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# Alcohol Consumption in Relation to Aortic Stiffness and Aortic Wave Reflections: A Cross-Sectional Study in Healthy Postmenopausal Women

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**Objective**—Moderate alcohol consumption has been postulated to be cardioprotective. Such an effect might be reflected in large-artery properties, such as arterial stiffness and wave reflections.

**Methods and Results**—Three hundred seventy-one healthy postmenopausal women aged 50 to 74 years were sampled from a population-based study. Alcohol intake was calculated from a standardized questionnaire. Applanation tonometry was applied to assess the augmentation index and aortic pulse-wave velocity. Those drinking 1 to 3, 4 to 9, 10 to 14, and 15 to 35 glasses of alcoholic beverages per week had a 0.044 (95% CI  $-0.47$  to  $0.56$ ),  $-0.085$  (95% CI  $-0.59$  to  $0.43$ ),  $-0.869$  (95% CI  $-1.44$  to  $-0.29$ ), and  $-0.225$  (95% CI  $-0.98$  to  $0.53$ ) m/s difference in mean pulse-wave velocity compared with nondrinkers, respectively, which indicates a J-shaped relationship. Adjustment for potential confounders of pulse-wave velocity or alcohol intake did not materially change the strength of the association. Adjustment for HDL further attenuated the relationship. The augmentation index was not related to alcohol consumption when adjustments were made for physiological determinants such as age, height, and ejection duration.

**Conclusions**—Among postmenopausal women, alcohol consumption is inversely associated with pulse-wave velocity. This supports the presence of a decreased risk of cardiovascular disease with moderate alcohol consumption, which may be mediated in part by HDL cholesterol. (*Arterioscler Thromb Vasc Biol.* 2004;24:342-348.)

**Key Words:** alcohol ■ aortic stiffness ■ postmenopausal women ■ pulse-wave velocity

The effects of alcohol on the cardiovascular system suggest a higher risk of cardiovascular disease (CVD) in nondrinkers and heavy alcohol consumers and a protective effect with moderate alcohol intake, leading to a J-shaped association. Mechanisms proposed to explain a positive health effect of moderate alcohol consumption involve prevention of atherogenesis through beneficial effects on lipoprotein metabolism,<sup>1,2</sup> hemostasis,<sup>3</sup> and inflammatory processes.<sup>4</sup> In addition, elevated levels of CVD risk factors are related to atherogenesis and vascular damage, such as stiffer arteries, specifically stiffness of the aorta.<sup>5-7</sup> Aortic pulse-wave velocity (PWV) is a noninvasive measurement of the distensibility of the aorta, which is reported to be a reliable index of aortic stiffness.<sup>8</sup> Increased aortic stiffness has been shown to predict future cardiovascular events.<sup>9</sup> A cardioprotective effect of moderate alcohol consumption should therefore be reflected in an inverse or J-shaped association between alcohol intake and aortic stiffness.

Alcohol has been suggested to have vasodilatory effects. This may affect PWV to some extent but more importantly may affect wave reflections. Information on wave reflection can be assessed by measurement of the augmentation index (AIx), which is defined as

the increment in pressure from the first systolic shoulder (inflection point) to the peak pressure of the aortic pressure waveform, expressed as a percentage of the peak pressure.<sup>10</sup> This index has been used as a measure of additional load imposed on the left ventricle as a result of wave reflection. The AIx depends in part on PWV but more on the arterial properties that determine the amount and site of wave reflection.<sup>11</sup> Recently, increased AIx has been shown to be related to the risk of coronary heart disease.<sup>12</sup> A cardioprotective effect of moderate alcohol consumption should therefore be reflected in an inverse or J-shaped association between alcohol intake and AIx.

To provide evidence for this hypothesis, we investigated the relation of alcohol consumption to aortic PWV and to AIx in a cross-sectional study in a well-defined group of healthy postmenopausal women.

