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Reviews

Systematic Review of the Effect of Daily Alcohol Intake on Blood Pressure

Christopher B. McFadden, Colleen M. Brensinger, Jesse A. Berlin, and Raymond R. Townsend

Numerous epidemiologic investigations have found an association between moderate intake of alcohol and increased blood pressure (BP). However, in controlled clinical studies that directly tested the effects of alcohol intake on BP, findings are inconsistent, perhaps because of differences in duration of alcohol use and the timing of BP measurements. In this setting, we performed a systematic review of trials that measured BP after a period of sustained alcohol intake (defined as daily intake of at least one alcoholic drink daily) in one group and that also had a control group of individuals who consumed no alcohol. Nine studies met the entrance criteria. The review demonstrated a significant rise in systolic blood pressure (SBP) and diastolic BP (DBP) of 2.7 mm and 1.4 mm Hg, respectively, after alcohol intake. An early effect of alcohol leading to a reduction BP (in the hours after exposure) and a later effect (next day) of raising BP led to smaller differences in the net effect of alcohol on BP when ambulatory BP monitoring measurements were compared with casual office- or clinic-based measurements. Our findings may have important implications for interpreting studies measuring the effect of alcohol on BP as well as for regular clinical care. These findings indicate that the timing of BP measurements after alcohol intake has a substantial effect on the magnitude and perhaps even the direction of BP change. Am J Hypertens 2005;18: 276–286 © 2005 American Journal of Hypertension, Ltd.

Key Words: Meta-analysis, ethanol, hypertension, human, controlled trials.

The observation that excessive intake of ethyl alcohol is associated with a higher BP is nearing its centennial mark. Lian, while caring for French military personnel, published his findings in 1915 demonstrating that soldiers consuming >2.5 L of wine per day were more likely to have higher BP[1] A landmark observational study published in 1977 reinforced a number of findings among smaller patient populations.[2–4] The 1977 report of the Kaiser-Permanente Multiphasic Health Examination Data, based on self-administered questionnaires from 83,947 men and women, reported difference in SBP as high as 11 mm Hg in individuals consuming six or more drinks per day compared with non-drinkers. Moreover, the investigators concluded that a threshold of three or more drinks per day (one drink generally being equal to 14 g of ethanol) was a risk factor for hypertension across races and in both sexes.[5] Other studies, challenging the threshold effect reported in the Kaiser-Permanente study, suggest an increase in BP at lower levels of intake.[6,7] With respect to temperance, the recent report of the Joint National Committee (JNC 7) suggests a fall in BP of 2 to 4 mm Hg associated with a reduction in alcohol intake, based largely on the meta-analysis data of Xin et al.[8]

Attempts to evaluate the association between alcohol intake and BP in a prospective manner are hindered by several limitations. These include the difficulty in designing experimental studies of chronic alcohol use, the potential for confounding due to alcohol withdrawal, the immediate vasodepressor effect of alcohol consumption, the appropriate timing and frequency of BP measurements, and the variability in type and frequency of alcohol intake. Small prospective studies suggest that daily alcohol intake, particularly when more than 42 g/day, raises BP.[9–19] However, most of these studies are not randomized and are contrasted by reports of well-designed trials using ambulatory BP (ABP) monitoring, finding no discernible effect of alcohol on mean BP.[20–22] Moreover, studies with more frequent BP monitoring have noted biphasic effects of

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From the Cooper Medical Center (CBMF), Camden, New Jersey; Division of Nephrology (RRT), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and Center for Clinical Epidemiology and Biostatistics (CMB, JAB), Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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Address correspondence and reprint requests to Dr. Raymond R. Townsend, University of Pennsylvania, 210 White Bldg, 3400 Spruce Street, Philadelphia, PA 19104; e-mail: townsend@mail.med.upenn.edu

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ethanol on BP,[22,23] suggesting that previous, well-recognized conclusions about the hemodynamic effects of ethanol on BP may have been exaggerated because of the timing and infrequency of BP measurement.

We performed a systematic review of prospective controlled human studies evaluating the influence of daily alcohol intake on BP to determine more precisely the hemodynamic effects of alcohol on BP. Specifically, we looked for investigations addressing change in BP after alcohol intake versus a non-ethanol control arm, during which no alcohol intake occurred, in hypertensive or nonhypertensive subjects whose baseline alcohol intake was light (<0.22 oz or 3 g/day), moderate (0.22 to <1.0 oz or 14 g/day), or heavy (>1.0 oz or 14 g/day) as defined by the National Institute on Alcohol Abuse and Alcoholism.[24]

Methods

A MEDLINE-based search used subject keywords "alcoholic beverages," "ethanol," "alcoholism," "alcoholic intoxication," and "temperance" to specify articles related to alcohol intake. This pool was then narrowed to articles including at least one of the following search terms: "hypertension," "anti-hypertensive agents," or "blood pressure." Articles were further limited to those published in English, containing abstracts, and regarding human subjects. A medical school liaison librarian assisted in the design and implementation of the search. These criteria and selected reference review produced 834 articles. Two authors (CBM, RRT) independently reviewed the abstracts or full articles to ensure compliance with the prespecified criteria. Nine articles were found to meet all criteria and included in the meta-analysis.[24–32] Reasons for exclusion of the remaining 825 articles include observational studies (214 articles), no ethanol intake or multiple interventions (147), review articles (146), BP not a prespecified endpoint (100), animal or in vitro studies (96), duration of observation <24 h (48), case series or case reports (46), poorly described non-ethanol control phase or ethanol during non-ethanol control phase (20), and unclear ethanol dose (eight articles).

