Journal of Diabetes and Its Complications 29 (2015) 1009–1014

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Moderate consumption of white and fortified wine is associated with reduced odds of diabetic retinopathy

Eva K. Fenwick [a,*], Jing Xie [a], Ryan Eyn Kidd Man [c], Lyndell L. Lim [a], Victoria M. Flood [b], Robert P. Finger [a], Tien Y. Wong [c,d], Ecosse L. Lamoureux [c,d]

[a] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, University of Melbourne, Australia
[b] Faculty of Health Sciences, University of Sydney, Australia and St Vincent's Hospital, Sydney, Australia
[c] Singapore Eye Research Institute, National University of Singapore, Singapore
[d] Duke–National University of Singapore Graduate Medical School, Singapore

ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form 1 September 2015
Accepted 1 September 2015
Available online 4 September 2015

Keywords:
Diabetic retinopathy
Alcohol consumption
Association
White wine
Fortified wine

ABSTRACT

Aim: To explore the association between alcohol consumption and the severity of diabetic retinopathy (DR).
Methods: In this cross-sectional study, patients with type 2 diabetes answered questions on consumption of low and full-strength beer, white wine/champagne, red wine, fortified wines, and spirits. Never, moderate and high consumption of each alcoholic beverage, and overall alcoholic beverage consumption, were defined as <1, 1–14 and >14 standard drinks/week, respectively. DR was categorized into none; non vision-threatening DR (VTDR) and VTDR. Multivariable logistic regression determined the associations between alcohol consumption and DR.
Results: Of the 395 participants (mean age ± SD [standard deviation] 65.9 ± 10.4 years; males = 253), 188 (47.6%) consumed alcohol and 235 (59.5%) had any DR. Compared to no alcohol consumption, moderate alcohol consumption (overall) was significantly associated with reduced odds of any DR (OR = 0.47, 95% CI [confidence interval] 0.26–0.85). Moderate consumption of white wine/champagne or fortified wine was also associated with reduced odds of any DR (OR = 0.48, 95% CI 0.25–0.91, and OR = 0.15, 95% CI 0.04–0.62, respectively). Similar results were observed for non-VTDR and VTDR.
Conclusions: The amount and type of alcohol are associated with risk of DR in patients with type 2 diabetes. A longitudinal study is needed to assess the protective effect of alcohol consumption and DR.

1. Introduction

People with type 2 diabetes who consume moderate amounts of alcohol have up to 36% lower relative risk of fatal coronary heart disease than non-consumers (Howard, Arnsten, & Gourevitch, 2004; Koppes et al., 2006). However, it is less clear how alcohol consumption influences the risk of microvascular complications, such as diabetic retinopathy (DR), a serious complication of diabetes and a leading cause of blindness. There are several plausible mechanisms through which alcohol may have a protective effect for DR. For example, alcohol consumption increases high-density lipoprotein (HDL), and decreases fibrinogen levels and platelet aggregability, all of which have been reported to be inversely related to development and progression of DR (Wang, Wang, & Wong, 2008). Similarly, a recent meta-analysis has reported that moderate alcohol consumption may decrease fasting insulin and HbA1c concentrations among non-diabetic subjects (Schrieks et al., 2015).

Few studies have explored the association between alcohol consumption and DR, with inconsistent results (Wang et al., 2008). Two cross-sectional studies reported that moderate alcohol consumption (Beulens et al., 2008) and being a current or former alcohol drinker (Moss, Klein, & Klein, 1992) were protective for proliferative DR (PDR). In contrast, in a study over three decades ago, Young et al. (1984) reported that heavy alcohol consumption (defined as >10 pints of beer or equivalent per week) was associated with twice the risk of developing severe DR; however, confounding variables such as glycaemic control and blood pressure levels were not controlled for in the analysis. Other cross-sectional studies (Xu, You, & Jonas, 2009; Yang et al., 2013) and several longitudinal studies (Del Canizo Gomez et al., 2011; Lee et al., 2010; Moss, Klein, & Klein, 1994) have reported no association between any type of alcohol consumption and risk of development or progression of DR, although the study by Lee et al. (2010) found that moderate and heavy alcohol consumption increased the risk of visual acuity loss in DR patients.

The relationship between alcoholic beverage types and DR severity has also not been comprehensively explored. In those studies which have assessed the association between different alcoholic beverage types and DR (Beulens et al., 2008; Harjutsalo et al., 2014; Lee et al.,

Declaration of interests: There are no conflicts of interest to declare.

* Corresponding author. Tel.: +61 412 204 144 (mobile).
E-mail address: fenwicke@unimelb.edu.au (E.K. Fenwick).

http://dx.doi.org/10.1016/j.jdiacomp.2015.09.001
1056-8727/

2010), low and high strength beers, and red and white wine, were not analyzed separately. Given the well-known differential effects of red and white wine on cardiovascular health (Sparwel et al., 2009), it is likely that the association between red and white wine consumption and DR may also differ.

Therefore, in this study we explored the hypothesis that alcohol consumption is associated with reduced risk of DR in a well-defined sample of Australian adults with type 2 diabetes. We also explored the relationship between low and high strength beer, red wine, white wine/champagne, fortified wines (sherry or port), and spirits, and severity of DR.

2. Subjects, materials and methods

Participants were recruited from the Diabetes Management Project (DMP), a clinical study conducted in Melbourne, Australia (Lamoureux et al., 2012). In brief, English-speaking adults aged 18 years or older, with type 1 or type 2 diabetes, free of significant hearing and cognitive impairment and living independently met the DMP inclusion criterion. Eligible participants were screened using medical records and invited to participate in the study by trained interviewers during their routine clinical appointments at the Royal Victorian Eye and Ear Hospital (RVEEH). The 6-item cognitive impairment test (6-CIT) (Brooke & Bullock, 1999) was used to assess patients' cognitive capacity, and those who failed were excluded from the main data analysis.

