Title: Exploring the Impact of Modifiable Risk Factors on Outcomes in the QUARTET USA Study: A Secondary Data Analysis

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**Abstract**

**Background**. Hypertension is a global health concern that contributes significantly to stroke and premature mortality. Lifestyle factors such as tobacco use, alcohol consumption, and caffeine intake are related to hypertension development and management. This secondary analysis of the completed QUARTET USA study aims to investigate the association between lifestyle factors and blood pressure among hypertensive individuals who have undergone medical therapy for their hypertension.

**Methods**. Primary outcomes of interest include systolic and diastolic blood pressure measured at a follow-up visit 12 weeks after random assignment in the QUARTET USA study. Predictors of interest include participants’ baseline smoking frequency, alcohol consumption, and caffeine consumption. Descriptive statistics summarized participant lifestyle and baseline clinical results overall and within the study arm. Primary analyses involved multiple linear regression models adjusting for the study arm and baseline blood pressure.

**Results**. Among 62 participants enrolled in this study, 32 were randomly assigned to receive ultra-low-dose quadruple-combination therapy, and 30 were allocated to receive a monotherapy comparator. Overall, 32%, 28%, and 77% of participants reported smoking, alcohol use, and caffeine intake at baseline, respectively. In terms of follow-up systolic blood pressure, the slope estimate of smoking was 0.58 (95% CI = [-0.09, 1.26]). The slope estimate of alcoholic drinks was 0.02 (95% CI = [-0.70, 0.74]). The slope estimate of caffeinated beverages was -0.20 (95% CI = [-0.67, 0.28]). We observed similar results for diastolic blood pressure.

**Conclusion**. While smoking, alcohol, and caffeine intake are known contributors to cardiovascular risk, their correlations with blood pressure after medication in this study's context were not evident. Comprehensive approaches integrating lifestyle modifications alongside medical treatment remain crucial for hypertension management. Further research with larger sample sizes and longer follow-up periods is warranted to illuminate the role of lifestyle factors in hypertension management comprehensively.

**Introduction**

Hypertension, or high blood pressure, stands as a significant global health concern due to its high prevalence and associated health risks. According to the World Health Organization, hypertension contributes to approximately 13% of deaths worldwide, making it one of the leading causes of cardiovascular diseases, stroke, and premature mortality.1 Given its multifaceted nature, many factors contribute to the development and exacerbation of hypertension, including lifestyle habits such as tobacco use, alcohol consumption, and caffeine intake.2 The possible roles of other factors such as caffeine consumption are less clear.3

The consumption of tobacco has long been recognized as a significant risk factor for hypertension. Nicotine, the primary psychoactive component of tobacco, has various physiological effects on the cardiovascular system, including vasoconstriction and increased heart rate, which can elevate blood pressure.4 Additionally, the toxins present in tobacco smoke can damage blood vessel walls, leading to arterial stiffness and hypertension over time.5 Despite widespread awareness campaigns and smoking cessation efforts, tobacco use remains a prevalent risk factor for cardiovascular diseases globally.

Similarly, excessive alcohol consumption has been linked to hypertension through multiple mechanisms. Chronic alcohol consumption can disrupt the balance of the renin-angiotensin-aldosterone system, leading to sodium retention and increased peripheral vascular resistance, thereby elevating blood pressure.6 Moreover, alcohol abuse can contribute to obesity and dyslipidemia, further exacerbating the risk of hypertension and cardiovascular complications.7 While moderate alcohol consumption has been associated with potential cardiovascular benefits,8 excessive intake leads to substantial health risks, including hypertension and its complications.

Besides tobacco and alcohol, caffeinated drinks are also widely consumed all over the world. Caffeine, a psychoactive stimulant found in coffee, tea, and various beverages, has complex effects on blood pressure regulation. Acute caffeine intake has consistently been shown to increase systemic blood pressure, predominantly through effects on systemic vascular resistance.9 However, habitual caffeine consumption may lead to tolerance and weakening of these acute effects, with some studies suggesting that moderate coffee intake may not significantly impact long-term blood pressure levels.3 Nonetheless, individual responses to caffeine vary, and excessive consumption or sensitivity to its effects may contribute to hypertension in susceptible individuals.