Statistical Analysis

There were two primary aims of the statistical analyses. The first aim was to provide an overall summary of the mean change in BP in subjects whose BP was measured after alcohol consumption compared with values after non-ethanol control consumption. Non-ethanol control typically comprised an isocaloric non-ethanol solution similar in volume to the ethanol consumed. The second aim was to explain differences in BP changes among the studies by evaluating factors that we anticipated, a priori, to potentially affect study results such as the study design (randomized versus non-randomized), ascertainment method (ambulatory BP monitoring versus office or clinic BP), and the dose of alcohol used. Because our search identified randomized and non-randomized studies, we tested whether differences were present in SBP or DBP based on this aspect of study design. We also evaluated the possibility of publication bias in the observed data, that is, the selective publication of results with statistically significant findings. All analyses were performed using STATA version 7.0 (STATA Corp., College Station, TX). All P values reported are two sided.

To accomplish the first aim, we determined fixed- and random-effects summaries of the data for SBP and DBP. All studies were of a cross-over design, making the outcome measure of interest the mean within-subject difference in BP between measurements after alcohol consumption versus after non-ethanol control consumption. In the fixed-effects summary, we took a weighted average of the within-study mean differences, with weights equal to the inverse of the variance of that within-study difference in means. In the random-effects summary, we also took a weighted average but incorporated the among-studies variability of the results into the weights.

Variance Imputation

Only one study[31] reported the mean and variance of the differences in BP. The remainder reported the mean and standard deviation for the BP after alcohol consumption and separately after non-ethanol control. Using the P value for the statistical difference in the means reported in the first study allowed us to calculate the variance of the differences in the remaining studies. Specifically, knowing the variance of the difference and the post–ethanol consumption and post–non-ethanol control consumption variances in the study allowed calculation of the implied correlation between the post-alcohol and post–non-ethanol control measurements. We estimated these correlations for SBP ($R = 0.05$) and DBP ($R = 0.39$) from the single study and then applied these correlation estimates to the estimates of the post-alcohol and post–non-ethanol control from the remaining studies to estimate the variance of the difference in each of those studies.[33] As a sensitivity analysis, we also assumed for the remaining studies that the correlation between the post-alcohol and post–non-ethanol control values was 0.5, re-estimated the change variances under that assumption, and re-calculated the summary estimates under this assumption. Because the results of the two approaches agreed very closely, we report only the main analysis involving the actual correlation estimates.

To assess the possible influence of study design on results, we used the STATA "meta reg" routine to perform meta-regressions. These analyses regress the mean difference in BP against individual study characteristics. Because of the small number of studies, we assessed only one study level covariate at a time. Specifically, the covariates that we examined were: the use of randomization (yes or no) in assigning the order of alcohol versus non-alcohol measurements; whether an ambulatory BP monitor was used; and dose of alcohol (analyzed in two ways: as a

continuous variable and dichotomized as <1 mg/kg/day *v* ≥1 mg/kg/day). We could not examine the effect of whether the subjects were fed versus fasted because all nine studies included only fed subjects.

Three studies reported BP at several times after alcohol consumption.[24,28,31] For these studies, the primary analyses used the average of all these measurements and are reported as "average value analyses." One study reported results for three independent groups[30]; these groups were treated as individual studies in the analysis, leading to a total of 11 groups in the final analysis.

To assess qualitatively the effects of time of measurement since alcohol consumption, we plotted the values of the change in BP (between the post-consumption and non-consumption values) against time. We then performed separate summaries including the longest and shortest follow-up times for each of the three studies. The results for the longest follow-up closely resembled those using the averages over time, so we report only the results for the average and the shortest follow-ups. Finally as a test of publication bias, we used the method described by Egger as implemented in the STATA "metabi/as" routine.[34]

Results

Table 1 lists characteristics of each of the included studies. Importantly, the nine studies included relatively limited variability in the levels of alcohol use, with most studies falling into the range of moderate to heavy drinking. Limitations in baseline ethanol intake data restricted exact classification as three studies did not report baseline alcohol intake, and several included ranges crossing the previously described category levels of the National Institute on Alcohol Abuse and Alcoholism. Baseline intake in the remaining six studies ranged from 10 to 70 g/day. Spirits in the form of vodka or whiskey were the predominant form of ethanol ingested. The studies included both hypertensive and non-hypertensive subjects. In the four studies that included hypertensive subjects, an antihypertensive medication washout period of at least 1 week was imposed before the initiation of the study. Similarly, among the studies reporting this aspect, an ethanol-free washout period of 7 days was included. Periods of at least 4 days of daily alcohol or non-ethanol control solution intake preceded any BP measurements in all studies (Table 1). Neither the baseline level of alcohol intake nor baseline BP was predetermined as entrance criteria.

The overall effect of alcohol intake on BP was a 2.7–mm Hg elevation in SBP and 1.4–mm Hg elevation in DBP (Table 2). For the three studies reporting measurements of BP at multiple time points after alcohol consumption, we used the average BP over the entire measurement period. In general, the effects were small and the findings were quite heterogeneous across studies. Results of the overall summaries (Tables 2 to 4) are presented using both fixed and random effects models; the text contains fixed effects results only. Differences result from heterogeneity of findings across studies and from the fact that small studies tended to show larger differences related to alcohol. Figures 1 and 2 display these results graphically for SBP and DBP, respectively.

