

## Review

# Alcohol consumption and risk of type 2 diabetes mellitus in Japanese: a systematic review

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**Objective:** To evaluate the association between alcohol consumption and the risk for type 2 diabetes (DM) in Japanese. **Methods:** We searched the MEDLINE data base with the key words 'alcohol intake' (or 'alcohol consumption') and 'Japanese' cross-linked with 'diabetes mellitus' (or 'impaired glucose tolerance'). The reports we sought were restricted to prospective cohort studies, randomized controlled trials, meta-analyses and systematic reviews. Computerized and hand searches were conducted in June 2007. **Results:** Seven prospective cohort studies were adopted. We previously reported that in lean Japanese men (BMI  $\leq$ 22.0 kg/m<sup>2</sup>), moderate to heavy alcohol intake is a risk factor for diabetes. One study found heavy alcohol intake to be associated with an increased risk in low-BMI men while moderate alcohol intake was associated with a reduced risk in higher-BMI men. Another study suggested daily alcohol consumption to be a risk factor in low-BMI participants, while being protective in middle-BMI participants. Yet another study demonstrated a U-shaped association between alcohol consumption and the risk of diabetes in men. Three other studies, which did not divide the subjects in terms of BMI values, indicated alcohol intake to be an increased risk for diabetes, two being in men and one being in women, respectively. **Conclusion:** For a large number of Japanese men who have relatively low BMI, alcohol intake is an established risk factor for diabetes.

**Key Words:** diabetes mellitus, alcohol, Japanese, body mass index

## INTRODUCTION

In Japan, the number of patients strongly suspected of having diabetes is estimated to be 7,400,000, but when those who may possibly have the disease are included, this figure rises to as many as 16,200,000, according to the 2002 report by the Ministry of Health, Labour and Welfare.<sup>1</sup> The prevalence of diabetes mellitus both for men over age 50 and women over 60 well exceeds 10% and most have type 2 diabetes mellitus, which is associated with excessive energy intake, lack of physical activity and obesity. The incidence of type 2 diabetes mellitus is closely related to lifestyle factors such as diet, alcohol intake, physical activities and smoking. Researchers in the USA and Europe have been attempting to elucidate the negative effects versus benefits of alcohol consumption, and several epidemiological studies on alcohol consumption and the risk of type 2 diabetes mellitus have been published over the past two decades.<sup>2-13</sup> Most of those data suggested that light to moderate alcohol consumption is a protective factor against type 2 diabetes mellitus in westerners.<sup>6-13</sup> Contrary to those results, however, there are several papers, including ours,<sup>14</sup> reporting that alcohol intake may be a risk factor for type 2 diabetes mellitus, especially in low-BMI (BMI  $\leq$ 22.0 kg/m<sup>2</sup>) Japanese.<sup>14</sup> Since there is no general agreement on this subject in our country, we tried to perform a systematic review of alcohol consumption and the risk of developing type 2 diabetes mellitus in Japanese.

## METHODS

We searched the MEDLINE data base for prospective cohort studies, randomized controlled trials, meta-analyses and systematic reviews. The search strategy was as follows: Key words for the database search were 'alcohol intake' (or 'alcohol consumption') and 'Japanese' cross-linked with 'diabetes mellitus' (or 'impaired glucose tolerance'). Publications were restricted to prospective cohort studies, randomized controlled trials, meta-analyses and systematic reviews. The search period was June 2007. The language was limited to English and computerized searches were carried out independently on separate occasions by two reviewers (NS and MN). Only full original reports were adopted. A hand search was conducted to extract suitable publications. Relative risk was used as outcome measure.

## RESULTS

In total, seven studies were identified using MEDLINE.<sup>14-20</sup> All were prospective cohort studies. We found no randomized controlled trials, meta-analyses or systematic reviews.

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**Table 1.** Participants, study design and characteristics. All are prospective cohort studies.

