Received: 6 January 2021 | Revised: 27 February 2021 | Accepted: 1 March 2021

DOI: 10.1111/jch.14238

ORIGINAL PAPER

WILEY

Age and aging effects on blood pressure: 15 years follow-up of Tehran lipid and glucose study

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Funding information
None.

Abstract

Age is a known predictor of blood pressure (BP); however, the literature mostly includes cross-sectional investigations. This prospective cohort study aimed to decompose the cross-sectional and longitudinal age effects on BP. The secondary data were obtained from the Tehran lipid and glucose study, which comprised six repeated measurements of participants, with median follow-up of 15.8 (interquartile range of 14.2-16.9) years. The sample is representative of the metropolitan area of Tehran, Iran, containing 7,460 participants aged 20-70. The cross-sectional and longitudinal effects of age (age at baseline and aging, respectively) were fitted in the mixed effects models, taking systolic, diastolic, and pulse BPs as response, adjusting for adiposity, smoking, diabetes, and antihypertensive medication, and stratifying for sex and 10-year age-groups. The mean age at baseline was 41.3 (SD = 12.9) years, and 41.7% of the participants were male. Age at baseline and aging were directly associated with BP, aging owned the weaker effect, and the largest distinction were for systolic blood pressure of men aged 40-49 years (0.75 vs 0.10, p-value < .001). Moreover, the aging effects on systolic and diastolic BPs were higher in men than women, in the age groups 40-49 and 30-39 years (0.35 vs 0.10 and 0.30 vs 0.07, p-values < .001), respectively. Adjusting for adiposity remarkably declined the impact of aging on BP, among the < 50 years old.

1 | INTRODUCTION

High blood pressure (BP) is a chronic medical condition, characterized with persistently elevated BP levels,[1] and is a major risk factor for cardiovascular diseases (CVD), chronic kidney diseases, and dementia.[2-6] The Global Burden of Disease study estimated that 31.8% of all global deaths in 2017 were due to CVD, and the risk factor behind 54.6% of the CVD deaths was high BP.[7] Noticeably, the corresponding values have reached to 42.5% and 56.0%, respectively, regarding Iran, the country which is experiencing an epidemiological transition along with population aging and the rapid increase of noncommunicable diseases.[8]

While factors such as genetics, obesity, and smoking are reported as important risk factors,[9,10] aging has been recognized as the underlying cause of elevated BP,[11] which is generally attributed to the arterial changes.[12] Importantly, different pathways may be more relevant with changing age; as it is shown that at younger age it may involve nitric oxide bioavailability,[13] though with advancing age it could include vascular geometry,[14] accelerated arterial aging,[15] and/or multiple organ damage.[16] However, there is a scarcity of research on separating the effects of birth cohorts and aging in each birth cohort (or the cross-sectional (CS) and longitudinal (LO) effects of age) on BP. Statistically speaking, cross-sectional studies are only able to measure the cohort effect, and to estimate both CS and LO effects of age, a sample of participants should be followed over time.[17] As most of the research on the age-BP association are of cross-sectional nature, and almost all of the performed longitudinal studies merely measure the aging effect,[18-20] we designed an investigation to decompose the cohort and aging effects on BP. This study benefits from a population-based cohort dataset with 15 years of follow-up, performed among Iranian population.

2 | METHODS

2.1 | Study population and variables

The Tehran Lipid and Glucose Study (TLGS) is a prospective cohort initiated in 1999 and designed to investigate CVD risk factors among a representative sample of Tehran.[21,22] Upon entering the study in the period 1999-2005 (phase 1), five more examinations (phases 2 to 6) were conducted, every 3 years until April 2018. TLGS included 12 139 participants aged 20-70 years old at baseline. To ensure the longitudinality needed for estimating the aging effect, 4,679 individuals with <4 out of six possible examinations were excluded. The remaining 7,460 individuals had ≥4 examinations until the end of follow-up. No remarkable difference was found in the baseline characteristics between these two groups (Table S1). The 7,460 participants with median follow-up of 15.8, interquartile range 14.2-16.9 years, formed the final sample for the current study. Written informed consent was obtained from all participants. The ethical committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences, Tehran, Iran approved study protocols.