Understanding the associations between these lifestyle habits and blood pressure can inform targeted interventions and public health strategies aimed at reducing the burden of hypertension and its associated complications in hypertensive populations, especially in generally underserved and underrepresented patient populations. In this secondary data analysis of a completed clinical trial, we seek to examine the association between lifestyle factors—including smoking frequency, alcohol intake, and caffeine intake—and blood pressure among individuals with hypertension, both cross-sectionally and after a period of treatment.

To accomplish these aims, we leverage the QUARTET USA study data;10,11 QUARTET USA is a double-blind randomized controlled trial conducted in federally qualiﬁed health centers (FQHC) in a large city in the US. It aimed to examine whether initiating treatment with ultra-low-dose quadruple-combination therapy (LDQT), or 4 drugs in 1 pill, will lower blood pressure more effectively with fewer side effects, compared with initiating standard dose monotherapy in treatment-naive patients and patients on monotherapy.10,11 The QUARTET USA study thus provides an opportunity to examine the relationship between blood pressure and the aforementioned lifestyle factors in a unique and underrepresented population from lower-resourced health settings who already have hypertension and have undergone medication therapy for it.

**Methods**

**Study Design**

This manuscript reports on a secondary analysis of the completed QUARTET USA study; the study design10 and primary results11 are published elsewhere and available on clinicaltrials.gov (NCT03640312). Briefly, the QUARTET USA study was an active comparator-controlled randomized trial assessing the efficacy and safety of an LDQT (combination therapy of candesartan 2 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg) for hypertension. Participants with high blood pressure (systolic 130-179 mmHg or diastolic 80-109 mmHg) were recruited for this 12-week double-blind, type-I hybrid effectiveness-implementation randomized controlled study and those who met the eligibility requirements were randomized 1:1 to either the LDQT arm or the active comparator arm (candesartan 8 mg; Figure 1). After the baseline visit and randomization, participants returned to the clinic for follow-up visits at 6 weeks and 12 weeks.

**Outcomes**

The primary outcomes of interest in this secondary analysis are systolic and diastolic blood pressure (SBP and DBP, respectively) measured at an in-person follow-up visit 12 weeks after randomization, both variables will be treated as continuous in analyses. We considered these co-primary outcomes and analyzed each of them separately, reserving a 5% type-I error rate for null hypothesis tests for each of them. Predictors of interest include participants’ baseline daily smoking frequency, weekly alcohol intake, and weekly caffeine intake. The QUARTET USA study participants self-reported the average amount of smoking (cigarettes, e-cigarettes, cigars, and pipes) per day, the average number of standard drinks (wine, spirits, and beer) per week, and the average number of caffeinated beverages per week. In these analyses, the average amount of smoking is calculated by adding together the consumption of cigarettes, e-cigarettes, cigars, and pipes per day, and the average number of standard drinks is calculated by adding together the consumption of wine, spirits, and beer per week.

**Analysis**

Descriptive statistics summarized participant lifestyle and baseline clinical outcomes overall and within the study arm: proportions with percentages for categorical variables and median with interquartile range for continuous variables. We evaluated pairwise relationships among smoking, alcohol, and caffeine use via Spearman’s correlation, along with 95% confidence intervals for correlation coefficient estimates. Primary analyses involved multiple linear regression models. Separate linear regression models were fit for each outcome (SBP and DBP) and risk factor (smoking, alcohol, and caffeine) of interest. Models included adjustment for the study arm, as data were collected as part of a randomized controlled trial, and baseline measure of the outcome (e.g., models for SBP included the baseline SBP). We note that the study arm is not the focus of inference for these analyses, but an important source of variation for which we need to control given the context of the trial. Though we emphasize estimated coefficients and their uncertainty, we conducted 2-sided hypothesis tests for risk factors (α=0.05). Analyses did not adjust null hypothesis tests for multiple comparisons since these are exploratory data analyses. Residual diagnostics were used to assess model fit. Missing data were assessed numerically by summarizing the number of participants missing key baseline and outcome variables. There were no formal power or sample size calculations conducted for these analyses given that we are using the data from an existing study which had its own power and sample size considerations.10,11 All analyses were performed via R version 4.3.1 or higher.

