications. 109 million Americans aged 12 or older are estimated to be current drinkers [6], and 15.8 million are estimated to have used an illicit drug other than marijuana in the past year [7]. Thus, practicing physicians are very likely to encounter patients who are both users of alcohol or illicit drugs, and have or are at risk for diabetes. Yet physicians are poorly informed about how their patients' alcohol or drug use can affect the risk for or management of their patients' diabetes. Although a considerable literature exists regarding the interaction of alcohol with diabetes, less has been written about the impact of heroin or cocaine use on diabetes, and neither literature has been

reviewed comprehensively for common themes. We therefore undertook a systematic review of the medical literature, with the goal of identifying findings that could be of practical use to the internist in the management of alcohol- or drug-using patients with or at risk for diabetes.

METHODS

Our review addressed the following questions: 1) What is the effect of alcohol consumption on diabetes incidence and glucose metabolism?; 2) Among diabetics, what is the effect of alcohol consumption on glycemic control?; 3) Among diabetics, what is the effect of alcohol consumption on self-care behaviors, including medication adherence, home glucose monitoring, diet and exercise?; 4) Among diabetics, what is the effect of alcohol consumption on medication-associated complications, including hypoglycemic agents and angiotensin-converting enzyme inhibitors?; and 5) Among diabetics, what is the effect of alcohol consumption on diabetic complications, including acute complications (e.g., diabetic ketoacidosis, hyperosmolar coma, infection, amputation), microvascular complications (e.g., retinopathy, peripheral neuropathy, nephropathy, erectile dysfunction), and macrovascular complications (e.g., cardiovascular disease, peripheral vascular disease, stroke)?. Our review also addressed the effects of heroin and cocaine abuse on the above outcomes.

Search strategies

The MEDLINE database (reports published from 1966 to July 2002) was searched using a comprehensive search strategy developed with a medical librarian. The search was limited to English-language studies in humans aged 19

or older. Separate searches were conducted for the Medical Subject Headings *diabetes mellitus*, *hypoglycemic agents*, and *receptors, angiotensin/antagonists & inhibitors*, combined with one of the following Medical Subject Headings: *ethanol, alcoholism, alcoholic beverages, alcohol-related disorders, alcohol drinking, cocaine, cocaine-related disorders, crack cocaine, heroin, or heroin dependence*. This strategy was supplemented by a manual search of the reference lists from retrieved articles and relevant reviews.

Study Collection

Two reviewers independently assessed each MEDLINE citation on the basis of explicit pre-defined inclusion and exclusion criteria. Investigators were not blinded to journal titles, author names, or institutional affiliations. To be included, a study needed to fulfill the following four criteria: 1) be either an experimental, cohort, or case-control study; 2) include subjects who were exposed to or were current users of alcohol, heroin, or cocaine; and 3) include subjects who were not exposed to or were not current users of alcohol, heroin, or cocaine. In addition, studies were required to include one of the following primary outcomes: For question #1: plasma glucose, hemoglobin A1c, serum insulin, impaired glucose tolerance or diabetes mellitus; for question #2: plasma glucose, hemoglobin A1c, serum insulin, or insulin resistance; for question #3: adherence to medications or diabetes self-care behaviors; for question #4: plasma drug levels or an adverse drug event involving a hypoglycemic agent or angiotensin converting enzyme inhibitor; and for question #5: a specific diabetic complication. Experimental studies in which alcohol, heroin, or cocaine was administered to

healthy normal volunteers were excluded. Citations were scored “include” if they met all inclusion criteria and “exclude” if they did not, if they met an exclusion criterion, or if insufficient information was available to fulfill all inclusion criteria. Cases of reviewer disagreement were resolved by discussion between the two reviewers.

Assessment of Study Quality

Two reviewers independently rated each study’s quality using criteria developed by the US Preventive Services Task Force to determine internal validity [8]. For cohort studies, these specifications include: consideration of and adjustment for potential confounders, maintenance of comparable groups, low and non-differential loss to follow-up rates, use of valid measurements, use of clearly-defined interventions, and consideration of important outcomes. For experimental trials, these specifications also include adequate randomization and intention-to-treat analysis. Based on these criteria, studies were assigned one of the following ratings: “good” (study meets all criteria well), “fair” (study does not meet at least one criterion but has no known important limitations that could invalidate its results), or “poor” (study has important limitations). Studies that were found to be “poor” were excluded from the analysis. Reviewer disagreements were resolved by consensus.

Data Extraction

From each included study, two investigators abstracted the study sample, alcohol dose (for experimental studies) or definition and method of determining alcohol or drug exposure, confounders controlled for, definition and method of

measuring outcome, number of events (for studies assessing the incidence of diabetic complications), study duration, measure of association, and associated *P* value.