## Methods

### Subjects

The participants in this study were primary enrolled with the objective to elucidate the role of endogenous sex hormones on

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several markers of frailty. The markers included assessment of large-artery properties, such as PWV and AIx. For the study, a selection procedure was applied to obtain 2 groups of women with great contrast in time since menopause. Because the selection procedure did not involve information about alcohol consumption or about results from large-artery measurements, we do not believe that selection bias for either exposure or outcome occurred. In short, participants were recruited from the PROSPECT study, 1 of the 2 Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC).<sup>13</sup> In PROSPECT, a total of 17 395 healthy breast cancer screening participants aged 49 to 70 years who were living in Utrecht, Netherlands, and surroundings were enrolled between 1993 and 1997. Using the baseline data from PROSPECT, we selected 2 groups of women who had experienced a natural menopause either between 1987 and 1989 ( $\approx 10$  years since menopause) or between 1969 and 1979 ( $\approx 20$  years since menopause). In addition, women had to have an intact uterus and at least 1 intact ovary and should not have used sex steroids after the reported date of last menstruation. Of 1802 eligible women (1149 and 653 from each respective group), 902 (451 and 451) were invited to participate, and 553 (61%) answered positively. The aim of the present study was to enroll 200 women in each group, and 403 (207 and 196) participants were ultimately included in the study. Women were considered sufficiently healthy to participate when they were physically and mentally able to visit the study center without assistance. Each participant underwent all tests and assessments during 2 visits to the study center. The study was approved by the Institutional Review Board of the University Medical Center Utrecht, and written informed consent was obtained from all participants. Data collection took place between September 1999 and March 2000.

## Measurements

Information on health was obtained by medical history, registration of current medication, and physical examination. A standardized questionnaire on alcohol consumption, smoking habits, and physical activity was obtained from each woman. Height, weight, waist, and hip circumference were measured with the participant in standing position wearing indoor clothes and no shoes. Fasting total cholesterol, HDL cholesterol, triacylglycerol, and glucose were measured reflectometrically with commercial enzymatic kits with a Vitros 250 (dry chemistry; Johnson & Johnson). The LDL cholesterol concentration was estimated with the Friedewald formula.<sup>14</sup> Blood pressure and heart rate were measured in duplicate before 11 AM after an overnight fast with an oscillometric-automated device (DINAMAP 8100, Critikon). Mean arterial blood pressure (MAP) was calculated as diastolic blood pressure +  $1/3 \times$  (systolic blood pressure – diastolic blood pressure). Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure.

The SphygmoCor system was used to noninvasively measure stiffness of the aorta<sup>11</sup> (PWV system, PWV Medical). After 5 to 10 minutes with the participant resting in the supine position, aortic PWV was measured by sequential recordings of the arterial pressure waveform at the carotid artery and the femoral artery with a hand-held micromanometer-tipped probe on the skin at the site of maximal arterial pulsation. Gating of the recordings at those 2 sites to the ECG allowed PWV to be measured. Distances from the carotid sampling site to the suprasternal notch and from the suprasternal notch to the femoral artery were measured with a compass.<sup>15</sup> The aortic PWV (in meters per second) was calculated automatically as the distance between the suprasternal notch and the femoral artery minus the distance between the carotid sampling site and the suprasternal notch, divided by the time interval between systolic R wave and femoral systolic upstroke minus the time interval between systolic R wave and carotid systolic upstroke. Aortic PWV was determined as the mean of at least 3 consecutive beats recorded during 10 seconds of data acquisition. All measurements were performed by the same observer (C.E.I.L.). We performed a reproducibility study among 27 participants who underwent a second PWV measurement within 2 weeks after the first examination. The mean PWV (SD) was 9.55 (2.36) m/s at the first visit and 9.56 (2.01)

m/s at the second visit, with a mean difference of 0.01 (1.0) m/s. The intraclass correlation coefficient was 89.6%, which indicates that 89.6% of the variance in PWV measurements was due to patient differences, whereas 10.4% could be attributed to differences between visits (measurement error and intraindividual variability).

Pressure waveforms were recorded from the right radial artery with a high-fidelity micromanometer (SPC 301; Millar Instruments). The obtained waveform data were then processed by the SphygmoCor radial/aortic transform module (PWV Medical) to produce an average aortic waveform. Ascending aortic pressures, ejection duration, and the AIx were derived from the aortic waveform.<sup>11</sup>