**Results**

**Baseline Characteristics**

While the target sample size for the overarching QUARTET USA study was 87 participants, the study halted early due to low enrollment of 62 participants. As is shown in Figure 1, among the 62 participants, 32 were allocated to the LDQT group, and 30 were allocated to the monotherapy comparator group. There were 9 patients lost to follow-up during the 12 weeks of treatment, with 3 in the LDQT group and 6 in the monotherapy comparator group.

Table 1 summarizes participants’ baseline characteristics including demographic information, lifestyle information, and clinical results overall and by study arm. In terms of the sample lifestyle characteristics, most participants reported not smoking at baseline (69% in the LDQT arm, 67% in the control arm). The median number of smoking episodes per day was 0 in both arms. However, among participants who reported that they smoked, typical consumption was 5 cigarettes per day in the LDQT arm and 7 cigarettes per day in the control arm. Most participants reported no alcohol use at baseline (69% in the LDQT arm, 75% in the control arm). The median number of alcoholic drinks consumed per week was 0 in both arms. However, among participants who reported alcohol use at baseline, typical consumption was 4 drinks per week in the LDQT arm and 5 drinks per week in the control arm. Only a few participants reported no caffeine consumption at baseline (31% in the LDQT arm, 12% in the control arm). The median number of caffeinated beverages consumed per week was 2.5 in the LDQT arm and 7 in the control arm. Among participants who reported that they had caffeinated beverages, typical consumption was 6.5 beverages per week in the LDQT arm and 7 beverages per week in the control arm. Refer to Table 1 for additional characteristics. Notably, the median blood pressure for participants was 139.0/85.3 mmHg overall, and study arms were comparable concerning baseline variables.

**Relationship between Lifestyle Variables**

The Spearman's correlation analyses did not provide evidence of significant associations among the 3 lifestyle variables of interest. The sample Spearman correlation coefficient between the daily smoking frequency and weekly alcohol intake was 0.19 with a 95% confidence interval of [-0.08, 0.44]. The correlation between smoking frequency and caffeine intake was 0.25 [-0.02, 0.49], and the correlation between alcohol and caffeine intake was -0.14 [-0.39, 0.14].

**Relationship between Blood Pressure and Lifestyle Variables**

Figure 2 consists of 4 boxplots that compare both the baseline and the follow-up blood pressure measured at Week 12 among all participants according to whether or not participants reported consuming any alcohol, tobacco, or caffeine. Overall, participants who reported smoking tended to have lower systolic and diastolic blood pressure at baseline; the difference between smokers’ and nonsmokers’ systolic blood pressure appeared less pronounced at 12 weeks, though smokers tended to have higher diastolic blood pressure than nonsmokers at 12 weeks. Participants reporting any alcohol use tended to have higher systolic and diastolic blood pressure at baseline, though the difference in systolic blood pressure appeared to decrease by 12 weeks. Participants who reported consuming caffeine appeared to have lower systolic and diastolic blood pressure at baseline, though the difference in systolic blood pressure seems to have decreased by week 12.

Table 2 reports the slope estimates and corresponding 95% confidence intervals of participants’ average amount of smoking per day, standard drinks per week, and caffeinated beverages per week in 6 linear regression models; these results are displayed graphically in Figure 3. The slope estimate for smoking frequency was 0.58 for the follow-up systolic blood pressure (95% CI = [-0.09, 1.26]) and 0.39 for the follow-up diastolic blood pressure (95% CI = [-0.03, 0.81]). This implies that an increase of 10 cigarettes per day is associated with an increase in systolic blood pressure of 5.8 mmHg and an increase in diastolic blood pressure of 3.9 mmHg. The slope estimate for the number of weekly alcoholic drinks was 0.02 for the follow-up systolic blood pressure (95% CI = [-0.70, 0.74]) and 0.05 for the follow-up diastolic blood pressure (95% CI = [-0.40, 0.50]). This implies that an increase of 10 alcoholic drinks per week is associated with an increase in systolic blood pressure of 0.2 mmHg and an increase in diastolic blood pressure of 0.5 mmHg. The slope estimate for the number of weekly caffeinated beverages was -0.20 for the follow-up systolic blood pressure (95% CI = [-0.67, 0.28]) and -0.25 for the follow-up diastolic blood pressure (95% CI = [-0.54, 0.04]). This implies that an increase of 10 caffeinated beverages per week is associated with a decrease in systolic blood pressure of 2.0 mmHg and a decrease in diastolic blood pressure of 2.5 mmHg.