2.2 | Response variables

This investigation comprised three response variables; systolic blood pressure, diastolic blood pressure, and pulse pressure (SBP, DBP, and PP, respectively), measured in millimeter of mercury (mmHg).

2.3 | Covariates of interest

The covariates of interest included CS and LO effects of age, measured via age at baseline and aging, respectively.

2.4 | Confounders

The potential confounders included antihypertensive drug use (yes/no), sex (male/female), body mass index (BMI), waist circumference(WC) (cm), ever-smoker (yes/no), and type 2 diabetes (yes/no).[23]

2.5 | Clinical and laboratory measurements

After an initial 15-min rest, a physician measured the blood pressures, two times, using the conventional auscultatory method, during physical examinations in a seated position. There were at least a 30-s interval between the two separate measurements, and the participant's BP was considered as the mean of the two measurements. Further details are presented elsewhere.[24] Fasting plasma glucose was measured on the day of blood collection, by the enzymatic colorimetric method that used glucose oxidase.

2.6 | Definition of terms

PP was calculated as the difference between SBP and DBP.[25] Aging was defined as the years passed since baseline. BMI was defined as weight (kg)/height (m^2). Current and past smokers were defined as ever-smokers. Type 2 diabetes was defined as having fasting plasma glucose ≥126 mg/dL, or being treated with antidiabetic drugs. Hypertension was defined as having SBP ≥140 or DBP ≥90 mmHg, or being treated with antihypertensive drugs. Being labeled as a new diabetic, hypertensive patient, or ever-smoker in any phase of study, that attribute was inherited afterward, until the end of follow-up.

2.7 | Statistical analysis

Initial assessments, using graphs and models revealed sex and 10-year age groups 20-29, 30-39, 40-49, 50-59, and 60-70 as sources of distinction, regarding the effect of age on BP. Thus, the analyses were performed, stratified for these factors.

The Equation (1) shows the fitted longitudinal mixed effects model,

$$y_{ij} = \beta_0 + \beta_1 \text{Age}_{\text{base}_i} + \beta_2 \text{Aging}_{ij} + b_{0i} + b_{1i} \text{Age}_{\text{base}_i} + b_{2i} \text{Aging}_{ij} + \beta_3 \text{Antihypertensive}_{ij} + \beta_4 \text{BMI}_{ij} + \beta_5 \text{WC}_{ij} + \beta_6 \text{Smoking}_{ij} + \beta_7 \text{Diabetes}_{ij} \quad (1)$$

in which, the subscripts i and j represent the i^{th} participant measured at the j^{th} time, j = 1,...,6. Moreover, the vectors $\underset{\sim}{\beta} = (\beta_0 \beta_1, \beta_2)$ and $\underset{\sim}{b}_i = (b_{0i}, b_{1i}, b_{2i})$ demonstrate fixed and random effects, respectively. The three random effects are assumed to follow the tri-variate normal distribution $N(\underset{\sim}{0}, G)$, having an unstructured variance matrix. Finally, the coefficients $(\beta_3, \beta_4, \beta_5, \beta_6, \beta_7)$ represent the adjusted confounders.

This model was once fitted in a crude form, and further adjusted for the time-varying confounders including antihypertensive drug usage, BMI, WC, smoking, and diabetes status. In addition to the CS and LO age effects, their equality was of interest, in the case of significance of both. As well, augmenting the additional terms.

$$\beta_8 \text{Gender}_i + \beta_9 \text{Gender}_i * \text{Age}_{\text{base}_i} + \beta_{10} \text{Gender}_i * \text{Aging}_{ij}$$

to the Equation (1), made it possible to assess the sex and age interactions.