## Data Analysis

PWV and alcohol consumption data were not available for 18 and 14 women respectively, which left 371 women for analyses. The association between alcohol consumption and PWV was examined in 2 ways. First, we determined whether alcohol intake as a continuous variable (glasses/week) was associated with PWV using multiple linear regression analysis, adjusted for age, MAP, heart rate, and ejection duration (model A). The latter adjustments were based on literature indicating that these variables are major determinants of PWV and should be controlled for in the analyses.<sup>10,16,17</sup> Model A was extended with potential risk factors related to either PWV or alcohol intake (model B). These included waist-to-hip ratio, body mass index, smoking (current or former smokers), glucose, triacylglycerol, and physical activity. Model C was model B extended with HDL cholesterol, because alcohol consumption is related to HDL cholesterol<sup>2</sup> and PWV,<sup>18</sup> and thus might explain in part the observed association as an intermediate. The associations were presented as linear regression coefficients ( $\beta$ ) with corresponding 95% CI.

Second, to check dose dependency of the association between alcohol intake and PWV, alcohol intake was divided into 3 levels: 1 to 3, 4 to 9, and 10 to 35 glasses of alcoholic beverages per week, so that  $\approx 20\%$  of the participants were in each level of alcohol intake. The alcohol intake levels were entered into the model as dummy variables, and multiple linear regression analyses were performed as described earlier.

In a similar manner, the relation between alcohol intake and central blood pressures and the relation between alcohol intake and AIx was evaluated. In our data set, factors that were significantly related to augmentation index were current smoking (positive), albumin (inverse), waist-hip ratio (inverse), and pulse pressure (positive). In addition, physiological factors related to AIx were heart rate (inverse), ejection duration (positive), and height (inverse). These factors were taken into account in multivariate analyses.

To evaluate whether the association between alcohol intake and PWV (or central pressure and AIx) differed across age, smoking (current or former smokers), body mass index, hypercholesterolemia, prevalence of CVD, prevalence of diabetes mellitus, prevalence of hypertension, early/late menopause, and physical activity, multiplicative interaction terms were constructed and estimated with a linear regression model. Because all interaction terms had a probability value  $>0.15$ , no evidence for effect modification was found. Therefore, only the findings for the main effects in the models are reported. Statistical analyses were performed with SPSS for Windows (version 9.0).

## Results

General characteristics of the study population are presented in Table 1.

### Alcohol Intake and PWV

Overall alcohol intake was inversely associated with PWV, after adjustment for age, MAP, heart rate, and ejection duration ( $\beta = -0.036$  m/s; 95% CI  $-0.065$  to  $-0.008$ , which reflects that PWV was reduced by 0.036 m/s for each extra glass of alcoholic beverage per week. Additional adjustment for potential confounders of PWV or alcohol consumption

**TABLE 1. General Characteristics of the Study Population (n=371)**

Characteristic	
Age, y	66.2 (3.8)
Height, cm	164 (6.1)
Body mass index, kg/m <sup>2</sup>	26.0 (4.1)
Waist-to-hip ratio	0.81 (0.07)
Current alcohol consumers, %	59
Alcohol consumption, glasses/wk	4.75 (6.5)
Use of lipid-lowering drugs, %	14.8
Use of blood pressure-lowering drugs, %	
Diuretics	8.6
$\beta$ -Blocking agents	10.8
Calcium antagonists	4.9
Renin angiotensin inhibitors	12.9
Current smokers, %	11.9
Former smokers, %	35.8
Physically active, %*	63
Diabetes mellitus, %	4.3
CVD, %	11.2
Total cholesterol, mmol/L	6.3 (1.0)
HDL cholesterol, mmol/L	1.53 (0.40)
LDL cholesterol, mmol/L	4.1 (1.0)
Triacylglycerol, mmol/L	1.45 (0.69)
Glucose, mmol/L	5.2 (1.2)
Systolic blood pressure, mm Hg	147 (20.7)
Diastolic blood pressure, mm Hg	76 (13.5)
MAP, mm Hg	99.8 (14.8)
Pulse pressure, mm Hg	71.9 (14.3)
Heart rate, bpm	69.2 (10.2)
Ejection duration, ms	328 (21)
PWV, m/s	9.22 (2.21)
Central systolic pressure, mm Hg	139 (20.2)
Central diastolic pressure, mm Hg	78.5 (13.9)
AIx, %	31.4 (7.9)

Values are expressed as mean (SD) for continuous variables and as percentages for categorical variables. For definitions, see text.

\*Physical activity was on average 13.2 (24.4) hr/y.