**Discussion**

The findings of this secondary analysis illuminate the relationship between lifestyle factors and follow-up blood pressure measurements among participants in the QUARTET USA study who had hypertension and underwent 12 weeks of medical intervention for it as part of the study. In this exploratory analysis based on a sample size of 56 participants, we did not find statistically significant evidence of a pairwise association among lifestyle habits including smoking, alcohol consumption, and caffeine intake, and estimated Spearman correlations were low. We also did not observe a statistically significant association between these lifestyle factors and blood pressure measurements 12 weeks following treatment initiation.

Our findings align with previous research highlighting the harmful effects of tobacco use on cardiovascular health, including its role in elevating blood pressure in the long term. The estimated positive association between smoking frequency and follow-up blood pressure at 12 weeks is consistent with established evidence linking smoking to increased cardiovascular risk.4 However, contrary to expectations, smoking frequency did not emerge as a significant predictor of blood pressure over the 12-week follow-up period in our analysis. This difference may suggest that other factors, such as medication adherence or genetic factors, could have influenced blood pressure among smokers in the study. Similarly, our analysis did not find statistically significant associations between alcohol consumption and follow-up blood pressure, despite previous evidence suggesting a potential link between excessive alcohol intake and hypertension. Also, the potential confounding effects of comorbidities and concurrent lifestyle factors may not be fully considered in this study. What is surprising is that these coefficients were nearly 0. Finally, the relationship between caffeine intake and blood pressure has been a subject of debate in the literature. While acute caffeine consumption has been shown to shortly elevate blood pressure, the long-term impact of habitual caffeine intake remains uncertain.12 Our analysis did not reveal statistically significant associations between caffeine consumption and follow-up blood pressure, which is concordant with previous findings suggesting that habitual caffeine intake may not have substantial effects on blood pressure regulation over time.3 However, more research is needed in this area to make confirmatory conclusions.

Several limitations should be considered when interpreting the findings of this analysis. The small sample size and short follow-up duration of the QUARTET USA study may have resulted in limited statistical power to detect subtle associations between lifestyle factors and follow-up blood pressure. Additionally, the reliance on self-reported measures of smoking, alcohol consumption, and caffeine intake introduces the potential for recall bias and misclassification. Future research investigations could benefit from larger sample sizes, longer follow-up periods, and objective measures of lifestyle habits to illuminate the complex interplay between lifestyle factors and hypertension outcomes more comprehensively.

The findings of this study have some implications for clinical practice and public health interventions targeting hypertension management. Despite the lack of statistically significant associations between lifestyle factors and follow-up blood pressure in our analysis, the high prevalence of tobacco use, excessive alcohol consumption, and caffeine intake shows the need for comprehensive risk assessment and tailored interventions in hypertensive populations, especially those in the setting of the trial—a Federally Qualified Health Center (FQHC), a generally underserved and underrepresented patient population. Clinicians should continue to emphasize the importance of lifestyle modifications, including smoking cessation, moderation of alcohol intake, and mindful caffeine consumption, alongside medical treatments to optimize blood pressure control and reduce cardiovascular risk.

In conclusion, this secondary analysis of the QUARTET USA study provides valuable insights into the relationship between lifestyle factors and follow-up blood pressure at 12 weeks among hypertensive individuals. While our findings did not demonstrate significant associations between smoking, alcohol consumption, and caffeine intake with follow-up blood pressure after 12 weeks of medication therapy, they highlight the importance of comprehensive approaches to hypertension management that integrate both medical and lifestyle interventions.

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