ref. number	Source, Year	Targeted subjects	Participants			Observation period	Follow-up methods	No. of new cases of Diabetes, IFG or IGT
			No.	Age at baseline	Male (%)			
20	Sugimori H, et al. 1998 (Tokyo, Japan)	general population	2573	18-69	72%	16 years	annual assessments of fasting plasma glucose	296 (DM): 243 men & 53 women
15	Tsumura M, et al. 1999 (Osaka, Japan)	employees of a large gas company	6362	35-61	100%	62016 person-years	annual assessments of fasting plasma glucose	456 (type 2 DM)
16	Watanabe M, et al. 2002 (Japan)	employees of an insurance company	5636	44±7	72%	1991-1999 (mean 5.7 years), 29 240 person-years	annual assessments of fasting plasma glucose	17 (DM) and 247 (IFG)
17	Nakanishi N, et al. 2003 (Japan)	office workers at large building constructor	2953	35-59	100%	May 1994-May 2001. 17871 person-years	annual assessments of fasting plasma glucose	370 (type 2 DM or IFG)
18	Kiyohara Y, et al. 2003 (Hisayama, Japan)	general population	1075	40-74	38%	1988-1993, 1994	75g OGTT in 1993/1994	24 (DM) and 119 (IGT)
19	Sawada SS, et al. 2003 (Japan)	employees of a large gas company	4747	20-40	100%	1985-1999, 14 years	annual assessments of fasting plasma glucose	280 (type 2 DM)
14	Waki, et al. 2005 (JPHC cohort I, Japan)	general population	28893	40-59	45%	10 years	follow-up questionnaires 5 and 10 years after the survey began	1185 (DM): 703 men and 482 women

Table 1 shows the participants and study design characteristics of seven studies we identified.<sup>14-17</sup> Among them, we picked up four studies which divided the subjects in terms of BMI values to investigate the relationships between the incidence of diabetes and daily alcohol intake for low and higher BMI persons. The four studies all examined Japanese men (Fig. 1).

Tsumura et al.<sup>15</sup> reported the relationship between daily ethanol intake and the risk of type 2 diabetes mellitus among lean men (BMI  $\leq 22.0$  kg/m<sup>2</sup>) and men with higher BMI ( $\geq 22.0$  kg/m<sup>2</sup>). Lean men who consumed  $\geq 50.1$  ml of ethanol per day had a multiple adjusted relative risk of 2.48 (95% CI: 1.31-4.71) compared with non-drinkers as a reference. On the other hand, men with a higher BMI who consumed moderate amounts of ethanol (29.1-50.0 ml/day) had a multiple adjusted relative risk of 0.58 (95% CI: 0.39-0.87) as compared with non-drinkers. The authors concluded that for men with a relatively high BMI, moderate alcohol consumption (29.1-50.0 ml/day) was associated with a reduced risk of type 2 diabetes mellitus, while higher consumption ( $\geq 50.1$  ml/day) by lean men was a risk factor for type 2 diabetes.

Watanabe et al.<sup>16</sup> examined the association between alcohol consumption and the risk of diabetes in subjects with low-BMI ( $\leq 22.0$  kg/m<sup>2</sup>), middle-BMI (22.1-24.9 kg/m<sup>2</sup>), and high-BMI ( $\geq 25.0$  kg/m<sup>2</sup>). Alcohol intake was divided into 4 categories, non-drinkers, drinkers with alcohol intake  $\leq 21$  g,  $>21$  g but  $\leq 42$  g, and  $>42$  g of ethanol per day. The multiple adjusted relative risks for current alcohol consumption were 3.19 (95% CI: 1.09-9.37) in low-BMI participants, 0.41 (*ditto*: 0.23-0.73) in middle-BMI participants, and 0.74 (*ditto*: 0.44-1.25) in high-BMI participants, with non-drinkers as the reference. The authors concluded current alcohol consumption to be a risk factor for diabetes in low-BMI subjects (men and women), while be protective in middle-BMI subjects.

According to Nakanishi et al.,<sup>17</sup> alcohol consumption was divided into 5 categories, non-drinkers, and drinkers with alcohol intakes of 0.1-22.9 g, 23.0-45.9 g, 46.0-68.9 g, and  $\geq 69.0$  g of ethanol per day. The multiple adjusted relative risks for IFG or diabetes of daily ethanol consumption of non-drinkers, drinkers with alcohol intake of 0.1-22.9, 46.0-68.9, and  $\geq 69.0$  g were 1.51 (95% CI: 1.07-2.13), 1.31 (*ditto*: 0.93-1.84), 1.18 (*ditto*: 0.87-1.61) and 1.43 (*ditto*: 1.01-2.02), respectively, with a consumption of 23.0-45.9 g per day as the reference. These results showed a U-shaped association between alcohol intake and the risk of IFG or type 2 diabetes mellitus, indicating that moderate alcohol consumption (23.0-45.9 g of ethanol per day) may be a protective factor against type 2 diabetes.