In the current study, only patients with type 2 diabetes were included ($n = 510$). Thirteen and 102 participants were excluded from the analysis due to missing DR severity data or alcohol consumption data, respectively, resulting in a final sample size of 395. Comparison of baseline characteristics of those included and those excluded due to missing alcohol data revealed that those with alcohol data were more likely to speak English as a first language ($p < 0.001$). There were no other significant differences between the two groups.

All study procedures adhered to the tenets of the Declaration of Helsinki and all privacy requirements were met. Written informed consent was obtained from each participant prior to the study assessment. Ethical approval for the study was provided by the Royal Victorian Eye and Ear Hospital (RVEEH) Human Research and Ethics Committee (08/815H).

2.1. Testing protocol

All examinations were conducted at the Centre for Eye Research Australia (CERA) Melbourne, Australia. A trained interviewer administered a range of psycho-social and behavioral questionnaires and data on socio-demographic and health-related parameters, such as age, gender, medical history, height, weight, lifestyle factors and duration of diabetes were also collected.

2.2. Alcohol consumption

Alcohol intake was assessed using a self-administered, validated 145 item food frequency questionnaire (FFQ) (Smith et al., 1998). This questionnaire has been shown to be valid, reliable and reproducible, with a Spearman ranked correlation of 0.66 between the alcohol data and three, four-day weighed food records spaced evenly over one year in older Australian adults. Participants were asked how often in the past 12 months they had drunk beer (high and low strength), red wine, white wine/champagne, fortified wines (sherry or port), and spirits (e.g. whisky/gin) (Supplementary Table 1). Consumption was quantified according to the following categories: 1) never; 2) less than 1 per month; 3) 1–3 per month; 4) 1 per week; 5) 2–4 per week; 6) 5–6 per week; 7) 1 per day; 8) 2–3 per day; and 9) 4+ per day. To analyze our data, we first standardized the frequency categories to units consumed per week, and second we converted the data into standard drinks according to the definition of a 'standard drink' by the Australian Government Department of Health. For example, one bottle/can of high strength beer (i.e. 4.8% alc. vol) was converted to 1.4 standard drinks. For white wine/champagne and red wine, we made the assumption that people would drink a 150 ml average restaurant serving, so one red wine glass was converted to 1.5 standard drinks (Supplementary Table 1).

For data analysis, alcohol consumption was categorized as: (a) binary variables (abstainer vs. alcohol consumer), (b) overall alcohol consumption (number of standard drinks per week, any alcohol type), and (c) consumption of each of the six types of alcoholic beverages. Never, moderate and high consumption of each alcoholic beverage, as well as overall alcohol consumption, were defined as <1, 1–14 and >14 standard drinks/week, respectively. High consumption of beer (low and high strength), fortified wines, and spirits was not assessed due to lack of data in those categories. Participants were also asked as part of the FFQ if they had changed their eating habits in any way in the last 5 years (yes/no).

2.3. Fundus photography and DR assessment

Two-field (macula and optic disc) dilated fundus photos were captured using a non-mydriatic retinal camera (Cannon CR6-45NM), Cannon Inc, Japan and were graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol (Dirani et al., 2011) and the American Academy of Ophthalmology classification (American Academy of Ophthalmology, 2002) for the presence and severity of DR and DME, respectively: no DR = 13–15, mild NPDR (non-proliferative DR) = 20; moderate NPDR = 31–41; severe NPDR = 51; PDR = 60–80; and severe DME = 50. Similar to previous studies by our group (Fenwick et al., 2012a, 2012b), DR severity was categorized into none, non-vision threatening DR (non-VTDR–mild/moderate NPDR) and VTDR (severe NPDR, PDR and/or severe macular edema). Presence and severity of DR were the main outcome variables.

2.4. Blood collection and blood pressure (BP) measurements

A total fasting blood sample of 34.5 ml was collected to assess glycosylated hemoglobin (HbA_{1c}) levels, fasting glucose and lipids (total cholesterol [TC], triglyceride [TG], low-density lipoproteins [LDL] and high-density lipoproteins [HDL]). All biochemical parameters were analyzed at Melbourne Pathology, Melbourne, Australia.

A BP assessment was completed on each individual using an automated BP machine, model 5200-103Z (Welch Allyn, New Zealand). The average of two separate measurements was recorded for systolic (SBP) and diastolic (DBP). In cases where there was a difference of 10 mm Hg for SBP or 5 mm Hg for DBP or greater, a third measurement was taken. The closest two BP measurements were then averaged.

2.5. Anthropometric measurements, physical activity, and energy intake

All individuals had their height and weight measured using a wall-mounted adjustable measuring scale (Surgical and Medical products, China) and a calibrated digital scientific weight scale (Oregon Scientific, PRC), respectively. Individuals were instructed to remove any footwear and heavy clothing prior to testing. BMI was calculated as weight (kg) divided by height in meters squared (kg/m^2). Physical activity (PA) was assessed using the validated 7-day recall of habitual physical activity (7-dPAR) which captures how often participants were engaged in moderate, hard and very hard PA, and how much sleep they had, and then infers time spent in light intensity activity (Sallis et al., 1985). An average daily energy expenditure (kcal/day) is then calculated based on time spent in these differing intensity activities (Richardson et al., 2001). Total energy intake (kcal/day) was calculated from the FFQ data using nutrient data from the electronic nutrient database for use in Australia (NUTTAB, 2010) (NUTTAB, 2010).