(model B) barely affected the strength of the association ( $\beta = -0.035$  m/s; 95% CI  $-0.064$  to  $-0.004$ ), whereas additional adjustment for HDL cholesterol (model C) slightly attenuated the association ( $\beta = -0.031$  m/s; 95% CI  $-0.064$  to  $-0.001$ ). In Table 2, mean alcohol intake, HDL cholesterol level, mean PWV, and mean AIx by category of alcohol intake are presented. With increasing alcohol intake, decreasing PWV and increasing HDL cholesterol concentrations were seen. The dose dependency of the association between alcohol intake and PWV was evaluated by comparing mean PWV values of the 3 levels of alcohol intake with the mean PWV value of nondrinkers (Table 3). The separate alcohol intake levels were inversely associated with PWV, after adjustment for age, MAP, heart rate, and ejection duration (model A). In this analysis, a significant inverse association

was only present for the highest level of alcohol intake (10 to 35 glasses/week). Additional adjustment for potential confounders of PWV or alcohol intake (model B) did not materially change the strength of the association, whereas additional adjustment for HDL cholesterol (model C) attenuated the association, particularly for the higher-intake categories. Because the intake range in the highest alcohol intake level was large (10 to 35 glasses/week), this level was divided into 2 subgroups with alcohol intake levels of 10 to 14 and 15 to 35 glasses/week, respectively. The adjusted mean (SEM) alcohol intake and PWV in the 2 subgroups were 12.11 (0.26) and 22.02 (0.37) glasses/week and 8.61 (0.26) and 9.14 (0.36) m/s, respectively. The inverse association between alcohol intake and PWV was attenuated in the highest-intake subgroup (15 to 35 glasses/week; Table 3).

Some subjects used blood pressure- or lipid-lowering drugs (Table 1). To discern the relation of alcohol with PWV, the use of these drugs in principle should be related to both alcohol consumption and PWV. Age-adjusted models showed that alcohol consumption was not related to diuretic use ( $P=0.13$ ),  $\beta$ -blocker use ( $P=0.56$ ), calcium antagonist use ( $P=0.74$ ), renin angiotensin inhibitor use ( $P=0.88$ ), or use of lipid-lowering drugs ( $P=0.17$ ). Therefore, we do not believe that the described relation of alcohol consumption to PWV is confounded by drug use.

### Alcohol Intake and Central Aortic Pressure

Overall alcohol intake was not related to estimated central systolic or diastolic pressure. For systolic pressure, the  $\beta$ -coefficient was  $-0.065$  mm Hg (95% CI  $-0.39$  to  $0.26$ ), which reflects that for each extra glass of alcoholic beverage per week, central systolic pressure was nonsignificantly ( $P=0.69$ ) reduced by  $0.065$  mm Hg. The relation for diastolic pressure was  $0.057$  m/s (95% CI  $-0.17$  to  $0.27$ ). Adjustment for potential confounders did not materially alter the magnitude, direction, or significance of the relations. No dose-dependency relationship was found. Mean (SE) central systolic pressures were 139 (1.7), 138 (2.4), 141 (2.2), and 138 (2.4) mm Hg in groups of alcohol consumption of 0, 1 to 3, 4 to 9, and 10 to 35 glasses per week, respectively. Findings for central diastolic pressures were 78.5 (1.2), 77.6 (1.7), 77.7 (1.5), and 80.2 (1.6) mm Hg, respectively. When the relation of alcohol intake with brachial systolic and diastolic blood pressures was analyzed, similar nonsignificant results were obtained.

### Alcohol Intake and AIx

Overall alcohol intake was not significantly related to AIx; the  $\beta$ -coefficient was  $0.023\%$  (95% CI  $-0.10$  to  $0.15$ ), which reflects that for each extra glass of alcoholic beverage per week, aortic AIx was nonsignificantly ( $P=0.72$ ) increased by  $0.023\%$ . When factors that physiologically relate to AIx, such as heart rate, ejection duration, and height, were taken into account, the relation did not materially change ( $\beta = 0.025\%$  [95% CI  $-0.08$  to  $0.13$ ]). Additional adjustment for other risk factors did not alter the findings. In Table 2, the relation of alcohol intake and AIx by level of mean alcohol intake is given, adjusted for the above-mentioned factors. There appeared to be no relation between alcohol intake and AIx.