RESULTS

Search Results

Our search strategy identified 956 potentially relevant abstracts. Of these, 68 citations appeared to meet inclusion criteria and were retrieved for full-text review. Four additional studies were identified from a manual search of the reference lists from retrieved articles. Of the 72 articles reviewed, 40 were excluded either because they did not meet inclusion criteria or they were found to be of “poor” quality using US Preventive Services Task Force criteria for internal validity. Table 1 summarizes the reasons for study exclusion. Thirty-two studies met inclusion criteria and contained primary data related to either 1) the effect of alcohol consumption on diabetes incidence or glucose metabolism [9-23]; 2) the effect of alcohol consumption on glycemic control in diabetics [24-29]; 3) the effect of alcohol consumption on hypoglycemic medication complications [30-32]; 4) the effect of alcohol consumption on risk of diabetic complications [33-38]; or 5) the effect of heroin abuse on glucose metabolism [39, 40].

Effect of Alcohol Consumption on Diabetes Incidence

Thirteen prospective cohort studies assessed the effect of alcohol consumption on diabetes incidence (Table 2), one of which was nested within a randomized clinical trial [17]. Six studies included only men [9, 15-17, 20, 21], one included only women [18], and one was limited to adults aged 65 years or

older [12]. Some studies specified exclusion criteria, such as hypertension [15], cardiovascular disease [16, 17], cancer [16, 17], or cirrhosis [15].

Ascertainment of exposure history varied among studies. Alcohol consumption was categorized in several ways, including grams per week or per day, drinks per week, ounces per day, ml per day, units per week, and times per week. To aid in comparing the results of these studies, we converted these measures of alcohol consumption to a single scale based on USDA definitions of a “standard drink” (one can/bottle/glass of beer = 12.8 g ethanol, one glass of wine = 11.0 g ethanol, and one glass of liquor = 14.0 g ethanol) [20].

The method by which incident diabetes was measured also varied among studies. Some studies performed oral glucose tolerance tests (OGTTs) [10, 11, 13, 15], or obtained fasting [10, 11, 13-16, 19] or random plasma glucose levels [19]. Others used self-report of a diabetes diagnosis [9, 17, 18, 20, 21], or new use of a hypoglycemic medication [12] as the only measure of diabetes incidence.

The most common confounders controlled for in these studies included age [9-21], body mass index (BMI) [10-15, 17, 19-21], smoking [9, 10, 14, 15, 17-21], family history of diabetes [10, 11, 14-16, 18-20], and physical activity [12, 13, 15, 17-21]. Six studies controlled for dietary factors [9, 13, 14, 18-20], one study controlled for race [21], and only one study controlled for waist-hip ratio [19].

All studies received a quality-score rating of fair. A limitation of many studies was that the outcome of interest, diabetes, was not measured using a standard screening test, e.g. a fasting plasma glucose level or an OGTT [9, 12,

17, 18, 20, 21]. Another common limitation was that the assessment of alcohol intake was performed at baseline only [9-11, 13, 15-17, 19, 21]. Many studies treated alcohol consumption as a dichotomous variable, and thus were unable to distinguish the risk of diabetes among moderate drinkers from that among heavy drinkers [9-11, 13, 14]. In addition some studies failed to control on potentially important confounders, including BMI, waist-hip ratio, family history of diabetes, and race.

Although all studies received a quality-score rating of fair, three studies were found to be methodologically superior to the others because they used both an objective measure of diabetes incidence and a precise, non-dichotomous measure of alcohol consumption [15, 16, 19]. Each of these studies, as well as one additional study [21], found a U-shaped relationship between alcohol consumption and diabetes incidence in men, where “moderate” drinkers had the lowest risk of diabetes and “heavier” drinkers had the highest risk. The quantity of alcohol that was associated with the lowest risk of diabetes ranged from approximately 1 drink per day [16] to between 2 and 4 drinks per day [21]. The greatest risk of diabetes was found in men who consumed more than 3 drinks per day in three studies [15, 16, 19], and more than 4 drinks per day in one study [21]. An additional study of adults aged 65 years or older found that the risk of diabetes was lowest in those who consumed approximately 1 drink per day, and higher in those who consumed greater than 1 drink per day [12].

Three studies found an inverse relationship between alcohol consumption and diabetes incidence [17, 18, 20]. In each of these studies, the prevalence of

heavy drinking was low, and thus there may not have been sufficient power to find a positive relationship between heavy alcohol use and diabetes incidence. The quantity of alcohol that was associated with the lowest risk of diabetes in these studies ranged from ≤ 1 drink per day in women [18] to about 3 drinks per day in men [20], making these studies consistent with those that found a U-shaped relationship between alcohol consumption and diabetes incidence.

In five studies, alcohol consumption was treated as a dichotomous variable. Two of these studies found no association between alcohol use and diabetes risk [9, 11]. One study reported an increased risk for diabetes with drinking alcohol more than 2-3 times per week [14]. Two additional studies found an increased risk for diabetes with alcohol consumption in men, but no association in women [10, 13].

Effect of Alcohol Consumption on Glucose Metabolism

Two prospective cohort studies assessed the effects of alcohol consumption on glucose metabolism in non-diabetics, both of which were rated fair. One study [23] assessed self-reported average daily alcohol consumption over a five-year period in a randomly selected sample of non-diabetics (N=771). Hemoglobin A1c and fasting and two-hour plasma glucose levels during an OGTT were measured at baseline and after five years of follow-up. The study found that the mean change in each index of glucose metabolism during the follow-up period did not vary significantly by daily alcohol consumption, after adjusting for sex, age, smoking, BMI, physical activity and social status.