The statistical analyses were performed using the software SAS (ver. 9.2), PROC MIXED and R (ver. 3.6.).

3 | RESULTS

The 7,460 participants had a mean baseline age (standard deviation (SD)) of 41.3 (12.9) years old, and 41.7% of them were men. At baseline, out of 1,406 hypertensive cases, 453 individuals asserted to be on antihypertensive medication (32.2%). Over the follow-up period, 3,631 persons were found to be hypertensive patients, among them 2,223 persons were receiving antihypertensive drugs (61.2%). Table 1 describes the response variables, covariates of interest, and confounders, at baseline and the last phase of follow-up.

Figures 1 and 2 show the CS and LO effects of age (along with 95% confidence intervals (CIs)) in crude and adjusted models, for men and women, respectively. The reference line 0 in these graphs reveals the statistical significance. Tables S2 and S3 present the fixed effects coefficients from the two models. For the adjusted model, significant CS effects were found on DBP, SBP, and PP in men aged 60-70, 40-59, and 40-70 years, respectively, and the noticeable LO effects were obtained on DBP in men aged 20-49 years and on SBP and PP in the 30-59 and 40-70 years old, respectively. The peaks of CS and LO effects belonged to PP of the 50-59 years old men, with the coefficients of 1.06 and 0.42, respectively (p-values <.001). Among women, significant CS effects were found on DBP, SBP, and PP in the 30-39, 30-59, and 30-70 years old, respectively, and the noticeable LO effects were obtained on DBP in the 50-70 years and on SBP and PP in the 60-70 and 40-59 years old, respectively. The highest CS and LO effects were 0.86 and −0.44 (p-values <.001), for PP and DBP in women aged 50-59 and 60-70 years, respectively.

Among the confounders, BMI generally had significant positive coefficients. The highest BMI coefficients were found for SBP of women aged 30-49 and men aged 20-49 years. Besides, WC significantly increased SBP and DBP of the women aged <50 years, and SBP of the men aged 40-59 years. Finally, smoking significantly decreased the SBP and DBP of men aged 20-49 and women aged 30-39 years. The adjustment slightly attenuated the CS effects on BPs, in both sexes and mainly of the 20-49 years old. Remarkably, it dramatically lowered the LO effects on DBP and SBP of the <50 years old men and <60 years old women. Notably, regarding SBP of the 20-29 years, the non-significant LO effects turned to negative effects, for both sexes.

Overall, among the 30 fitted models (5 age-groups × 2 sexes × 3 dependents), as Figures 1 and 2 show, in the adjusted model, 46.7 and 6.7% of CS, and 46.7 and 36.7% of LO effects were significant, with positive and negative signs, respectively. Among the setups of CS and LO effects both significant, the PP of men and women aged 40-59, the SBP of women aged 30-49 years, and the DBP of women aged 30-39 years demonstrated significant differences between two effects, in all of them both CS and LO effects were positive and the CS was the larger one. The greatest difference went to SBP in women aged 40-49 years old (0.75 vs. 0.10, p-value <.001). Comparing men and women, when both sexes had significant effects, the CS effects showed no significant differences, but the LO effects on DBP of the 30-39 and SBP of the 40-49 years were positive and significantly higher in men (p-values <.001). Additionally, both sexes owned negative LO effect on PP of the 20-29 years, with a larger effect for men (p-value <.001).

As a sensitivity analysis, we rerun our data analysis among the participants not on any antihypertensive drugs at any phase of the study (n = 5,237). The findings were generally the same, excluding the attenuated LO effect on DBP among the 50-70 years old, and the Lo effect on SBP among the 60-70 years old which became significant (Data not shown).

Finally, as another sensitivity analysis, we selected persons who had never smoked at any phase of the study and the models were refitted. No remarkable changes were observed, comparing with the main findings (data not shown).