2.6. Statistical analysis

Patient demographics and baseline characteristics were summarized by mean and standard deviation (SD) for normally distributed continuous data, or the median and inter-quartile range for skewed distributed data, and counts and percentages for categorical data. Key covariables included age (years), gender, education (<14 years/≥14 years), income (<$30,000/≥$30,000), smoking status (non-smoker/current or past smoker), insulin use (yes/no), change in dietary habit in the last five years (yes/no), use of hypertensive medication (yes/no), use of lipid-lowering medication (yes/no), poor diabetes control (HbA1c ≥ 7%, yes/no), presence of comorbidity (none/at least one), presence of at least one other diabetes complication (renal, peripheral vascular disease, neuropathy: yes/no), country of birth (Australia/other), physical activity (total daily energy expenditure, kcal/day); total energy intake (kcal/day), main language spoken at home (English/other), body mass index (BMI), duration of diabetes (years), systolic and diastolic BP (SBP and DBP, mm Hg), HbA1c (%), fasting glucose (mmol/L), TC (mmol/L), LDL (mmol/L); HDL (mmol/L), and TG (mmol/L). Multivariable logistic regression analysis was used to examine the relationship between alcohol consumption and DR, adjusted for age, gender and all covariables that were significant in univariate analysis. When analysing each of the specific beverage types (e.g. red wine), we adjusted for all confounders as well as each of the other beverage types.

Associations were considered statistically significant if $p < 0.05$; all statistical analyses were undertaken using Stata version 12.0 (StataCorp, College Station, TX).

3. Results

A total of 395 people with type 2 diabetes participated in this study (alcohol consumers = 188, 47.6%; Table 1). The mean age ± SD [standard deviation] of the sample (males = 253) was 65.9 ± 10.4 years old and $n = 235$ (59.5%) had DR. Of those with DR ($n = 235$, 59.5%), 130 (55.3%) and 105 (44.7%) had non-VTDR and VTDR, respectively. Those who consumed alcohol were more likely to be male, older, a current or past smoker, and not using insulin, and were less likely to have changed their dietary habits in the last five years compared to abstainers (all $p < 0.05$, Table 1). Those who consumed alcohol also had a higher energy intake and a lower BMI compared to abstainers; however, given that both groups had a mean BMI in the obese range, this result may not be clinically significant. There was no significant difference between duration of diabetes between abstainers and alcohol consumers. However, alcohol consumers had significantly lower HbA1c levels ($p < 0.05$) compared to abstainers.

In multivariable models adjusted for age, gender, poor diabetes control (HbA1c ≥ 7%), diabetes duration, smoking, BMI, SBP, insulin use, and presence of at least one other diabetes complication, moderate alcohol consumption (overall) was associated with reduced odds for any DR compared to abstainers (OR = 0.47, 95% CI [confidence interval] 0.26–0.85, $p = 0.013$). In the beverage-specific analysis, those who consumed moderate amounts of white wine/champagne and fortified wine had reduced odds of any DR compared with abstainers (OR = 0.48, 95% CI 0.25–0.91, $p = 0.024$ and OR = 0.15, 95% CI 0.04–0.62, $p = 0.009$, respectively) (Table 2). The plots in Figs. 1 and 2 display all significant risk and protective factors for DR in the multivariate regression models for white wine/champagne and fortified wine (exposures).

Looking at severity of DR, moderate alcohol consumption (overall) was also associated with reduced odds for non-VTDR and VTDR compared to abstainers (OR = 0.52, 95% CI 0.27–0.98, $p = 0.044$ and OR = 0.40, 95% CI 0.19–0.83, $p = 0.015$, respectively). Moderate consumption of white wine/champagne was associated with lower odds for VTDR (OR = 0.35, 95% CI 0.15–0.80, $p = 0.013$), and moderate consumption of fortified wine was associated with lower odds for both non-VTDR and VTDR (OR = 0.21, 95% CI 0.05–0.91, $p = 0.038$ and OR = 0.07, 95% CI 0.01–0.82, $p = 0.034$, respectively) (Table 3). Other alcoholic beverages were not associated with the presence or severity of DR.

Table 1
Sociodemographic and clinical characteristics of the participants ($n = 395$).

Characteristic	Abstainers ($n = 207$)[a]		Alcohol consumers ($n = 188$)		p
Categorical variables	n	%	n	%	
Gender (male)	**106**	**51.2**	**147**	**78.2**	**<0.0001**
Current/past smoker (yes)	**99**	**48.7**	**111**	**59.4**	**0.036**
Income					
<$30,000	139	73.9	121	69.9	0.398
≥$30,000	49	26.1	52	30.1	
Education					
<14 years	147	73.1	136	73.5	0.933
≥14 years	54	26.9	49	26.5	
Language spoken at home (English)	144	83.2	134	82.2	0.803
Country of birth (Australia)	94	45.4	71	37.8	0.124
Insulin use (yes)	**85**	**41.3**	**52**	**27.8**	**0.005**
Lipid-lowering medication (yes)	59	29.7	46	25.4	0.357
Hypertension medication (yes)	68	34.2	63	34.8	0.896
At least one diabetes complication[b]	65	31.4	62	33.0	0.737
At least one comorbidity[c] (yes)	183	88.4	157	83.5	0.160
DR severity					
No DR	76	36.7	84	44.7	0.137
Non-VTDR	68	32.9	62	33.0	
VTDR	63	30.4	42	22.3	
Alcohol consumption (standard drinks)					
Beer (low strength)	n/a	n/a	18	11.3	
Beer (high strength)	n/a	n/a	31	19.4	
Red wine	n/a	n/a	56	35.0	
White wine or champagne	n/a	n/a	38	23.8	
Sherry or port	n/a	n/a	13	8.1	
Spirits			28	17.5	
Change in dietary habit in last 5 years (yes)	**126**	**63.3**	**86**	**47.8**	**0.002**
Continuous variables[d,e]	Mean/ median	SD/IQR	Mean/ median	SD/IQR	p-Value
Age (years)	**64.9**	**10.3**	**67.0**	**10.5**	**0.043**
Systolic blood pressure (mm Hg)	138.9	19.9	141.9	17.8	0.120
Duration of diabetes (years)[f]	12.1	14.5	12.0	14.0	0.949
Body mass index (kg/m^2)	**31.9**	**6.4**	**30.5**	**6.1**	**0.036**
HbA1c (%)[f]	**7.6**	**1.9**	**7.2**	**1.4**	**0.015**
Fasting glucose (mmol/L)[f]	8.1	3.5	7.4	2.7	0.145
Total cholesterol (mmol/L)[f]	4.4	1.5	4.4	1.7	0.695
HDL cholesterol (mmol/L)[f]	1.3	0.6	1.3	0.5	0.184
Triglycerides (mmol/L)[f]	1.6	1.1	1.5	1.0	0.214
LDL cholesterol (mmol/L)[f]	2.2	1.2	2.2	1.3	0.618
Total daily energy expenditure (kcal/day)	39.7	6.5	40.0	5.7	0.691
Total energy intake (kcal/day)	**1730.6**	**641.1**	**1879.2**	**661.9**	**0.033**