The other study [22] assessed weekly alcohol consumption (number of drinks per week) at baseline and after 11 years of follow-up in a cohort of 425 Danish men who were not using hypoglycemic agents. Fasting serum insulin levels were also measured at baseline and after 11 years of follow-up. The study found that the change in alcohol consumption during the follow-up period was not associated with a change in fasting serum insulin level, after controlling for change in BMI, fasting glucose, tobacco use and physical activity.

Effect of Alcohol Consumption on Glycemic Control in Diabetics

Six randomized crossover studies assessed the effect of alcohol consumption on glycemic control in type 1 [24, 26] and/or type 2 [24-29] diabetics (Table 3). Most studies included both diet-controlled diabetics and those who required hypoglycemic medications.

The experimental conditions varied among studies. The dose of ethanol was approximately 1-2 drinks in some studies [24, 27-29], and 5-6 drinks in others [25, 26]. Four studies were conducted after a period of fasting [26-29]. Ethanol was ingested with food in three studies [25, 26, 28], without food in two studies [24, 27], and administered intravenously in one study [29]. In all studies the subjects served as their own controls, completing each arm of the study in random order. In one study, the design was double-blinded [29].

The method of outcome assessment also varied among studies. Plasma glucose was measured repeatedly for between 1 and 24 hours after the administration of ethanol, and expressed either as mean concentration or as area

under the curve (AUC). Serum insulin was assessed in a similar fashion in most studies [25-29]. The quality score for all studies was fair.

Two studies found a decrease in plasma glucose after alcohol consumption with [26] or without [24] a meal in type 2 diabetics; in one study [26], the decline was statistically (but not clinically) significant, and was preceded by an acute rise in insulin after alcohol ingestion. One study found a statistically significant decrease in plasma glucose after infusion of ethanol during a short-term fast in type 2 diabetics, but no effect on insulin levels [29]. Three studies found that ingestion of small to moderate amounts of alcohol with [25, 28] or without [27] food had no acute effect on glycemic control in type 2 diabetics, even if there was an accompanying increase in insulin levels [27, 28]. Of the two studies that included type 1 diabetics, one found a nonsignificant decrease in plasma glucose after alcohol consumption [24], and the other found that ethanol had no effect on postprandial glucose or insulin levels [26].

Effect of Alcohol Consumption on Adherence

No study meeting inclusion criteria assessed the effects of alcohol consumption on adherence to medications or self-care behaviors in diabetics.

Effect of Alcohol Consumption on Medication Complications

Three experimental studies assessed the effect of alcohol consumption on hypoglycemic medication-related complications. One study assessed the interaction of alcohol and a thiazolidinedione (troglitazone), and two assessed the interaction with sulfonylureas. No study meeting inclusion criteria assessed the interaction of alcohol and angiotensin converting enzyme inhibitors in

diabetics. The quality of one study was good [32], and of the other two was fair [30, 31].

In a double blind, placebo-controlled parallel-group study in 23 diet-controlled type 2 diabetics, subjects were randomized to receive a daily dose of 200 mg troglitazone or placebo for a 45-day treatment period [32]. On days 42 and 45, subjects undertook a single blind, crossover, placebo-controlled alcohol challenge test [0.6 g/kg ethanol (equivalent to 3 drinks) in orange juice or orange juice alone] with the evening meal. Plasma glucose was measured for 4 hours after the alcohol challenge test. There was no significant difference in the glycemic response to alcohol between the two treatment groups. In addition, no serious adverse events were noted during the study period.

In a randomized crossover study of 10 nondiabetic subjects, three studies were performed in random order on each subject, with subjects serving as their own controls [30]. After an overnight fast, subjects were given 2.5 mg glipizide, 2.5 mg glipizide and 0.4 g/kg ethanol (about 2 drinks) 30 minutes later, or placebo and 0.4 g/kg ethanol 30 minutes later. Plasma glucose was measured for 3 hours. Ethanol prolonged but did not augment the hypoglycemia induced by glipizide. In addition, the average glipizide concentration did not differ when ethanol was taken. In another cross-over trial, 0.5 g/kg ethanol in 40% solution (about 2.5 drinks) was administered to 5 groups of 10 type 2 diabetic subjects both before and after 10 days of treatment with one of the following sulfonylurea derivatives: tolbutamide, chlorpropamide, glibornuride, glibenclamide, or glipizide [31]. Plasma glucose levels were measured for six hours after alcohol ingestion,

and no significant difference was found in the glycemic response to ethanol in the presence of a sulfonylurea. In addition, chlorpropamide was found to significantly decrease the rate of elimination of ethanol from the blood.

Effect of Alcohol Consumption on Risk of Diabetic Complications

Coronary heart disease

Four prospective cohort studies assessed the effect of alcohol consumption on coronary heart disease (CHD) mortality in diabetics (Table 4), one of which was nested within a randomized clinical trial [34]. Three of the studies also assessed the effect of alcohol consumption on CHD incidence [34-36]. Two studies included only men [34, 36]; one included only women [35]; and three included only individuals in whom diabetes was diagnosed at age 30 or older (“older-onset” diabetics) [33, 35, 36].