Investigations of potential sources of heterogeneity revealed no association between study findings and either the use of randomization in the study or the dose of alcohol administered, for the average value analyses. In particular, the *P* values comparing the BP in the randomized with the non-randomized studies were .88 for the SBP pressure and .54 for the DBP. However, there was a very pronounced effect of the use of ABP monitoring on study results ($P < .001$ for the difference between the effect of alcohol in studies using ABP compared with studies not using ABP, for both SBP and DBP). Table 3 presents the summary effects of alcohol separately for the ABP and non-ABP studies. Overall, ABP-based studies noted a 0.6–mm Hg decrease in SBP and 0.2–mm Hg decrease in DBP after alcohol consumption. This contrasted sharply with non-ABP studies, with the latter showing an 8.8–mm Hg increase in SBP and 5.9–mm Hg increase in DBP after alcohol consumption. Only non-ABP results are significant between post-ethanol and post–non-ethanol control. The heterogeneity of the findings was considerably reduced after stratification on ABP use. Consequently, the results of fixed and random-effects models agree closely in these stratified analyses.

The effects of time between alcohol consumption and measurement of BP are shown in Figs. 3 and 4 using data from the three studies reporting multiple time points. All of these studies used ABP recordings. To quantify these findings, the effect of alcohol is summarized separately using the shortest and the longest time period measured in these three studies. For the longest period, the results closely paralleled those using the average over the entire period. For the shortest periods, the results are displayed in Table 4. The effect of alcohol at the shortest time period is significantly negative, averaging an 11.6–mm Hg SBP decrease and a –7.9 mm DBP decrease at an average time of 5 h in the three studies analyzed.

In the longer-value analyses, we were unable to assess the association between dose and the magnitude of the BP effect because of the lack of variability in dose across studies. In other regression models, the association between ABP and the effect of alcohol on outcome was consistent even after adjusting for other variables.

There was no significant evidence of publication bias, as evidenced by the non-significant *P* values of .40 for SBP and .29 for DBP generated by the Egger test.[34]

Discussion

The data in this systematic review reveal important information regarding the relationship between alcohol intake and BP elevation, the temporal nature of this relationship, and the manner in which measurement technique can influence these findings. Alcohol raises BP in a small but

Table 1. Study characteristics

et al, 1984([24])	14	33 g/day	2,8	Spirits	0.47 g/day	7 days	136/83	137/82	No	Yes	Yes	Yes	Not given	7d + 4d
Howes et al, 1990(25)	11	Not described	Not described	Vod	1 g/day	4 days	134/77	132/77	Yes	Yes	Yes	No	Not given	Ns + 4d
Howes LG et al, 1990(26)	8	10–70 g/day	Not described	Vod	66 g/day	4 days	122/70	116/2	Yes	No	No	No	Not given	Ns + 5d
Howes LG et al, 1995(27)	10	g/day	Not described	Bser or Spirits	60 g/day	4 days	120/66	112/10	Yes	No	No	No	Not given	Ns + 4d
Kawano Y et al, 1986(28)	16	31 g/day	103	Spirits	0.47 g/day	7 days	137/83	133/84	No	Yes	Yes	Yes	Japanese	7d + 7d
Kumagai Y et al, 1993(29)	7	39 g/day	28	Spirits	g/day	6 days	121/71	128/70	Yes	Yes	Yes	No	Japanese	7d + 5d
Malhotra H et al, 1995(30)	10	<150 g/ week	Not decribed	Spirits	g/day	5 days	123/32	130/0	No	No	No	No	Not given	14d + 5d
	10	<150 g/ week	Not decribed	Spirits	g/day	5 days	178/101	183/38	No	No	No	Yes	Not given	14d + 5d
	10		Not decribed	Spirits	g/day	5 days	176/105	183/38	No	No	No	Yes	Not given	0d + 5d
Ocallaghan CS et al, 1985(31)	12	9.7 g/day	10.7	Spirits	g/day	4 days	124/50	125/8	No	Yes	Yes	No	Not given	Ns + 4d
Howes LG et al, 1992(32)	11	Not described	Not described	Vod	g/day	4 days	124/50	126/10	Yes	Yes	Yes	No	Not given	Ns + 4d

ABP = ambulatory blood pressure; BP = blood pressure; Etoh = ethanol; NS = not stated in Methods; Tx = treatment.

*One single value reported

†Values reported as mean if

‡

§First value is alcohol time period, second value is duration of -alcohol before

Table 2. Blood pressure change overall using average

	Pooled Est.	95% CI Lower	95% CI Upper	*P* Value	Number
SBP					
Fixed	2.7	0.9	4.5	.003	11
Random	3.6	0	7.3	.052	11
Test for heterogeneity, $P < .01$					
DBP					
Fixed	1.4	.5	2.2	.002	11
Random	2.2	0	4.4	.046	11
Test for heterogeneity, $P < .01$					

DBP = diastolic blood pressure; Est. = estimate; SBP = systolic blood pressure.

statistically significant manner, averaging 2.7 mm for SBP and 1.4 mm Hg for DBP across all studies using a fixed-effects model.