Bolded values indicate significant results.
DR = diabetic retinopathy; HbA1c = hemoglobin A1c; IQR = interquartile range; SD = standard deviation.
[a] Chi-square test assessed difference in frequency distributions between abstainers and alcohol consumers.
[b] Includes nephropathy, peripheral vascular disease, and neuropathy.
[c] Includes hypertension, angina, irregular heartbeat, stroke, high cholesterol, asthma, anaemia, migraine, arthritis, and osteoporosis.
[d] Student's unpaired t-test was used for the comparison of continuously distributed variables.
[e] Wilcoxon rank-sum test was used for the comparison of nonparametric variables.
[f] Characteristics were expressed as the median (interquartile range (IQR)) for non-normally distributed continuous variables.

4. Discussion

Our study demonstrates that both the amount of alcohol and the type of beverage are associated with the risk of DR in patients with Type 2 diabetes. Individuals who consumed moderate amounts of alcohol and, in particular, white wine/champagne or fortified wines, had reduced the odds of any DR, non-VTDR and VTDR compared to non-consumers. This is the first study to specifically assess a range of

Table 2
Association between overall alcohol consumption and consumption of six alcoholic beverage types, with any diabetic retinopathy.

	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)[a]	*p*
Alcohol consumption (overall)				
None	1			
Moderate[b]	0.69 (0.45, 1.07)	0.095	**0.47 (0.26, 0.85)**	**0.013**
High	0.83 (0.40, 1.73)	0.619	0.75 (0.25, 2.20)	0.599
Beer (low strength)[c]				
None	1		1	
Moderate	1.29 (0.70, 2.38)	0.418	0.86 (0.38, 1.91)	0.703
Beer (high strength)[c]				
None	1		1	
Moderate	0.64 (0.36, 1.12)	0.118	0.56 (0.27, 1.17)	0.123
Red wine				
None	1		1	
Moderate	0.73 (0.47, 1.14)	0.166	0.62 (0.34, 1.14)	0.122
High	1.09 (0.31, 3.82)	0.893	1.43 (0.36, 5.70)	0.613
White wine or champagne				
None	1		1	
Moderate	**0.57 (0.33, 0.96)**	**0.036**	**0.48 (0.25, 0.91)**	**0.024**
High	1.24 (0.30, 5.05)	0.765	1.07 (0.13, 8.82)	0.951
Sherry or Port[c]				
None	1		1	
Moderate	**0.25 (0.09, 0.70)**	**0.009**	**0.22 (0.05, 0.93)**	**0.039**
Spirits[c]				
None	1		1	
Moderate	0.98 (0.57, 1.70)	0.955	1.28 (0.62, 2.65)	0.497

Bolded values indicate statistically significant associations ($p < 0.05$) between amount and type of alcohol consumption, and any diabetic retinopathy.

[a] Adjusted for: age, gender, smoking, body mass index, systolic blood pressure, diabetes control, insulin use, duration of diabetes, and presence of at least one other diabetes complication. We also simultaneously adjusted for each of the other beverage types.

[b] None = <1 standard drink/week; moderate consumption = 1–14 standard drinks/week; High consumption = >14 standard drinks/week; CI = confidence interval; OR = odds ratio.

[c] High consumption not assessed due to lack of data.

alcoholic beverages including fortified wine and to differentiate between red and white wine. We are also the first study to find a significant association between any type of alcohol consumption, and any DR and non-VTDR, with all other studies reporting an association with VTDR only. Overall, these findings suggest that a drinking pattern whereby alcohol (particularly white or fortified wine) is consumed on several days of the week in moderation may be a healthy pattern for the development and progression of DR in people with type 2 diabetes.

Our findings support previous cross-sectional studies, which have reported a protective effect for overall alcohol consumption (Moss et al., 1992) and moderate wine consumption (defined as 30.0–69.0 grams of alcohol per week) (Beulens et al., 2008) on PDR, and for age-related macular degeneration (AMD) (Obisesan et al., 1998). Similarly, abstainers and former drinkers have been shown to have greater odds of DR compared to light alcohol consumers in another cross-sectional study (Harjutsalo et al., 2014). However, the same study also found that alcoholic spirit drinkers had more than twice the odds of having severe DR than wine or beer drinkers, which was not consistent with our results where consumption of spirits was not significantly associated with severity of DR (Harjutsalo et al., 2014). Our results also differ from studies finding no association between any type of alcohol consumption and DR (Del Canizo Gomez et al., 2011; Lee et al., 2010; Moss et al., 1994; Xu et al., 2009; Yang et al., 2013); however, in some of these studies, 'alcohol consumption' was either a dichotomous variable (yes/no) (Xu et al., 2009; Yang et al., 2013), poorly defined (Del Canizo Gomez et al., 2011; Yang et al., 2013), or only heavy consumption was assessed, which may have limited their capacity to find a significant association between alcohol consumption and DR (Yang et al., 2013). We found no association between high alcohol consumption and DR, unlike other eye-related studies which have reported an association between high alcohol consumption, and increased risk of AMD (Adams et al., 2012) and cataract (Gong et al., 2015).