Ascertainment of exposure history varied among studies. Alcohol consumption was expressed as grams of alcohol consumed per day (range: 0 to ≥ 5 g/day [35], or 0 to ≥ 14 g/day [33]); number of drinks consumed per day (range: 0 to >2 drinks/day) [36]; and frequency of consumption (range: rarely to daily) [34]. In classifying nondrinkers, only one study distinguished former drinkers from lifetime abstainers [33].

The method of outcome assessment also varied. CHD mortality was confirmed either by death certificates [33, 34], or medical records and autopsy reports [35, 36]. Incident CHD was defined either as cases of myocardial infarction (MI) only [35, 36], or also including cases of coronary artery bypass graft or percutaneous transluminal coronary angioplasty procedures [34].

The most common confounders controlled for in these studies were smoking [33-36], physical activity [34-36], body mass index (BMI) [34-36], high cholesterol [34-36], hypertension [34-36], family history of myocardial infarction [34-36], and age [33-35]. Only two studies controlled for aspirin use [34, 35].

The quality-score ratings varied among the studies; two received a rating of good, and two were fair. A limitation of many studies was that alcohol consumption was only assessed at baseline [33-35]. In some studies, the CHD outcome was inconsistently measured; although most cases were confirmed by medical records, some were ascertained through self-report and verification of hospitalization only [35, 36].

Each of the studies reported decreased CHD mortality risk associated with alcohol use; in three of the four studies, the results were statistically significant [33-35]. Of the three studies that assessed CHD incidence, each demonstrated an inverse association between alcohol consumption and CHD risk; in two of the studies, the results were statistically significant [35, 36].

Diabetic Retinopathy

Two prospective cohort studies assessed the effect of alcohol consumption on the risk of diabetic retinopathy (Table 4). One study was comprised of men recruited from a diabetic clinic [37], and the other included a population-based sample of both men and women with either younger- or older-onset diabetes [38]. Both assessed alcohol consumption at baseline only. One defined heavy drinking as consuming >10 pints of beer or the equivalent per week [37], and the other expressed the odds of retinopathy per ounce of alcohol

consumed per day [38]. The prevalence of heavy drinking also differed between the studies, and different methods of outcome assessment were employed (direct ophthalmoscopy [37] and stereoscopic fundus photography [38]).

One study (rated good) found no association between alcohol consumption and incidence or progression of diabetic retinopathy [38], while the other study (rated fair) found an increased risk for diabetic retinopathy with heavy alcohol use (≥ 10 pints of beer or the equivalent per week) [37].

Effect of Heroin Abuse on Glucose Metabolism

Two experimental studies assessed the effects of heroin use on glucose metabolism in non-diabetic subjects, both of which were rated fair. In one study, a 50 g OGTT was administered after an overnight fast to 12 chronically injecting heroin users and 12 healthy controls [39]. The mean time between the subjects' last heroin dose and the start of the test was 54.7 minutes (range 8-126). Blood glucose and plasma insulin were measured at five time points between 0 and 120 minutes after the glucose load. Although heroin users and controls had similar fasting blood glucose levels [mean (mg/dl) 79.9 ± 2.5 vs. 73.7 ± 1.9 , respectively], heroin users had a significantly smaller and delayed rise in blood glucose in response to the glucose load compared to controls. The heroin users also had a significantly higher mean fasting insulin level, with a delayed peak response to the glucose load, and significantly higher levels of insulin at 60, 90, and 120 minutes. Although the higher mean fasting insulin level among the heroin users suggests that they were insulin resistant, their diminished post-load glucose response is not consistent with this interpretation.

In the other study, a 100-g OGTT was performed in 15 chronic heroin users and 15 healthy controls [40]. The time between the subjects' last heroin dose and the start of test was at least 3 hours. Controls were matched with subjects on sex, age and weight. Blood glucose and plasma insulin were measured at 10 time points between 0 and 240 minutes after the glucose load. In contrast to the previous study, heroin users in this study had significantly higher fasting (mean (mg/dl) 82 ± 4 vs. 73 ± 3) and peak glucose levels in comparison to controls. Furthermore, plasma glucose levels did not return to baseline by 4 hours after glucose ingestion, indicating that the heroin users were glucose intolerant. Although both studies found that heroin users had significantly higher fasting insulin levels, this study found that they had lower insulin peaks as well, suggesting that heroin use may also be associated with impaired insulin secretion.