**TABLE 2. Alcohol Intake, HDL Cholesterol, PWV, and AIx by Level of Alcohol Intake**

Alcohol Intake Level, Glasses/wk	n	Alcohol Intake, Glasses/wk	HDL Cholesterol,* mmol/L	PWV,* m/s	AIx, %†
0	151	0	1.43 (0.033)	9.35 (0.15)	31.8 (0.52)
1–3	70	1.96 (0.09)	1.55 (0.048)‡	9.39 (0.22)	31.0 (0.74)
4–9	74	6.16 (0.17)	1.54 (0.047)	9.26 (0.21)	32.2 (0.74)
10–14	51	12.1 (0.28)	1.68 (0.056)‡	8.48 (0.25)‡	31.3 (0.89)
15–35	25	22 (1.17)	1.74 (0.080)‡	9.12 (0.35)	30.9 (1.28)

Values are mean (SE).

\*Values adjusted for age, MAP, heart rate, and ejection duration.

†Adjusted for ejection duration, height, pulse pressure, albumin, smoking, waist-to-hip ratio, and body mass index.

‡Significant different from reference group (0 glasses/wk).

Table 4 describes results from analyses of alcohol intake on AIx with different models for adjustment. Model A shows the crude relation. There appears to be a U-shaped relationship, with the highest AIx among those drinking 4 to 9 glasses of alcohol per week. This U-shaped relation for AIx is, however, opposite to that found for PWV. The relation remained after adjustment for risk factors (model B). However, the U-shaped relationship with AIx was attenuated when physiological factors were taken into account (model C).

In a crude analysis, there was no apparent relation between PWV and AIx (Pearson correlation coefficient  $-0.04$ ,  $P=0.46$ ). However, when ejection duration, heart rate, and height were taken into account, a modest positive relation was found: an increase in PWV of 1 m/s was related to an increase in AIx of 0.27% (95% CI  $-0.04$  to 0.58;  $P=0.09$ ). Yet, when blood pressure (MAP or pulse pressure) was taken into account, the relation was completely attenuated ( $P=0.98$ ).

## Discussion

This cross-sectional study among postmenopausal women provides evidence that alcohol consumption is inversely associated with aortic stiffness as measured by PWV, most markedly for an alcoholic beverage intake of 10 to 35 glasses/week. In addition, we found some evidence for the presence of a J-shaped relation. HDL cholesterol adjustment took away part of the magnitude of the associations. No relation between alcohol consumption and wave reflection was found. These observations are in agreement with the notion that moderate alcohol intake decreases the risk of

CVD by an effect on atherogenesis, which in part may be mediated by HDL cholesterol.

Some characteristics of the study need to be addressed. The use of self-reported information on alcohol intake may have introduced misclassification of exposure, most likely underestimation of the true consumption, especially in those in the heavier drinking groups.<sup>19</sup> However, selective misclassification of heavy drinkers as nondrinkers appears to be unlikely, because we observed a positive graded association between alcohol consumption and HDL cholesterol, a finding that supports the rank-order validity of self-reported alcohol intake.

No information was available on beverage type consumed, drinking pattern, or changes in drinking behavior. However, the focus here was on the long-term effect on arterial stiffness, and because drinking patterns among middle-aged and older subjects tend to be stable over time,<sup>20</sup> we do not expect a major impact on the validity of the data. Finally, our analyses pertain to postmenopausal women only, and results may only be applicable to this group, because wave reflections in particular appear to differ across gender.<sup>21</sup> Compared with men, women have a longer time to systolic peak, a longer ejection time, and a higher AIx.<sup>21</sup> These factors may affect the relationships with alcohol intake, especially because ejection duration is related to alcohol intake. Therefore, similar analyses in men are warranted.