Waki et al.,<sup>14</sup> divided alcohol consumption into 4 categories: non-drinkers, drinkers with daily ethanol intake: light ( $0 < \leq 23.0$  g/day), moderate (23.0  $< \leq 46.0$  g/day) and heavy ( $>46.0$  g/day). For men with a BMI  $\leq 22$  kg/m<sup>2</sup>, the multiple adjusted relative risks for moderate and heavy drinkers were 1.91 (95% CI: 1.05-3.46) and 2.89 (*ditto*: 1.63-5.11), respectively, with non-drinkers as the reference. The authors concluded moderate to heavy alcohol intake to be associated with a risk of developing diabetes in lean Japanese men.

Over all, the four studies except Nakanishi's report strongly suggest that alcohol intake to be a risk factor of diabetes in low-BMI men. On the other hand, there is a possibility that the relationship of higher BMI and moderate to heavy alcohol intake to be an inverse risk of diabetes except ours (Waki et al.).<sup>14</sup> (Fig. 1)

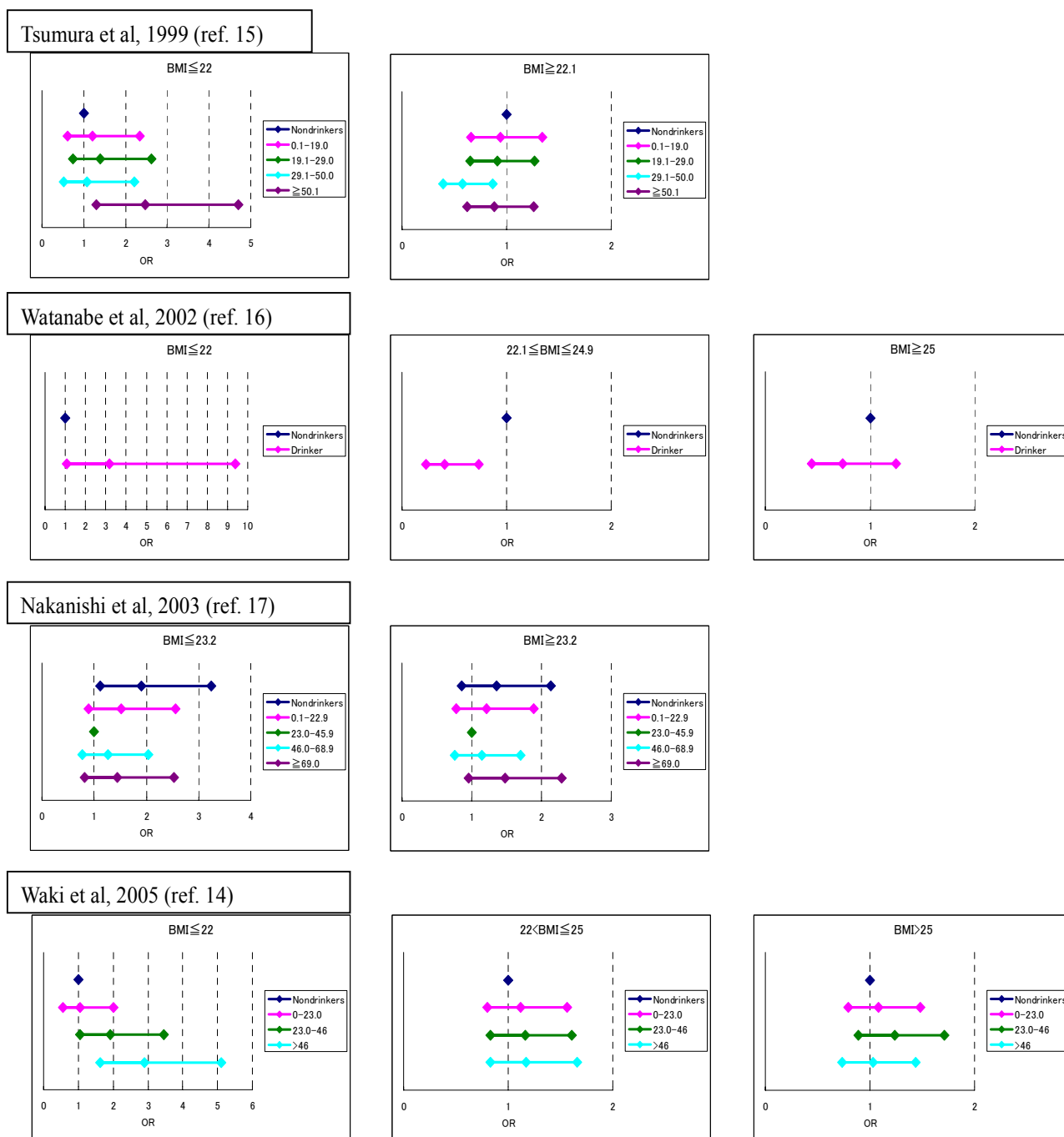
Three studies<sup>18-20</sup> which did not divide the subjects in terms of BMI values all concluded the same way that alcohol intake to be an increased risk for diabetes, two<sup>18,19</sup> being in men and one<sup>20</sup> being in women, respectively.