DISCUSSION

We performed a comprehensive systematic review of the literature to assess the impact of alcohol consumption and drug abuse on the risk for and complications and management of diabetes mellitus. Although the precise effect of alcohol use on diabetes risk has not been clearly established, the balance of evidence suggests that moderate alcohol consumption is associated with a decreased risk of diabetes, while heavy alcohol consumption is associated with an increased risk. Further, among diabetics, ingestion of moderate amounts of alcohol has no acute effect on glycemic control. The existing data also suggest that alcohol ingestion while using either a sulfonylurea or thiazolidinedione is

safe. Our analysis demonstrates that mild to moderate alcohol consumption in diabetics is associated with a decrease in cardiovascular events. However, the effect of alcohol use on other diabetic complications, including retinopathy, remains uncertain. The few studies that assessed the effect of heroin abuse on diabetes were inconclusive; higher quality studies of this topic are needed.

Although some of the results from studies of the effects of alcohol use on diabetes incidence were conflicting, the balance of evidence suggests that there is a U-shaped relationship between alcohol consumption and diabetes risk. Compared to nondrinkers, “moderate” drinkers (those who consume between 1 and 3 drinks per day) have a lower risk of developing diabetes, while “heavy” drinkers (those who consume 4 or more drinks per day) have a greater risk. It has been proposed that the diabetogenic effect of alcohol is a result of an increase in obesity, and particularly of truncal adiposity, which is known to result in insulin resistance [41]. Although many of the reviewed studies controlled for body mass index, most did not control for anthropometric indices that are more closely correlated with intra-abdominal obesity, such as the waist-hip ratio. A plausible biological mechanism by which moderate alcohol consumption may reduce diabetes risk is less apparent. Alcohol consumption was not found to be associated with changes in fasting insulin levels, a marker of insulin resistance, on longitudinal analysis [22]. It is possible that moderate alcohol consumption is a marker for a healthy lifestyle that was not entirely accounted for by adjusting for physical activity and diet.

Our review suggests that consumption of a moderate amount of alcohol does not acutely impair glycemic control in diabetics. Although experimental conditions varied among studies, the data suggest that consuming 1-2 drinks on an empty stomach, or up to 5-6 drinks with food, is safe for both type 1 and type 2 diabetics. Furthermore, consumption of 2-3 drinks while taking either a sulfonylurea or thiazolidinedione appears to be safe. Of note, the consumption of alcohol after an overnight fast was found to prolong the effects of glipizide in non-diabetics [30], and the use of chlorpropamide was found to decrease ethanol elimination from the blood [31]. Data regarding the long-term effects of alcohol consumption on glycemic control are lacking, and further research on this topic is needed.

Our review demonstrates that among diabetics, mild to moderate alcohol consumption is associated with a decreased risk of coronary heart disease incidence and mortality. This finding is in concordance with the findings of epidemiological studies conducted in general populations, which have consistently demonstrated an inverse association between moderate alcohol consumption and coronary heart disease [42]. The protective effect of alcohol may be due to the increase in HDL cholesterol [43], the decrease in platelet aggregation [44], or the increase in fibrinolytic activity [45] associated with moderate alcohol consumption. These beneficial effects of alcohol use are particularly relevant in the diabetic population, where coronary risk factors such as dyslipidemia and a predilection to thrombosis are highly prevalent. Although these findings suggest that moderate alcohol consumption is safe and may be

beneficial with regard to cardiovascular risk in diabetics, the effect of alcohol use on the risk of other diabetic complications, including retinopathy, remains uncertain.

High quality studies that assess the impact of heroin and cocaine use on diabetes are lacking. Although the data reviewed suggest that heroin use may be associated with insulin resistance [39, 40], more definitive studies of the effect of heroin use on glucose metabolism are needed. There is also a dearth of information regarding the effects of both alcohol and drug use on diabetic self-care behaviors, including adherence to hypoglycemic medications, home glucose monitoring, diet, and exercise. It is likely that substance abuse has a negative impact on diabetic self-care behaviors, as active drug and alcohol abuse have been associated with medication nonadherence in other chronic disease states, such as HIV infection [46, 47]. Given the importance of adherence in reducing diabetes-associated morbidity and mortality, further research is needed to assess the impact of alcohol and illicit drug use on self-care behaviors in diabetics.

The epidemiological studies included in this review had several important limitations. The methods for diagnosing diabetes were inconsistent among studies, with most using self-report of diabetes diagnosis or hypoglycemic use rather than more objective measures, such as fasting plasma glucose levels or an OGTT. Even if self-report were reliable for detecting diagnosed cases in these study populations, misclassification of undiagnosed cases is still likely to have occurred, since as many as 44% of Americans with type 2 diabetes are undiagnosed [1]. If heavy drinkers were more likely to be screened for diabetes

with an objective test than more moderate drinkers or nondrinkers, differential misclassification may have contributed to the observed increase in diabetes risk associated with heavy drinking in some studies.

Methods of measuring alcohol consumption were also inconsistent among studies. Lack of a standardized measure of alcohol use complicates the interpretation of findings across studies, especially since some investigators used frequency of consumption rather than quantity consumed. In addition, many longitudinal studies only assessed alcohol consumption at baseline, while a minority of studies incorporated repeated measures of alcohol consumption into their analyses. Most studies combined lifetime abstainers and former drinkers into one “nondrinker” referent group, rather than analyzing their risk of diabetes separately. It has been argued that combining these two groups could introduce bias, because if many of the former drinkers stopped using alcohol because of health reasons, an artifactual protective effect of alcohol use would result. Finally, the distribution of alcohol consumption differed among the study samples. For example, several studies contained few heavy drinkers, and were thus underpowered to detect a relationship between heavy drinking and diabetes incidence.