To the best of our knowledge, there are a limited number of studies reporting the effect of alcohol consumption on aortic PWV. A cross-sectional study in Japanese-American men and women reported that the risk for high aortic PWV

**TABLE 3. Linear Regression Coefficients (95% CI) Describing the Difference in PWV (m/s) per Category of Alcohol Intake Compared With Nondrinkers**

Alcohol Intake Level, Glasses/wk	n	Model A	Model B	Model C
1–3	151	0.044 (−0.47 to 0.56)	0.170 (−0.34 to 0.68)	0.191 (−0.32 to 0.70)
4–9	70	−0.085 (−0.59 to 0.43)	−0.015 (−0.52 to 0.49)	−0.015 (−0.49 to 0.52)
10–14	51	−0.869 (−1.44 to −0.29)*	−0.743 (−1.32 to −0.16)*	−0.685 (−1.27 to −0.010)*
15–35	25	−0.225 (−0.98 to 0.53)	−0.172 (−0.94 to 0.60)	−0.101 (−0.88 to 0.68)
$R^2$		34.7%	39.8%	40.0%

Model A: adjusted for age, MAP, heart rate, and ejection duration; Model B: same as model A with additional adjustment for waist-to-hip ratio, body mass index, smoking (current or former smokers), glucose, triacylglycerol, and physical activity; Model C: same as model B with additional adjustment for HDL cholesterol.

\* $P<0.05$  vs reference group.  $R^2$  reflects proportion of variance in PWV data explained by the model.

was lower among current drinkers and ex-drinkers than among nondrinkers.<sup>22</sup> In a follow-up study in middle-aged Japanese men, the incidence of aortic stiffness was not related to alcohol intake,<sup>23</sup> whereas another longitudinal study in Japanese men suggested that alcohol is an important risk factor for development of aortic stiffness.<sup>24</sup> However, the risk for increased PWV was only significant in subjects who consumed more than 16 glasses of alcoholic beverages per week.<sup>24</sup> A similar trend to increased PWV was seen in the subgroup in the present study that consumed 15 to 35 glasses/week. Although the number of participants in this highest alcohol intake subgroup in the present study was low ( $n=25$ ) and the increase in PWV was not significant, this could suggest that there is a J-shaped association between alcohol consumption and aortic stiffness. This would be compatible with the reported J-shaped curve in the association between dose of alcohol intake and CVD risk. A recent study on acute and chronic alcohol consumption and arterial stiffness reported only a chronic effect on AIx (positive), although no mention was made of PWV.<sup>25</sup>

Arterial stiffness is a combination of effects of the media (elastin/collagen content), lumen diameter, local blood pressure, smooth muscle tone (as affected by nervous activity, hormones, locally produced vasoactive substances, and drugs).<sup>26</sup> As a consequence, there are a large number of factors that can influence aortic stiffness. The most consistently described factors are increasing age, increasing heart rate, height, blood pressure, other cardiovascular risk factors (lipids, indicators of glucose metabolism), and vasoactive drugs.<sup>10,27–31</sup> In the present study, the decrease in PWV in the highest alcohol intake group (10 to 35 glasses/week) compared with nondrinkers was  $\approx 6\%$ , and an 8% decrease was shown in the subgroup with an intake of 10 to 14 glasses/week. The decrease in PWV was only significant with an alcoholic beverage intake of 10 to 35 glasses per week, whereas HDL cholesterol had already increased significantly at much lower levels of alcohol intake. There could be several explanations for this discrepancy. Only high HDL cholesterol levels may cause a decrease in PWV (threshold effect). Alternatively, the decrease in PWV is only partly dependent on the alcohol-induced increase in HDL cholesterol. The latter may also clarify why the relation between

alcohol and PWV at the highest alcohol intake level could not be explained entirely by the increase in HDL cholesterol (see Table 3, model C). Finally, PWV can be regarded as a measurement that reflects long-term “damage” or exposure to elevated risk factors. It may be that an HDL measurement performed once does not capture that long-term exposure, and thus in a multivariate model, some relationship between alcohol consumption and PWV may remain. From a physiological point of view, part of the mechanism may be through atherosclerosis development being retarded in subjects with chronically higher levels of HDL. Because there is more than 1 determinant of atherosclerosis, this might explain the observed relation between alcohol consumption and PWV, independent of HDL levels.

Despite the adjustments made for several putative confounders, the possibility exists that the association between alcohol consumption and aortic stiffness may be due to some unmeasured factors, eg, diet or residual confounding. In addition, aortic PWV is an indirect marker of increased aortic stiffness or decreased aortic compliance and is affected by various hemodynamic factors such as blood pressure apart from the presence of atherosclerosis.

Although high alcohol consumption is associated with increased blood pressure,<sup>32</sup> this could not have influenced the results, because we adjusted for MAP. To determine the full effect of alcohol on the arterial wall, the use of ultrasound technology, which can estimate both function (stiffness) and morphology, may be preferable.