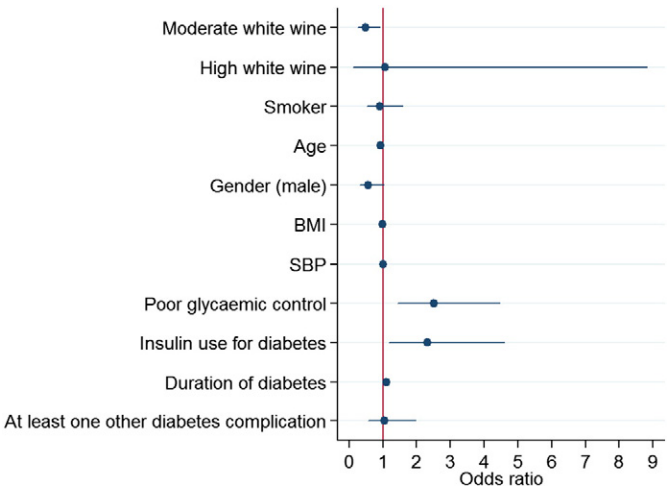

Fig. 1. Odds ratios (95% confidence intervals) of our multivariable regression model exploring the association between consumption of white wine/champagne (exposure) and DR (outcome). This plot shows that moderate consumption of white wine/champagne is an independent protective factor for DR. Notes: BMI = body mass index; SBP = systolic blood pressure.

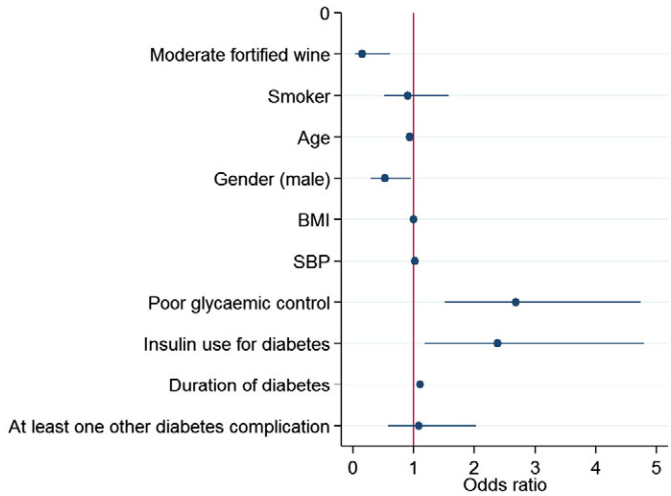

Fig. 2. Odds ratios (95% confidence intervals) of our multivariable regression model exploring the association between moderate consumption of fortified wine (exposure) and DR (outcome). This plot shows that moderate consumption of fortified wine is an independent protective factor for DR. Notes: BMI = body mass index; SBP = systolic blood pressure.

It has been hypothesized that wine may be protective for DR due to its high polyphenolic content, which contains anti-oxidants that combat sustained oxidation (Bola, Bartlett, & Eperjesi, 2014). Indeed, resveratrol – the main active polyphenol in wine – inhibits angiogenesis; prevents inflammation; and facilitates vaso-relaxation, all of which result in increased blood flow in the retina and counteract the reduced blood flow resulting from DR (Bola et al., 2014). Interestingly, in our study, white wine/champagne, but not red wine, was a protective factor for DR. Although red wine is more often associated with reduced risk of cardiovascular and other diseases, some studies have shown that moderate regular consumption of both red and white wines has similar beneficial effects in reducing markers of cardiovascular diseases (Williams et al., 2004), with white wine delivering even better results than red wine for some parameters (Lachtermann et al., 1999). Moreover, a recent study has found that caffeic acid, a phenol found in white wine, may exert a protective effect on endothelial cell function which may limit cardiovascular and kidney disease progression associated with oxidative stress-mediated endothelial injury (Migliori et al., 2015). Similarly, another study has shown that polyphenols present in champagne wine may induce a neuroprotective effect against oxidative neuronal injury (Vauzour et al., 2007). It is possible that

Table 3
Association between overall alcohol consumption and consumption of six alcoholic beverage types, with severity of diabetic retinopathy.