In summary, moderate alcohol consumption by patients with or at risk for diabetes appears to be safe, and may even reduce the risk of diabetes and diabetes-associated coronary heart disease. Heavy alcohol consumption, in contrast, appears to be associated with an increased incidence of diabetes, and thus represents a potentially modifiable risk factor for type 2 diabetes. Studies

that assess the long-term effects of alcohol consumption on glycemic control and non-cardiac complications are needed before any recommendations to change drinking behavior can be made. While little is known about the effects of heroin or cocaine use on diabetes, data from other chronic illnesses suggest that illicit drug use may have an adverse impact on self-care behaviors. Given the high prevalence of diabetes, and of drug abuse in the United States, further research is urgently needed to determine the effects of substance abuse on diabetes-related outcomes.

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Table 1. Reasons for Study Exclusion

Reason for Exclusion	Studies, <i>n</i>
Citation did not include an abstract	270
No or poor measure of exposure to alcohol, heroin, or cocaine	230
Outcomes of interest were not evaluated	182
Inappropriate study population	83
Citation was a case study or case series	50
Inadequate adjustment for confounding	40
Study design was weak (e.g. cross-sectional, ecological, in vitro)	33
Citation was a review article	33
Study was reported subsequently in full form	4
Follow-up was inadequate	2
Statistical significance of findings not reported	1

Wannamethee, et al. (British Regional Heart Study), 2002 [21]	5221 men	16.8 years (mean)	Self-report of diabetes confirmed by medical record review	Baseline	None <1 unit/week 1-15 units/week 16-42 units/week >42 units/week (1 unit = 8-10 g ethanol)	Relative Risk 1.1 (0.61, 2.00) 1.0 0.81 (0.55, 1.20) 0.66 (0.44, 0.99) 0.96 (0.60, 1.52)	0.03 for quadratic trend	Age, BMI, prevalent CHD, physical activity, smoking, social class	Fair
Gurwitz et al. (East Boston Senior Health Project), 1994 [12]	2737 adults aged 65 or older	Two 3 year intervals	New use of hypoglycemic medication	Baseline and year 4	None 0-<0.5 oz/day 0.5-<1 oz/day ≥1 oz/day	Odds Ratio 1.2 (0.85, 1.8) 1.0 0.41 (0.17, 0.99) 0.98 (0.53, 1.50)		Age, sex, BMI, physical activity level, blood pressure, high blood sugar by self-report	Fair
Conigrave et al. (Health Professionals Follow-up Study), 2001 [20]	46,892 men	12 years (508,901 person-years)	Self-report of diabetes	Baseline and every two years	None 0.1-4.9 g/day 5.0-9.9 g/day 10-14.9 g/day 15-29.9 g/day 30-49.9 g/day ≥50 g/day	Relative Risk 1.00 1.05 (0.92, 1.20) 0.80 (0.68, 0.95) 0.71 (0.59, 0.86) 0.64 (0.53, 0.78) 0.57 (0.45, 0.71) 0.61 (0.43, 0.86)	<0.0001 for trend	Age, BMI, smoking, dietary glycemic load, fiber, physical activity, trans-fats and polyunsaturated fats (energy adjusted), profession, hypertension, hypercholesterolemia, CHD, cancer, family history of diabetes	Fair
Hu et al. (Nurses' Health Study), 2001 [18]	84,941 women	16 years (1,301,055 person-years)	Self-report of diabetes	Year 4, 8, 10, 14	0 g/day 0.1-5.0 g/day 5.1-10.0 g/day >10.0 g/day 0 g/day 0.1-5.0 g/day 5.1-10.0 g/day >10.0 g/day 0 g/day 0.1-5.0 g/day 5.1-10.0 g/day >10.0 g/day	Relative Risk BMI <25.0: 1.0 0.85 (0.65, 1.11) 0.64 (0.42, 0.98) 0.85 (0.63, 1.14) BMI 25.0-29.9: 1.0 0.70 (0.60, 0.82) 0.62 (0.48, 0.81) 0.57 (0.46, 0.71) BMI ≥30.0: 1.0 0.81 (0.72, 0.90) 0.60 (0.48, 0.76) 0.61 (0.50, 0.74)		Age, time, family history of diabetes, menopausal status, hormone replacement therapy, dietary score (intake of trans fat, fiber, glycemic load, polyunsaturated fat/saturated fat ratio), exercise, smoking	Fair