The effect is significantly influenced by whether ABP measurements are taken as part of the evaluation; a major reason for this effect is the early vasodepressor effect of alcohol intake, as seen in Figs. 3 and 4. This phenomenon has been described[22,23]; yet, determining how to integrate these findings into non-ABP studies and, more importantly, into clinical care is not well understood. Specifically, after the vasodepressor effect, a moderate but significant elevation is observed. That this change occurs 10 to 15 h after ingestion—similar to when many patients may have been seen in casual BP measurement studies and in regular physician visits—is of clinical concern, given the common scenario of drinking alcohol during evening hours. This potential confounder may explain the rather striking differences between the ABP and non-ABP studies observed in this study and previous publications. Alternatively, the immediate vasodepressive effect of alcohol may bias studies assessing hypertensive status in an uncontrolled setting.

In our findings, the difference between the average change in SBP and DBP associated with alcohol intake, as measured by casual versus ABP recordings, was 9.4 and 6.1 mm Hg, respectively (Table 3). The overall average BP change, as

Table 3. Blood pressure change by recording method

	Pooled Est.	95% CI Lower	95% CI Upper	*P* Value	Number
ABP					
SBP					
Fixed	−0.6	−2.8	1.6	.6	6
Random	−0.6	−2.8	1.6	.6	6
Test for heterogeneity, $P = .99$					
DBP					
Fixed	−0.2	−1.2	0.8	.7	6
Random	−0.2	−1.2	0.8	.7	6
Test for heterogeneity, $P = .93$					
Non-ABP					
SBP					
Fixed	8.8	5.8	11.8	<.01	5
Random	8.3	3.5	13.1	<.01	5
Test for heterogeneity, $P = .04$					
DBP					
Fixed	5.9	4.2	7.6	<.01	5
Random	5.7	3.5	7.9	<.01	5
Test for heterogeneity, $P = .17$					

Abbreviations as in Table 2.

Table 4. Effects for shortest time periods (5 hs)

	Pooled Est.	95% CI Lower	95% CI Upper	*P* Value	Number
SBP					
Fixed	−11.6	−14.2	−9	<.01	3
Random	−9.8	−15.7	−3.8	<.01	
Test for heterogeneity, *P* = .06					
DBP					
Fixed	−7.9	−9	−6.8	<.01	3
Random	−7.9	−9	−6.8	<.01	
Test for heterogeneity, *P* = .69					

Abbreviations as in Table 2.

recorded by ABP devices only, was negative, although it did not reach statistical significance. Other studies evaluating the effect of interventions as measured by ABP versus casual office BP measurement have reported similar findings, which have been ascribed to a lack of placebo and white-coat hypertension effects on ABPM.[35,36]

A unique feature described here is the comparison of BP differences between the shortest and longest follow-up periods in the ABP studies. The SBP and DBP decreased 11.6 and 7.9 mm Hg, respectively, at the early time period in the three studies that presented multiple readings. The long-term readings, at an average of 20 h, were not sub-