	Non-VTDR		VTDR		Non-VTDR		VTDR	
	Unadjusted OR	*p*	Unadjusted OR	*p*	Adjusted OR[a]	*p*	Adjusted OR[a]	*p*
Alcohol consumption (overall)								
None	1		1		1		1	
Moderate[b]	0.78 (0.48, 1.28)	0.327	**0.60 (0.36, 1.02)**	**0.060**	**0.52 (0.27, 0.98)**	**0.044**	**0.40 (0.19, 0.83)**	**0.015**
High	1.04 (0.46, 2.36)	0.930	0.60 (0.23, 1.58)	0.306	0.97 (0.33, 2.90)	0.963	0.39 (0.09, 1.65)	0.199
Beer (low strength)[c]								
None	1		1		1		1	
Moderate	1.43 (0.72, 2.84)	0.302	1.11 (0.52, 2.38)	0.779	0.97 (0.42, 2.25)	0.941	0.69 (0.25, 1.91)	0.479
Beer (high strength)[c]								
None	1		1		1		1	
Moderate	0.67 (0.34, 1.30)	0.239	0.59 (0.29, 1.23)	0.161	0.64 (0.29, 1.41)	0.271	0.44 (0.16, 1.21)	0.114
Red wine								
None	1		1		1		1	
Moderate	0.79 (0.48, 1.32)	0.368	0.66 (0.38, 1.15)	0.144	0.67 (0.35, 1.27)	0.217	0.55 (0.26, 1.16)	0.117
High	0.86 (0.19, 3.93)	0.843	1.36 (0.33, 5.64)	0.665	1.12 (0.20, 6.29)	0.900	2.20 (0.52, 9.22)	0.282
White wine or champagne								
None	1		1		1		1	
Moderate	0.65 (0.35, 1.20)	0.168	**0.46 (0.23, 0.95)**	**0.034**	0.56 (0.28, 1.12)	0.100	**0.35 (0.15, 0.80)**	**0.013**
High	1.14 (0.23, 5.78)	0.874	1.36 (0.27, 6.87)	0.714	1.16 (0.15, 8.83)	0.888	0.91 (0.06, 14.95)	0.948
Sherry or Port[c]								
None	1		1		1		1	
Moderate	0.36 (0.11, 1.13)	0.080	**0.11 (0.01, 0.85)**	**0.034**	**0.21 (0.05, 0.91)**	**0.038**	**0.07 (0.01, 0.82)**	**0.034**
Spirits[c]								
None	1		1		1		1	
Moderate	1.33 (0.73, 2.41)	0.349	0.60 (0.28, 1.28)	0.185	1.64 (0.77, 3.49)	0.197	0.72 (0.29, 1.79)	0.475

Bolded values indicate statistically significant associations ($p < 0.05$) between amount and type of alcohol consumption, and severity of diabetic retinopathy.

[a] Adjusted for: age, gender, smoking, body mass index, systolic blood pressure, diabetes control, insulin use, duration of diabetes, and presence of at least one other diabetes complication. We also simultaneously adjusted for each of the other beverage types.

[b] None = <1 standard drink/week; moderate consumption = 1–14 standard drinks/week; high consumption = >14 standard drinks/week; CI = confidence interval; OR = odds ratio.

[c] High consumption not assessed due to lack of data.

similar mechanisms underlie the protective effect of white wine and champagne on DR since both endothelial and neuronal dysfunction have been implicated in DR pathogenesis (Cheung, Mitchell, & Wong, 2010).

It is also interesting that fortified wine but not red wine was protective for DR. Being derived from red wine, fortified wines also have high polyphenolic content, which could explain the positive association, although this does not explain why we did not find an association with red wine. Data are scarce on the health benefits of fortified wines; however, moderate consumption of fortified wine has been found to be inversely associated with peripheral arterial disease (Vliegenthart et al., 2002). However, it is possible that white wine or champagne drinkers, and fortified wine drinkers may differ from drinkers of other beverages, such as beer and spirits, in a number of sociodemographic characteristics, such as healthier diet, more exercise, and higher socioeconomic background (Barefoot et al., 2002), all of which could be driving the protective effect of these beverages on DR. To explore whether physical activity and energy intake had a confounding effect on the association between alcohol consumption and DR, we added them to our multivariable model (data not shown) but the associations were not affected. However, there may still be a chance of residual confounding.

Strengths of our study include a well-characterized sample of Australian persons with type 2 diabetes and DR. However, certain limitations have to be addressed. First, as our study was cross-sectional, we are unable to determine causality. Importantly, we do not know if current abstainers were former drinkers who may have modified their lifestyle upon diagnosis of DR. Indeed, evidence is emerging to suggest that the frequently found benefit from moderate alcohol use is actually due to confounding and mis-classification of former and occasional drinkers as abstainers, rather than a true protective association (Chikritzhs et al., 2015). We accounted for this issue to some extent by exploring whether change of dietary habit in the last five years confounded the association between alcohol and DR, but it had no effect (data not shown); however, given that the mean duration of diabetes was over 10 years in our sample, this variable would not capture change in drinking behavior at diagnosis of DR when it may be most likely to occur. Therefore, current consumption levels may underestimate the true relationship between alcohol and DR and the findings of this study must be interpreted very cautiously. Longitudinal studies are required to determine if our findings could simply be cross-sectional data phenomena among people who may have changed their alcohol consumption patterns following a diagnosis of diabetes.

Second, consumption of alcohol was self-reported, leading to potential recall bias and the possibility for under-reporting due to the social stigma associated with heavy drinking. However, at present there is no objective means to quantify alcohol consumption. Therefore, to increase measurement validity (Feunekes et al., 1999), we included a detailed assessment of alcohol consumption using a valid and reliable food frequency questionnaire (Smith et al., 1998), which included overall alcohol consumption, frequency of consumption, and specific beverage type. Future studies, particularly those longitudinal in design, could consider using an 'alcohol consumption' diary with frequent text message reminders, as well as collecting data on previous drinking habits, which would optimize data quality. In addition, data could be collected on alcohol-related illnesses, which would reveal if misclassification of heavy drinkers as abstainers has occurred.