Ajani, et al. (Physicians' Health Study), 2000 [17]	20,951 men aged \geq 40y without cardiovascular disease, or cancer	12.1 years (mean)	Self-report of diabetes	Baseline	Rarely/never 1-3x/month 1x/week 2-4x/week 5-6x/week \geq 1/day	Relative Risk 1.00 0.89 (0.68, 1.18) 0.86 (0.67, 1.12) 0.70 (0.55, 0.90) 0.69 (0.52, 0.92) 0.54 (0.42, 0.70)	<.001 for linear trend	Age, smoking, BMI, physical activity	Fair
Sugimori et al., 1998 [14]	2573 Japanese adults	16 years	Fasting glucose \geq 110 mg/dl, OR initiated hypoglycemic medication	Entire observation period (16 years)	Never-sometimes 2-3 times/week-daily	Hazard Ratio 1.00 1.80 (1.34, 2.42)		Age, BMI, fasting blood glucose, smoking, eating breakfast, dairy intake, family history of diabetes, hypertension, hyperlipidemia, hyperuricemia	Fair
Holbrook et al. (Rancho Bernardo Study), 1990 [10]	604 adults	14 years	Fasting glucose \geq 140 mg/dl OR 2-hour glucose \geq 200 mg/dl during OGTT, OR self-report of physician-diagnosed diabetes	Baseline (average weekly consumption and 24-hour recall)	per 137.8 g/week per 24.5 g/24 hours	Relative Risk Men: 1.5 (1.01, 4.48) 1.5 (1.01, 4.4.8) Women: no association		Age, BMI, smoking, systolic blood pressure, family history of diabetes	Fair
Hodge et al., 1993 [11]	574 Nauruan adults	5 years	Fasting glucose \geq 140 mg/dl, OR 2-hour glucose \geq 200 mg/dl during OGTT, OR taking hypoglycemic medication	Baseline	Alcohol intake	Odds Ratio 0.649 (0.332, 1.309)		Age, family history of diabetes, BMI, sex, 2-hour glucose at baseline, 2-hour insulin at baseline	Fair
Monterrosa et al. (San Antonio Heart Study), 1995 [13]	844 Mexican American adults	8 years	Fasting glucose \geq 140 mg/dl OR 2-hour glucose \geq 200 mg/dl during OGTT, OR taking hypoglycemic medication	Baseline	10 g/week	Odds Ratio Men: 2.31 (1.03, 5.15) Women: no association	.041	Age, socioeconomic status, structural assimilation, dieting, physical activity, BMI	Fair

Feskens et al. (Zutphen Study), 1989 [9]	841 men	25 years	Self-report of diabetes verified by general practitioner	Baseline	>=10 g/day none	Hazard Ratio 1.1 (0.6, 2.3) 1.0		Age, heart rate, smoking, energy intake, subscapular skin fold	Fair
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^aOGTT = oral glucose tolerance test; BMI = body mass index; EKG = electrocardiogram; MI = myocardial infarction; CHD

= coronary heart disease

Table 3. Studies of the Effect of Alcohol Intake on Glycemic Control in Diabetics^a

Study, Year [Reference]	Study Sample	Study Arms	Outcomes Measured	Effect of Alcohol on Glucose	Effect of Alcohol on Insulin	Study Quality
Walsh et al., 1974 [24]	20 diabetics (3 diet-controlled, 10 on oral medication, 7 on insulin)	<ul style="list-style-type: none"> No drink 35 ml ethanol PO 	Glucose over 24 hours	Nonsignificant decrease at all time points	Not measured	Fair
Koivisto et al., 1993 [26]	10 type 1 diabetics 16 type 2 diabetics (2 diet-controlled, 14 on oral medication)	<ul style="list-style-type: none"> Dinner and water after overnight fast Dinner and 1g/kg ethanol PO after overnight fast 	Glucose and insulin over 14.5 hours	Type 1: no effect Type 2: decreased fasting level in morning (not clinically significant)	Type 1: no effect Type 2: Increased level 2-3 hours after ingestion	Fair
McMonagle et al., 1975 [25]	5 type 2 diabetics (1 diet-controlled, 4 on medication)	<ul style="list-style-type: none"> Meal and low-calorie beverage Meal followed by 15 ml ethanol PO every hour x 4 	Glucose and insulin over 1 hour after 4 th dose	None	None	Fair
Christiansen et al., 1993 [27]	10 type 2 diabetics (2 diet-controlled, 8 on medication)	<ul style="list-style-type: none"> 500 cc beer with 0% ethanol after fast 500 cc beer with 2.7% ethanol after fast 500 cc beer with 5.4% ethanol after fast 	Glucose AUC and Insulin AUC over 4 hours	None	Increased AUC with 5.4% ethanol	Fair
Christiansen et al., 1994 [28]	10 type 2 diabetics (3 diet-controlled, 7 on medication)	<ul style="list-style-type: none"> Light meal after fast Light meal and 24 g ethanol PO after fast 	Glucose AUC and Insulin AUC over 4 hours	None	Nonsignificant increase	Fair
Burge et al., 1999 [29]	10 elderly type 2 diabetics on 20 mg glyburide	<ul style="list-style-type: none"> Saline IV after fast 4.35 mmol/kg/h ethanol IV over 2 hours after fast 	Glucose and insulin over 10 hours after infusion	Lower nadir and greater absolute decline	No effect	Fair

^aPO = orally; AUC = area under the curve; IV = intravenously

Table 4. Studies of the Association between Alcohol Consumption and Risk of Diabetic Complications^a