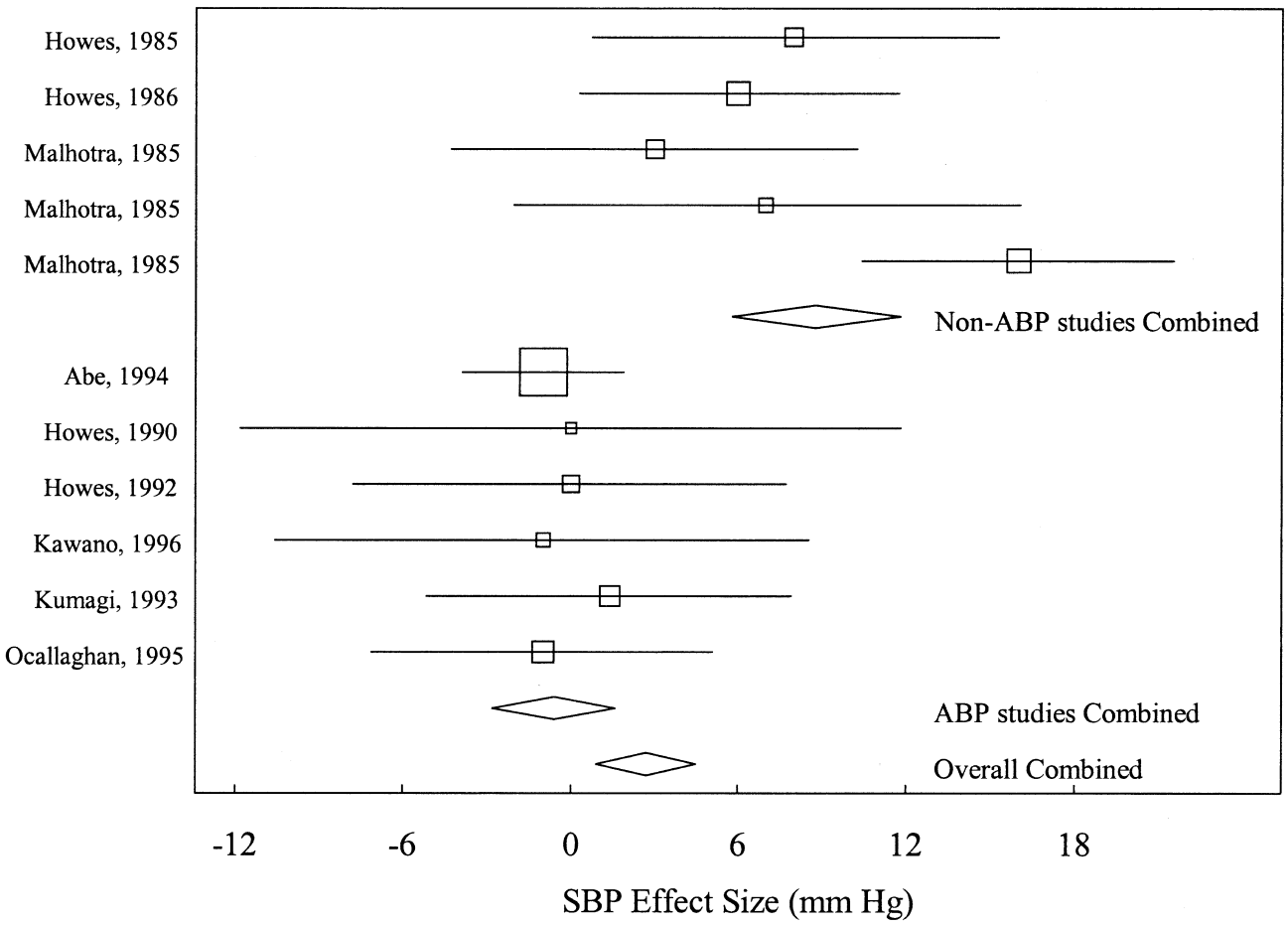

FIG. 1. Effect on systolic blood pressure (SBP) across all studies after ethanol intake, including 95% confidence intervals (CI). Box sizes are proportional to numbers of enrollees. Upper five studies used conventional SBP measurements, whereas the lower six studies used ambulatory blood pressure (ABP) monitoring recordings for SBP measurements. Size of **diamond** beside each blood pressure measurement method is proportional to SBP effect with 95% CI. Summary **diamond** at bottom of figure incorporates combined SBP effect.

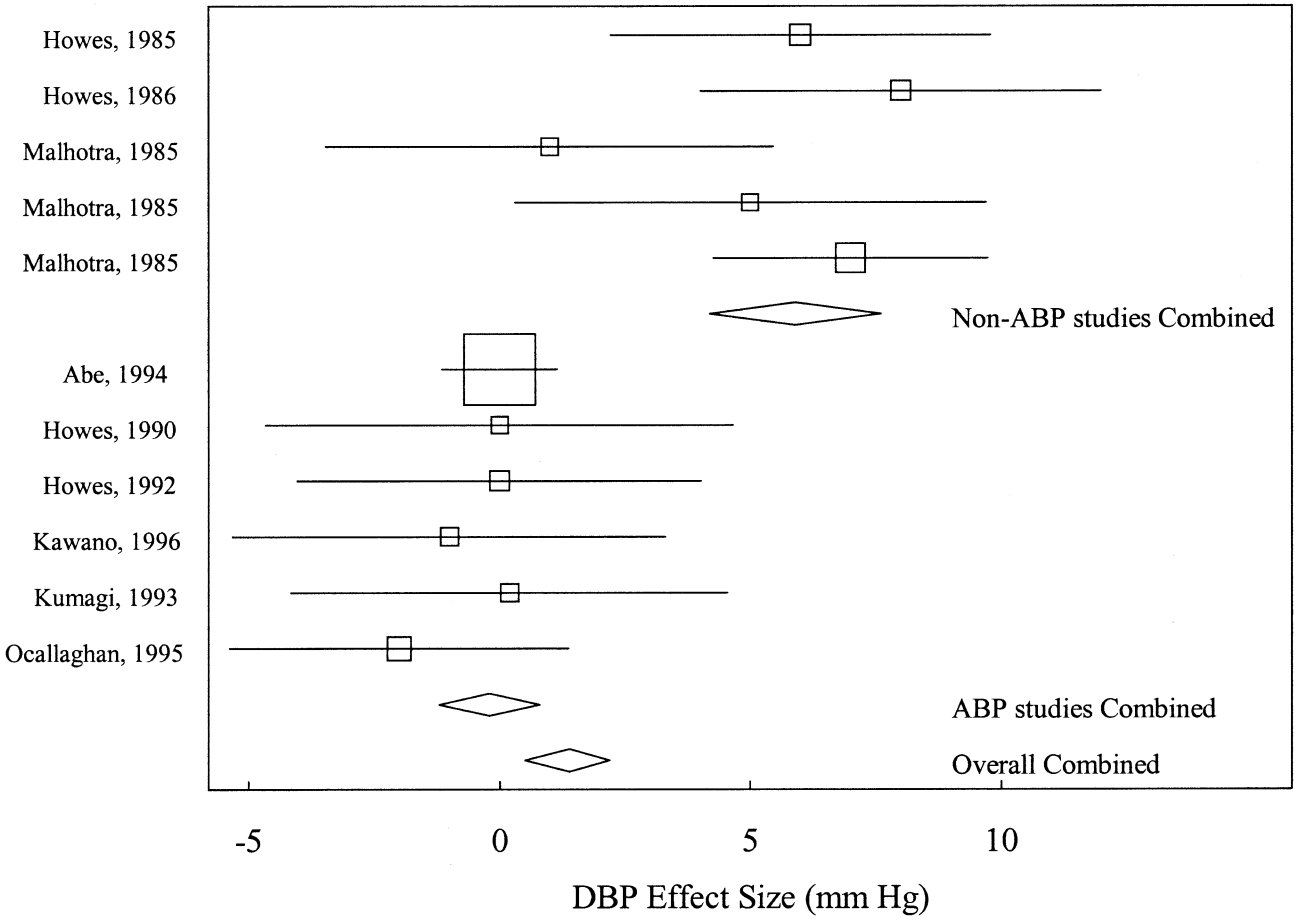

FIG. 2. Effect on diastolic blood pressure (DBP) across all studies after ethanol intake, including 95% confidence intervals. **Box sizes** are proportional to numbers of enrollees. Upper five studies used conventional DBP measurements, whereas lower six studies used ABP recordings for DBP measurements. **Diamond** beside each blood pressure measurement method is proportional to DBP effect with 95% confidence interval (CI). Summary **diamond** at bottom of figure incorporates the combined DBP effect.