Third, we had to exclude 20% of our sample from the analysis due to missing alcohol data, which could have introduced selection bias. This likely occurred because the alcohol questions were part of the very long (145-item) FFQ and were usually conducted at the end of the assessment procedure, which was approximately three hours in total and which included a battery of clinical tests and other questionnaires. For these reasons, the FFQ was often excluded if the patient was fatigued, the interview was running overtime, or communication was difficult. This suggests that the selection bias introduced by these missing data is not related to the questions themselves (e.g. the topic of drinking habits), but rather about time and convenience issues. Although there were no significant differences between those with and without alcohol data on most sociodemographic and clinical variables, we found that those who had alcohol data were more likely to have English as a first language. Similar results have been observed in

a New Zealand study, which found that non-responders to a survey measuring alcoholic drinking behavior were more likely to be male, younger, of Maori descent and living in deprived areas (Maclennan et al., 2012). Therefore, the results of our study may not be generalizable to the wider Australian population who have English as their second language. Finally, the low frequency counts in some of our high consumption categories (e.g. beer, fortified wine and spirits) meant that we were unable to explore the association between high consumption of these beverage types and DR.

In summary, we found that moderate consumption of alcohol overall, and white wine/champagne and fortified wines specifically, was associated with reduced odds of any DR, non-VTDR and VTDR in this cross-sectional study of people with type 2 diabetes. Our findings need further exploration in a longitudinal study of people with diabetes to assess whether the found association translates into a protective effect for the incidence and progression of DR, and to better understand how alcohol consumption might mediate the risk of DR.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2015.09.001.

Acknowledgments

This study was supported by the National Health and Medical Research Council Centre for Clinical Research Excellence (CCRE) (No. 529923)—Translational Clinical Research in Major Eye Diseases; CCRE Diabetes; Australian Research Council (ARC) Grant LP0884108; Royal Victorian Eye and Ear Hospital (RVEEH); and Operational Infrastructure Support from the Victorian Government. Dr Eva Fenwick is funded by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (No. 1072987). The funding organizations had no role in the design or conduct of this research.

References

Adams, M. K., Chong, E. W., Williamson, E., Aung, K. Z., Makeyeva, G. A., Giles, G. G., ... Simpson, J. A. (2012). 20/20—Alcohol and age-related macular degeneration: The Melbourne Collaborative Cohort Study. *American Journal of Epidemiology*, *176*(4), 289–298.

International Clinical Classification of Diabetic Retinopathy Severity of Macular Oedema. (2002).American Academy of Ophthalmology.

Barefoot, J. C., Gronbaek, M., Feaganes, J. R., McPherson, R. S., Williams, R. B., & Siegler, I. C. (2002). Alcoholic beverage preference, diet, and health habits in the UNC Alumni Heart Study. *The American Journal of Clinical Nutrition*, *76*(2), 466–472.

Beulens, J., Kruidhof, J., Grobbee, D., Chaturvedi, N., Fuller, J, & Soedamah-Muthu, S. (2008). Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: The EURODIAB Prospective Complications Study. *Diabetologia*, *51*(9), 1631–1638.

Bola, C., Bartlett, H., & Eperjesi, F. (2014). Resveratrol and the eye: Activity and molecular mechanisms. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *252*(5), 699–713.

Brooke, P., & Bullock, R. (1999). Validation of a 6-item cognitive impairment test with a view to primary care usage. *International Journal of Geriatric Psychiatry*, *14*, 936–940.

Cheung, N., Mitchell, P., & Wong, T. Y. (2010). Diabetic retinopathy. *Lancet*, *376*(9735), 124–136.

Chikritzhs, T., Stockwell, T., Naimi, T., Andreasson, S., Dangardt, F., & Liang, W. (2015). Has the leaning tower of presumed health benefits from 'moderate' alcohol use finally collapsed? *Addiction*, *110*(5), 726–727.

Del Canizo Gomez, F. J., Fernandez Perez, C., Moreno Ruiz, I., de Gorospe Perez-Jauregui, C., Silveira Rodriguez, B., Gonzalez Losada, T., & Segura Galindo, A. (2011). Microvascular complications and risk factors in patients with type 2 diabetes. *Endocrinología y Nutrición*, *58*(4), 163–168.

Dirani, M., Xie, J., Fenwick, E., Benarous, R., Rees, G., Wong, T. Y., & Lamoureux, E. L. (2011). Are obesity and anthropometry risk factors for diabetic retinopathy? The diabetes management project. *Investigative Ophthalmology & Visual Science*, *52*(7), 4416–4421.

Fenwick, E. K., Xie, J., Pesudovs, K., Ratcliffe, J., Chiang, P. P., Finger, R. P., & Lamoureux, E. L. (2012a). Assessing disutility associated with diabetic retinopathy, diabetic macular oedema and associated visual impairment using the Vision and Quality of Life Index. *Clinical & Experimental Optometry*, *95*(3), 362–370.

Fenwick, E. K., Xie, J., Ratcliffe, J., Pesudovs, K., Finger, R. P., Wong, T. Y., & Lamoureux, E. L. (2012b). The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Investigative Ophthalmology & Visual Science*, *53*(2), 677–684.

Feunekes, G. I., van 't Veer, P., van Staveren, W. A., & Kok, F. J. (1999). Alcohol intake assessment: The sober facts. *American Journal of Epidemiology*, *150*(1), 105–112.

Gong, Y., Feng, K., Yan, N., Xu, Y., & Pan, C. W. (2015). Different amounts of alcohol consumption and cataract: A meta-analysis. *Optometry and Vision Science*, *92*(4), 471–479.

Harjutsalo, V., Feodoroff, M., Forsblom, C., Groop, P., & FinnDiane Study Group (2014). Patients with Type 1 diabetes consuming alcoholic spirits have an increased risk of microvascular complications. *Diabetic Medicine*, *31*(2), 156–164.

Howard, A. A., Arnsten, J. H., & Gourevitch, M. N. (2004). Effect of alcohol consumption on diabetes mellitus: A systematic review. *Annals of Internal Medicine*, *140*(3), 211–219.

Koppes, L. L., Dekker, J. M., Hendriks, H. F., Bouter, L. M., & Heine, R. J. (2006). Meta-analysis of the relationship between alcohol consumption and coronary heart disease and mortality in type 2 diabetic patients. *Diabetologia*, *49*(4), 648–652.