Study, Year [Reference]	Study Sample	Follow- up time	Outcome Measure	Number of Events	Measurement of Alcohol Consumption	Alcohol Consumption	Relative Risk (95% Confidence Interval)	<i>P</i> value	Confounders Controlled for	Quality Rating
Ajani et al. (Physicians' Health Study), 2000 [34]	2790 male diabetics by self-report (enrollment cohort)	5.5 years (480,876 person- years)	Coronary Heart Disease Mortality, (confirmed by death certificates)	133	Baseline	Rarely Monthly Weekly Daily	1.00 1.11 (0.66, 1.89) 0.67 (0.42, 1.07) 0.42 (0.23, 0.77)	For trend .0019	Age, aspirin use, smoking, physical activity, BMI, history of angina, hypertension, high cholesterol	Good
	510 male diabetics by self-report (randomize d cohort)	12 years (1187 person- years)	Incident coronary heart disease (MI, CABG, or PTCA) (confirmed by medical records)	120	Baseline	Rarely Monthly Weekly Daily	1.00 0.84 (0.46, 1.54) 0.75 (0.45, 1.26) 0.66 (0.38, 1.16)	For trend .13	Age, randomized treatment assignment (aspirin, beta- carotene), smoking, physical activity, BMI, parental history of MI, angina, hypertension, high cholesterol	

Tanasescu et al. (Health Professionals' Follow-up Study), 2001 [36]	2419 male diabetics by self-report	11,411 person-years	MI by self-report (majority confirmed by medical records)	71	Baseline and 2 follow-up interviews	None 0-0.5 0.5-2.0 >2.0 drinks/day	1.00 0.78 (0.52, 1.15) 0.62 (0.38, 1.00) 0.48 (0.25, 0.94)	For trend .03	Physical activity, BMI, smoking, hypertension, high cholesterol, diabetes duration, family history of MI, vitamin E use, intake of fiber, folate, energy intake, percent calories from polyunsaturated fat and trans fat	Good
			Fatal coronary heart disease (confirmed by medical records or autopsy reports)	32		None 0-0.5 0.5-2.0 >2.0 drinks/day	1.00 0.79 (0.44, 1.41) 0.59 (0.29, 1.21) 0.45 (0.17, 1.14)	For trend .08		

Solomon et al. (Nurses' Health Study), 2000 [35]	5103 female diabetics by self-report	39,092 person- years	Self-reported MI (majority confirmed by medical records)	204	Baseline	None 0.1-4.9 g/day >=5 g/day	1.00 0.72 (0.54, 0.96) 0.45 (0.29, 0.68)	For trend .0003	Age, time, BMI, smoking, parental history of MI, hypertension, hypercholesterolemia, menopausal status/postmenopausal hormone use, aspirin use, vitamin E use, physical activity	Fair
			Fatal MI (confirmed by medical records or autopsy reports)	72		None 0.1-4.9 g/day >=5 g/day	1.00 0.60 (0.36, 1.01) 0.43 (0.21, 0.88)	For trend .03	Age, time, BMI, smoking, parental history of MI, hypertension, hypercholesterolemia, menopausal status/postmenopausal hormone use, aspirin use, vitamin E use, physical activity	

Valmadrid et al. (Wisconsin Epidemiologic Study of Diabetic Retinopathy), 1999 [33]	983 older-onset diabetics recruited from primary care	12.3 years (7004 person-years)	Coronary Heart Disease Mortality, (confirmed by death certificates)	198	Baseline	Never Former <2 g/day 2-13 g/day ≥14 g/day	1.00 0.69 (0.43, 1.12) 0.54 (0.33, 0.90) 0.44 (0.23, 0.84) 0.21 (0.09, 0.48)		Age, sex, smoking, insulin use, glycosylated hemoglobin level, C-peptide level, history of angina or MI, digoxin use, presence and severity of retinopathy	Fair
Moss et al. (Wisconsin Epidemiologic Study of Diabetic Retinopathy), 1994 [38]	436 younger-onset and 193 older-onset diabetics	6 years	Incident retinopathy assessed by stereoscopic fundus photography	32 (younger-onset) 98 (older-onset)	Baseline	Increase of 1 oz/day	Younger-onset: OR 2.09 (0.04, 1.07) Older-onset: OR 0.75 (0.40, 1.42)		Age, sex, glycemia	Good
	439 younger-onset diabetics and 478 older-onset diabetics		Progression of retinopathy assessed by stereoscopic fundus photography	246 (younger-onset) 227 (older-onset)			Younger onset: OR 1.25 (0.75, 2.08) Older onset: OR 0.73 (0.44, 1.20)			

Young et al., 1984 [37]	296 males from a diabetic clinic	4 years, 8 months (mean)	Incident retinopathy assessed by direct ophthalmoscopy		Baseline	None to moderate (≤ 10 pints of beer or equivalent/w week) Heavy (>10 pints of beer or equivalent per week)	1.00 2.25 (1.15, 4.42)		Duration of diabetes, glycemic control, impotence	Fair
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^aBMI = body mass index; MI = myocardial infarction; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; OR = odds ratio