stantively different from the average change, which for ABP studies alone did not reach statistical significance. In contrast, non-ABP average BP recorded at a similarly long follow-up did reach significance.

Our study includes both ABP and casual BP measurement investigations. Because studies that used ABP measured post-treatment (alcohol) or post–non-ethanol control consumption with the same method, we believe that this is comparison is valid and should not be thought of as mixing distinct measurement techniques. Instead, the change in BP, regardless of measurement technique, was the measurement from which conclusions were drawn. Ideally, however, studies that include both casual and ABP methods of BP change ascertainment would be the best way to ensure the similarity of these methods of BP determination in studying the effects of alcohol on BP. Thus, some caution in the interpretation of our data is warranted.

Previous literature has called attention to the period after alcohol consumption as a potentially important mediator of alcohol-associated vascular damage.[22,37] As we show in this systematic review, despite limited changes in the mean BP readings, there is a significant rise in BP between the 4-h nadir in BP readings and peak levels approximately 10 h later (Figs. 3 and 4). An extension of this finding is the potential effects of alcohol on the normal circadian rhythm of BP.[20]

This study adds to the meta-analysis of Xin et al.[8] Their work examined the effect on BP of a reduction in alcohol intake using randomized clinical trial data, whereas our efforts were directed toward studies that directly administered alcohol. The magnitude of their pooled responses, a reduction in SBP of 3 mm Hg and a reduction in DBP of 2 mm Hg, are very similar to the values that we observed when alcohol was given. Their studies included mostly heavy drinkers (those who consumed more than three drinks per day), whereas our study included a greater range of baseline alcohol intake. In our study we noted the differences in BP outcome depending on the type of BP determination method used, whereas all but one of the studies by Xin et al were based on office or clinic BP.

The potential for weight gain associated with alcohol intake is an important issue. In the group of studies included in our review, four studies documented equal weight during the alcohol and non-ethanol control phase, and four studies did not document weight. Importantly,