## DISCUSSION

Type 2 diabetes mellitus is closely related to life style factors, including diet, physical activities, alcohol and smoking, as well as obesity and a family history of diabetes. Number of epidemiological studies have examined the association between alcohol consumption and the development of diabetes mellitus. Among western epidemiological studies, some found no association.<sup>2-3</sup> Other reports suggested that heavy drinking was a risk factor for diabetes.<sup>4-5</sup> On the other hand, 5 studies found that light to moderate alcohol consumption was protective against diabetes incidence.<sup>6-10</sup> In addition, 2 studies indicated a U-shaped association between alcohol consumption and the risk for type 2 diabetes mellitus with the most reduced risk in light to moderate drinkers.<sup>11-12</sup> One study suggested that frequent consumption of alcohol had a consistently protective effect against type 2 diabetes, even when the level of consumption was relatively high.<sup>13</sup> In this study, however, the greatest risk reduction was seen in moderate drinkers, and the cohort included few heavy drinkers, possibly rendering the results for this category less reliable.

Goude et al.<sup>21</sup> suggested light to moderate alcohol consumption to be significantly associated with increased insulin-mediated glucose uptake, as confirmed for the first time by the clamp technique. No significant differences in alcohol intake between subjects with and without metabolic syndrome were observed in this study, which reflected homogeneity among the groups. This result is consistent with those of previous reports suggesting that low to moderate alcohol intake increases insulin sensitivity.<sup>22-25</sup> From these western epidemiological studies, we interpreted low to moderate alcohol consumption as presumably being associated with reduced risk of diabetes, due to enhanced insulin sensitivity. Furthermore, in most cases heavy alcohol consumption might actually be a risk factor for the development of diabetes.

Since Japanese are different from westerners in terms of genetic background, especially with regard to the mitochondrial aldehyde dehydrogenase 2 gene<sup>26,27</sup> that alters ethanol metabolism, physique, diet, physical activities, alcohol intake and smoking status, we suspected that the results obtained in American and European studies might not be relevant to ours. Fukushima et al.<sup>28</sup> studied insulin secretion and insulin sensitivity in Japanese subjects. They concluded that Japanese type 2 diabetic patients showed much larger decreases in insulin secretion, especially in the basal and early phases of insulin release, than in insulin sensitivity. Torrens et al.<sup>29</sup> conducted a population based cohort, to examine ethnic differences in insulin sensitivity and  $\beta$  cell function in 5 ethnically distinct



**Fig. 1** The relationship between the incidence of diabetes and daily alcohol intake (g/day) according to BMI values.

groups of women without diabetes. They reported that Japanese Americans, as compared with non-Hispanic whites, had decreased insulin sensitivity with lack of a compensatory increase in  $\beta$  cell function.<sup>29</sup> Decreased  $\beta$  cell function could be one of the major reasons that Orientals, including Japanese, are at higher risk of diabetes, even with relatively mild obesity, than westerners.<sup>30,31</sup> Hence, these results strongly suggest that Japanese differ genetically in terms of insulin sensitivity and  $\beta$  cell function from westerners, as well as ability to metabolize ethanol.<sup>26,27</sup>

The strengths and the limitations of each study need to be discussed. Firstly, regarding the study participants, those of Tsumura et al.,<sup>15</sup> Watanabe et al.,<sup>16</sup> Nakanishi et al.,<sup>17</sup> Kiyohara et al.,<sup>18</sup> Sawada et al.,<sup>19</sup> and Sugimori et

al.<sup>20</sup> may not be recognized as to be representative of the entire Japanese population, because some of them are work-site based cohort<sup>15-17,19</sup> and/or they are handling relatively small number of subjects.<sup>17,18,20</sup> In contrast, our previous investigation<sup>14</sup> were based on the subjects of the Japan Public Health Center-based prospective study cohort that consisted of a wide variety of Japanese general population with a relatively large number, which might be considered to be representative of Japanese population.