Lachtermann, E., Turhanova, L., Rodziewicz, M., Stein-Hammer, C., Schicketanz, K., Nagel, D., ... Jung, K. (1999). Moderate red and white wine consumption and the risk of cardiovascular disease. *Herz Kreislauf*, *31*(1), 25–31.

Lamoureux, E. L., Fenwick, E., Xie, J., McAuley, A., Nicolaou, T., Larizza, M., ... Dirani, M. (2012). Methodology and early findings of the Diabetes Management Project: A cohort study investigating the barriers to optimal diabetes care in diabetic patients with and without diabetic retinopathy. *Clinical & Experimental Ophthalmology*, *40*(1), 73–82.

Lee, C., Stolk, R., Adler, A., Patel, A., Chalmers, J., Neal, B., ... AdRem project team and ADVANCE management committee (2010). Association between alcohol consumption and diabetic retinopathy and visual acuity—The AdRem Study. *Diabetic Medicine*, *27*(10), 1130–1137.

Maclennan, B., Kypri, K., Langley, J., & Room, R. (2012). Non-response bias in a community survey of drinking, alcohol-related experiences and public opinion on alcohol policy. *Drug and Alcohol Dependence*, *126*(1–2), 189–194.

Migliori, M., Cantaluppi, V., Mannari, C., Bertelli, A. A., Medica, D., Quercia, A. D., ... Panichi, V. (2015). Caffeic Acid, a phenol found in white wine, modulates endothelial nitric oxide production and protects from oxidative stress-associated endothelial cell injury. *PloS One*, *10*(4), e0117530.

Moss, S. E., Klein, R., & Klein, B. E. (1992). Alcohol consumption and the prevalence of diabetic retinopathy. *Ophthalmology*, *99*(6), 926–932.

Moss, S. E., Klein, R., & Klein, B. E. (1994). The association of alcohol consumption with the incidence and progression of diabetic retinopathy. *Ophthalmology*, *101*(12), 1962–1968.

NUTTAB (2010). *Australian Food Composition: Food Standards Australia New Zealand.* (Canberra).

Obisesan, T. O., Hirsch, R., Kosoko, O., Carlson, L., & Parrott, M. (1998). Moderate wine consumption is associated with decreased odds of developing age-related macular degeneration in NHANES-1. *Journal of the American Geriatrics Society*, *46*(1), 1–7.

Richardson, M. T., Ainsworth, B. E., Jacobs, D. R., & Leon, A. S. (2001). Validation of the Stanford 7-day recall to assess habitual physical activity. *Annals of Epidemiology*, *11*(2), 145–153.

Sallis, J. F., Haskell, W. L., Wood, P. D., Fortmann, S. P., Rogers, T., Blair, S. N., & Paffenbarger, R. S., Jr. (1985). Physical activity assessment methodology in the Five-City Project. *American Journal of Epidemiology*, *121*(1), 91–106.

Schrieks, I. C., Heil, A. L., Hendriks, H. F., Mukamal, K. J., & Beulens, J. W. (2015). The effect of alcohol consumption on insulin sensitivity and glycemic status: A systematic review and meta-analysis of intervention studies. *Diabetes Care*, *38*(4), 723–732.

Smith, W., Mitchell, P, Reay, EM, Webb, K, & Harvey, PW (1998). Validity and reproducibility of a self-administered food frequency questionnaire in older people. *Australian and New Zealand Journal of Public Health*, *22*, 456–463.

Sparwel, J., Vantler, M., Caglayan, E., Kappert, K., Fries, J. W. U., Dietrich, H., ... Rosenkranz, S. (2009). Differential effects of red and white wines on inhibition of the platelet-derived growth factor receptor: Impact of the mash fermentation. *Cardiovascular Research*, *81*(4), 758–770.

Vauzour, D., Vafeiadou, K., Corona, G., Pollard, S. E., Tzounis, X., & Spencer, J. P. (2007). Champagne wine polyphenols protect primary cortical neurons against peroxynitrite-induced injury. *Journal of Agricultural and Food Chemistry*, *55*(8), 2854–2860.

Vliegenthart, R., Geleijnse, J. M., Hofman, A., Meijer, W. T., van Rooij, F. J., Grobbee, D. E., & Witteman, J. C. (2002). Alcohol consumption and risk of peripheral arterial disease: The Rotterdam study. *American Journal of Epidemiology*, *155*(4), 332–338.

Wang, S., Wang, J. J., & Wong, T. Y. (2008). Alcohol and eye diseases. *Survey of Ophthalmology*, *53*(5), 512–525.

Williams, M. J., Sutherland, W. H., Whelan, A. P., McCormick, M. P., & de Jong, S. A. (2004). Acute effect of drinking red and white wines on circulating levels of inflammation-sensitive molecules in men with coronary artery disease. *Metabolism*, *53*(3), 318–323.

Xu, L., You, Q. S., & Jonas, J. B. (2009). Prevalence of alcohol consumption and risk of ocular diseases in a general population: The Beijing Eye Study. *Ophthalmology*, *116*(10), 1872–1879.

Yang, J. Y., Kim, N. K., Lee, Y. J., Noh, J. H., Kim, D. J., Ko, K. S., ... Kim, D. J. (2013). Prevalence and factors associated with diabetic retinopathy in a Korean adult population: The 2008–2009 Korea National Health and Nutrition Examination Survey. *Diabetes Research and Clinical Practice*, *102*(3), 218–224.

Young, R., McCulloch, D., Prescott, R., & Clarke, B. (1984). Alcohol: Another risk factor for diabetic retinopathy? *British Medical Journal (Clinical Research Ed.)*, *288*(6423), 1035–1037.