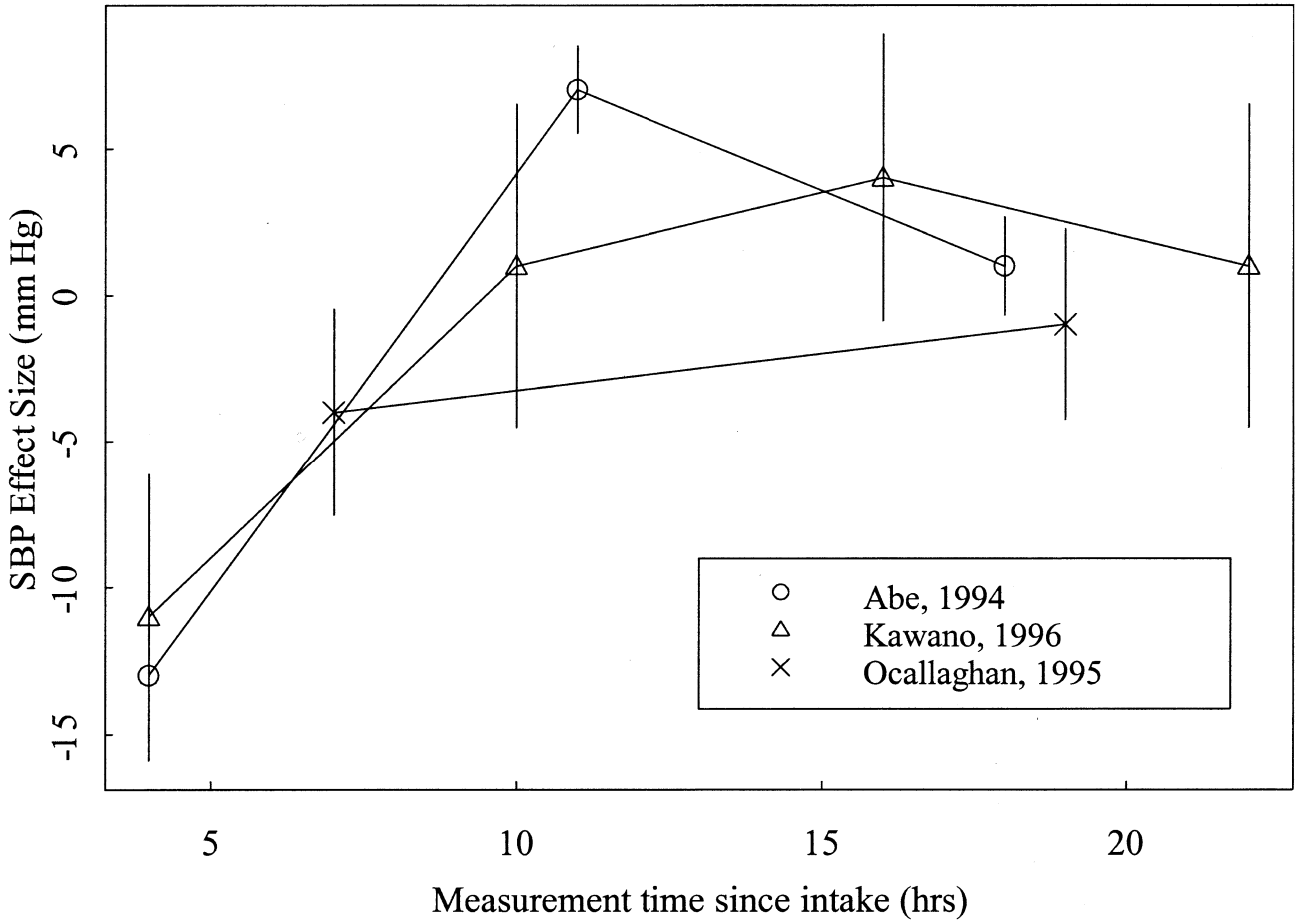

FIG. 3. Overall results (systolic blood pressure [SBP]) for studies reporting multiple readings after alcohol intake. All three studies used ambulatory blood pressure measurements.

three of the studies not documenting weight included isocaloric diets during the study interventions. One study did not describe either,[29] and one study noted a significant decrease in weight during the alcohol intake phase.[28] Given that this is opposite to the expected role of weight gain confounding the positive effect of alcohol on BP,[13,14] it is likely that this finding only reduced any potential effect of alcohol intake on BP elevation.

Most interventional studies, whether included or not included in our study, use alcohol intake over a set period for a reasonable reproduction of social alcohol intake. The included studies ranged from 1 to 8 h in the evening; none exceeded an 8-h intake period. Although at least one study exists that evaluates a more continuous intake of alcohol in a population of alcoholic patients, in this case by regular intravenous infusion, methodologic issues make generalizable conclusions from that study difficult.[9] Defining the importance of timing of intake, particularly sustained versus intermittent, is another area needing further investigation.

A wide variation in alcohol intake at baseline existed in the studies included in this review. Nonetheless, an adequate washout removed the potential for alcohol withdrawal to influence findings. Interestingly, in the one study that stratified groups by alcohol intake,[30] the group with a higher baseline alcohol intake had higher BP after controlled alcohol intake. This point is worth further investigating in a prospective fashion.

Efforts to provide information about hypertension and "binge" drinking have been revealing. After exposure to 2.2 g of alcohol per 1 kg of body weight in one evening, in comparison to a control evening, a group of subjects were noted to increase SBP and DBP by 5 mm Hg during the period of intoxication.[38] Blood pressure subsequently fell during the periods when alcohol levels were falling. These findings suggest some threshold level at which the previously described vasodepressor effect of alcohol is overcome, perhaps by excessive sympathetic stimulation. As evident in Table 1, seven of nine studies that we reviewed used 1 *g* of alcohol per 1 kg of body weight daily, which did not allow us to contrast the effects of alcohol amounts on BP changes. Better defining this dose-response relationship is one area of potential future research. We were unable to factor in amount and duration of previous alcohol consumption because such information was inconsistently reported in the studies that we reviewed.