Secondly, on the contrary, our study (Waki et al.)<sup>14</sup> had some disadvantage regarding the diagnosis of diabetes because we gathered its information only by self-reports so that the incidence rate might be underestimated. In five out of the other 6 studies<sup>15-17,19,20</sup> fasting glucose values were employed for the diagnosis of type 2 diabetes

that strengthened, though not fully, the diagnosis. The other one study has had the most strength for the diagnosis, *i.e.*, Kiyohara et al.<sup>18</sup> performed 75g OGTT for all participants to this end. In addition, as for alcohol consumption, data were obtained from the self-reports in all the studies herein argued.

Thirdly, regarding the focus of this report, *i.e.*, the role of BMI as a modulator of the relation between alcohol consumption and incidence rate of type 2 diabetes, there is some difference among the studies being discussed here as follows. Four studies<sup>14-17</sup> divided the study subjects according to both BMI values and the amount of ethanol consumption. Out of these, all three studies<sup>14-16</sup> that classified the subjects to strict low BMI category (BMI  $\leq$ 22.0 kg/m<sup>2</sup>) drew the same conclusion that alcohol intake was associated with an elevated risk of type 2 diabetes among the population. One study<sup>17</sup> classified the subjects according to the median (23.2 kg/m<sup>2</sup>), namely "below median" and "at or above median".

After the previous publication<sup>14</sup> that was a large-scale cohort study containing nearly as many as 29,000 Japanese participants that should mostly warrant detecting power even in view of the self-report-based diagnosis, we further sought evidences regarding the relationship between alcohol consumption and incidence of type 2 diabetes systematically. We found two more studies<sup>19,20</sup>, of which the results were that alcohol intake was associated with an increased risk of diabetes as a whole although they did not divided the study participants by BMI, essentially being supportive of our previous result. We also reassured and illustrated that in strict low BMI Japanese populations, alcohol intake is associated with an elevated risk of type 2 diabetes<sup>14-16</sup> (Fig. 1).

In conclusion, for a large number of Japanese men who have relatively low BMI values<sup>32</sup>, alcohol intake is an established risk factor for developing diabetes. Since Japanese might have  $\beta$  cell dysfunctions such as being unable to compensate for diminished insulin sensitivity, we speculate that the increased insulin sensitivity produced by alcohol intake, which would have a positive effect on prevention of diabetes, might not overcome its adverse effects in Japanese. In practice, clinicians should encourage Japanese to decrease alcohol consumption, because 23 g of ethanol is equivalent to only 1 gou (gou: a traditional unit of Japanese sake that equals to 180 ml of volume) of Japanese sake, which is relatively small amount.

Finally, we must keep in mind that on some occasions it is advisable to make use of data from the same or similar populations, in this case to Japanese, instead of western data when discussing epidemiological issues relevant to a specific population, since there might be significant ethnic differences as discussed above.

#### AUTHOR DISCLOSURES

All the authors declare no financial supports nor relationships that may pose conflicts of interest.

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## Review

## Alcohol consumption and risk of type 2 diabetes mellitus in Japanese: a systematic review

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### 日本人酒精消耗量与 2 型糖尿病之风险关系：系统综述

**目的：**评价日本人群中酒精消耗量与 2 型糖尿病（DM）发病风险之间的关系。**方法：**我们利用关键词‘alcohol intake’（或者‘alcohol consumption’）和‘Japanese’交叉结合‘diabetes mellitus’（或者‘impaired glucose tolerance’）在 MEDLINE 数据库中进行了检索。我们查询的文献限于前瞻性群组研究、随机对照试验、荟萃分析以及系统综述。计算机检索与手工检索在 2007 年 6 月实施。**结果：**采用了 7 项前瞻性群组研究的结果。我们以前的报告曾指出在体瘦的日本男性人群（身体质量指数（BMI） $\leq 22.0$  kg/m<sup>2</sup>）中，中度至重度酒精摄入是糖尿病的一项危险因素。有一项研究发现在低 BMI 男性中，重度酒精摄入增加了糖尿病风险；而在高 BMI 男性中，中度酒精摄入却减少了糖尿病风险。另一篇报告提示日常的酒精消费量对于低 BMI 者是一项危险因素，但是对于中等 BMI 者却有保护作用。然而，另一个研究显示在日本男性中，酒精消费量与糖尿病风险呈 U-型关系。在另外 3 项未按照 BMI 值区分试验对象的研究中，都指出酒精摄取会增高糖尿病的发病风险，其中两项研究的对象为男性，另一项研究针对女性。**结论：**对于 BMI 较低的多数日本男性而言，酒精摄入是糖尿病的一项已确认的危险因子。

**关键字：**糖尿病、酒精、日本人、身体质量指数