Information on the relation of alcohol intake and AIx is limited. In one study among 233 men, alcohol intake of  $>21$  drinks per week was related to a higher AIx, whereas for women ( $n=101$ ), no difference was found.<sup>25</sup> Unfortunately, no information was presented on dose dependency. Also, it appears from that study that no adjustments were made for physiological parameters or for cardiovascular risk factors.<sup>25</sup>

In the present data, unadjusted results showed a U-shaped relation between alcohol and AIx (Table 4, models A and B), with the highest AIx at an alcohol intake of 4 to 9 glasses per week. Yet, after adjustment for height and ejection duration, the relationship was attenuated (Table 4, model C). The main underlying mechanism of the effect of this adjustment is that in the present data, ejection duration and AIx were related to alcohol con-

**TABLE 4. Linear Regression Coefficients (95% CI) Describing the Difference in AIx (%) per Category of Alcohol Intake Compared With Nondrinkers**

Alcohol Intake Level, Glasses/wk	n	Model A	Model B	Model C
1–3	151	0.80 (–1.44 to 3.05)	1.11 (–1.09 to 3.30)	–0.14 (–1.95 to 1.68)
4–9	70	3.31 (1.10 to 5.52)*	2.82 (0.64 to 5.00)*	1.05 (–0.76 to 2.86)
10–14	51	0.33 (–2.21 to 2.86)	0.40 (–2.13 to 2.93)	0.08 (–1.99 to 2.15)
15–35	25	0.03 (–3.33 to 3.37)	–0.43 (–3.78 to 2.93)	–0.30 (–3.05 to 2.45)
$R^2$		2.5%	10.3%	40.7%

Model A: unadjusted; Model B: same as model A with additional adjustment for age, waist-to-hip ratio, body mass index, albumin, pulse pressure, and smoking; Model C: same as model B with additional adjustment for height, heart rate, and ejection duration.

\* $P<0.05$  vs reference group.  $R^2$  reflects proportion of variance in augmentation data explained by the model.

sumption in a similar manner: an increase at the low-intake level and a decrease at higher-consumption categories. Because AIx strongly depends on ejection duration, the crude analyses most likely reflect the relation of alcohol consumption with ejection duration. As far as we are aware, this has not been described previously and merits further research. Also, it again indicates that adjustments for physiological determinants of AIx are important to consider in such analyses, as has been proposed previously.<sup>10,26</sup>

Recently, it has been suggested that a gender-specific transfer function may preferably be used when radial applanation tonometry is used to estimate central aortic pressures.<sup>33,34</sup> That suggestion was based on the differences found in estimated central parameters and directly measured central parameters obtained in 87 subjects who underwent PTCA or coronary angiography. Hope and coworkers<sup>33,34</sup> found that in general, transfer function may underestimate or overestimate central indicators. Whether the overestimation or underestimation involves a random phenomenon or would lead to a shift in the distribution is unclear. The first possibility would lead to attenuation of the associations under study, a null finding as found in the present study. Some evidence is presented by Hope and coworkers on this aspect. However, if the transfer function would give completely "random" values from the true values, one would expect that no relations with risk factors would be seen. This clearly was not the case in the present study. The latter possibility, a systematic shift in distribution, would lead to a biased estimate of the magnitude of the association but would not affect the internal validity of the study. If this were applicable to the present results, it would imply that our findings are correct.

There are several markers of arterial stiffness that can be assessed noninvasively. All have their pros and cons, as recently outlined by O'Rourke and coworkers.<sup>26</sup> In addition, the relation between aortic stiffness and AIx is not straightforward, because both parameters clearly reflect different aspects of the arterial tree and may have different determinants.<sup>10</sup> This was further exemplified in the analyses in the present study in which PWV and AIx showed relations with similar but also with different risk factors, which also differed in direction of the association, eg, ejection duration or alcohol consumption. Also, there was a modest positive relation between PWV and AIx. Again, a confounding role here was observed for height and ejection duration.

In conclusion, the results of the present study support a direct preventive effect of moderate alcohol intake on arterial stiffness, assessed by PWV measurements. This may explain part of the reduced risk of CVD associated with moderate alcohol use.

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