One important criterion for study inclusion was the

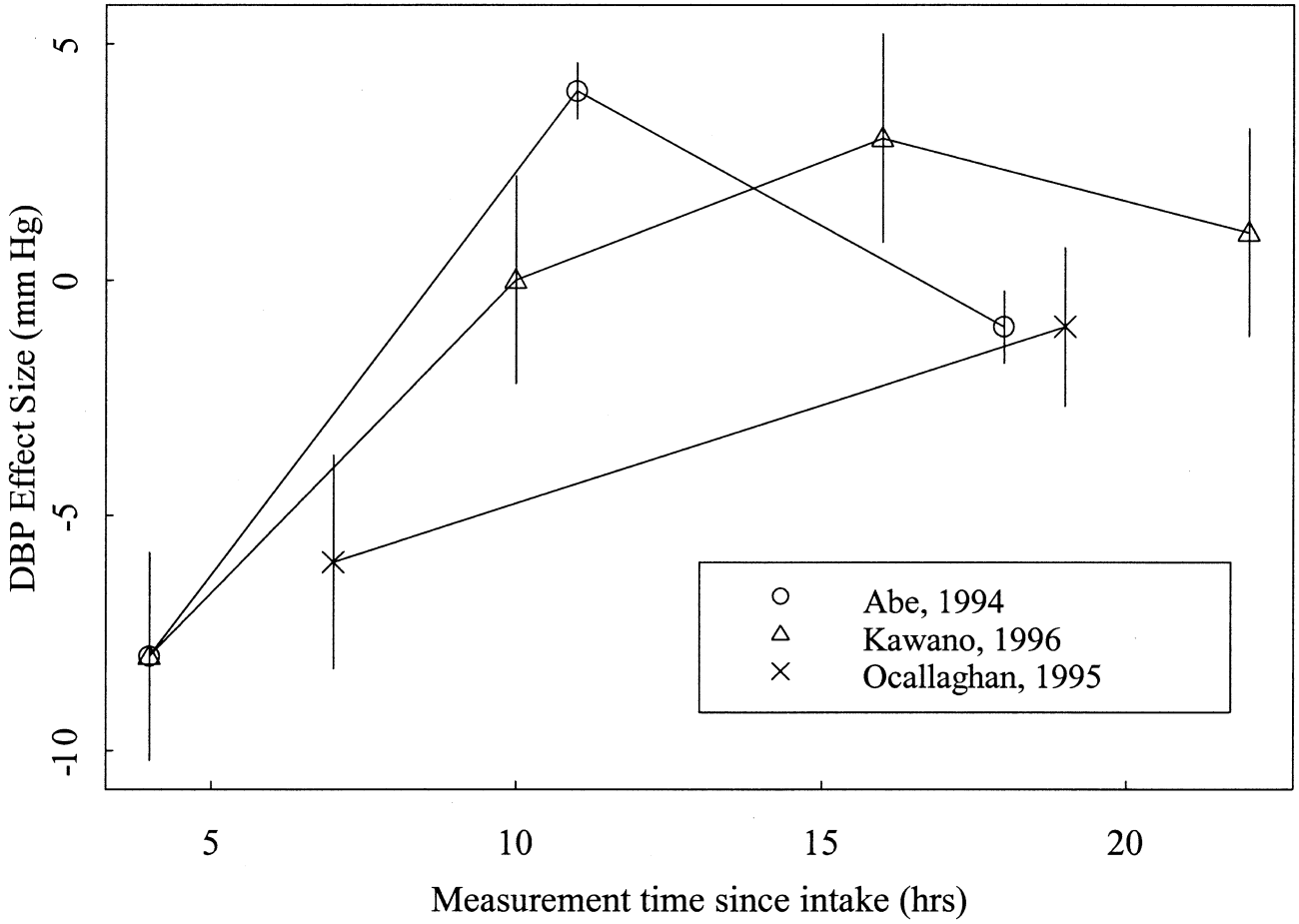

FIG. 4. Overall results (diastolic blood pressure [DBP]) for studies reporting multiple readings after alcohol intake. All three studies used ambulatory blood pressure measurements.

absence of alcohol intake in the non-ethanol control phase. As a result, some well-designed studies do not show up in the analysis but deserve mention nonetheless. One set of investigators prospectively evaluated the effect of reduction of chronic alcohol intake, although not to zero, through questionnaires in series of hypertensive and nonhypertensive patients. In the hypertensive group, a reduction of alcohol intake sustained for 6 weeks, from 472 mL/week (222 *g*/week) to 64 mL/week (30 *g*/week), was associated with reductions in BP.[13] When controlled for weight loss, the reduction in alcohol intake was associated with falls in SBP and DBP of 0.8 mm Hg and 0.7 mm Hg, respectively, for each 100 mL/week (47 *g*/week) decrease in alcohol intake. A study in normotensive men demonstrated similar findings.[14] These data are similar to our findings.

Limitations of this review can be considered in two regards. First, the review is limited by the strengths and weaknesses of its composite studies. An important finding is the lack of a variety of racial groups and the paucity of female subjects included in the studies. Most studies involved white or Asian (generally Japanese) men. African Americans are not well represented, though several studies do not describe the racial/ethnic backgrounds of their participants. Similarly, women are not appropriately represented, with only one of nine studies including women.[27] Given observed the differences in the risk of hypertension in African American men in a recent cohort study,[39] ensuring adequate racial representation in further studies is essential.

Additional limitations include the relative small number of studies and sample size, the over-representation of one group's work because of our entry criteria, and the lack of long-term follow-up. In defense of these criticisms, our a priori entry criteria were intended to exclude settings in which partial dose reduction, particularly when quantified by retrospective questionnaires, increased the variability of findings. Similarly, rigorous dose-response studies can only feasibly be accomplished in a relative short period.

The meta-analysis technique used in this review relies on assumptions about the majority of studies regarding the variance of the differences. For our primary analyses, we based these assumptions on the variance observed in one study,[31] and the correlation between post-alcohol and post–non-ethanol control BP implied by those variance estimates. We assessed the sensitivity of our results to that assumption by applying a correlation of 0.5 to alcohol

intake and BP. Similar findings were observed, consistent with reports validating this imputation approach in the methodologic literature.[33] These studies also revealed little evidence of publication bias. The use of aggregate-level (published) data also precluded examining predictors of BP at the individual subject level.

Finally, our review identifies several aspects of this relationship that should be kept in mind and that deserve further attention. First, the temporal relationship is critical. This confounding issue warrants the more frequent use of ABP devices to assess better the 24-h alcohol and BP interaction. Supporting this recommendation is one study showing that although alcohol consumption was not related to ABPM measurements of BP, there was a significant relationship found between alcohol consumption and the difference in clinic BP compared with values obtained by ABPM (that is, a "white-coat" component).[40] This variability likely requires the use of other surrogate cardiovascular markers besides BP in any future studies evaluating the beneficial effect of reducing alcohol intake. Further studies are needed to scrutinize more closely the timing of alcohol intake and cardiovascular risk. In addition, future studies should include a broader racial profile and increased number of female subjects. Finally, future studies should aim to clarify the dose-response effect, which appears to reach a threshold at some point between 1 and 2 *g*/kg/day. Pending further answers, alcohol intake is certainly worth questioning about when pursuing lifestyle modifications and the treatment of resistant hypertension.

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