3.1 | DISCUSSION

This investigation separated the longitudinal and cross-sectional effects of age on systolic, diastolic, and pulse blood pressure, using a 15-year follow-up data, stratified by age groups and sex, and controlling for total and visceral obesity, diabetes, smoking, and antihypertensive drug usage.

Accordingly, the effect of aging on BP was always weaker than the cross-sectional effect, when both effects were significant, with the highest impact of cohort effect for SBP of women aged 40-49 years. Moreover, the increasing impacts of aging on SBP and DBP were more prominent among men, rather than women, in the age groups 40-49 and 30-39 years, respectively.

TABLE 1 A description of variables and their valid number of observations

Variables		*N* = 7,460	Percent/ Mean(SD)
Age groups, at baseline	20-29	1564 (574 men)	21.0%
	30-39	2121 (913 men)	28.4%
	40-49	1676 (678 men)	22.5%
	50-59	1254(519 men)	16.8%
	60-70	845 (428 men)	11.3%
Antihypertensive drug use (Yes)	Phase 1	7460	6.1%
	Phase 6	7460	29.8%
Diabetes (Yes)	Phase 1	7460	6.9%
	Phase 6	7460	21.9%
Ever-smoker (Yes)	Phase 1	7460	20.1%
	Phase 6	7460	33.3%
Body mass index (kg/m^2)	Phase 1	7245	27.0 (4.6)
	Phase 6	5012	29.0 (4.9)
Waist circumference (cm)	Phase 1	7215	88.3 (12.0)
	Phase 6	5015	97.3 (11.4)
Systolic blood pressure(mmHg)	Phase 1	7306	117.9 (17.6)
	Phase 6	5228	119.9 (18.6)
Diastolic blood pressure (mmHg)	Phase 1	7306	77.2 (10.5)
	Phase 6	5232	77.4 (10.3)

Abbreviation: SD: standard deviation

In the current study, through following the metropolitan residents of Tehran, we found that among hypertensive population about 61% were on antihypertensive medication. In other large studies conducted in the country, the prevalence of using antihypertensive medication among Iranian hypertensive patients were 17.6 and 25.0%.[26,27] Therefore, we found a remarkably higher level of receiving antihypertensive medication, which could be explained to some extent by the better socioeconomic and educational status of Tehran residents, compared with the mentioned studies.[26,27] However, contrary to the two aforementioned studies, we did not have data on awareness and control of hypertension. They reported 32.1 and 24.0% of treated patients having controlled hypertension.

In detail, adjusting for the confounders, the men demonstrated positive cohort effects on DBP of 30-39, and also on SBP and PP of 40-70 years. Other studies support the idea of progressive rise of SBP and PP, while the DBP being smoothed in the middle ages.[28] Compatibly, the women provided positive cohort effects on DBP of 30-39, on SBP of 30-59, and on PP of 30-70 years old. Remarkably, in men, the cohort effect on DBP of 60-70 years was found to be negative, despite its wide confidence interval. The cohort effect on PP in women demonstrated a monotone increasing pattern through 30-70 years old.

On the other hand, while adjusting for the confounders, men showed positive aging effects for DBP of 20-49, SBP of 30-59, and PP of 40-70 years old, these effects were mostly attenuated in the women of the same ages. Moreover, the aging effect on SBP was negative in men and women of 20-29 and women of 60-70 years old, on DBP in men of 50-70 and women of 40-70 years old, and on PP in men of 20-39 and women of 20-29 years old. As Figure 1 shows, the peak of aging effect on SBP and PP of men and on PP of women happened in the 50-59 years age group. Similar to the findings of a Framingham study, the effects of aging were different on three forms of BP; SBP and PP increased after the age of 30 and 40 years, respectively, but DBP increased until 50 years and then smoothed.[29]

Men and women were not different, in terms of the cross-sectional effect of age on BP, but the effects of aging on DBP of the 30-39 and the SBP of 40-49 years old were higher in men. Our finding conforms with a Global Burden of Disease result indicating the higher risk of CVD death attributable to high SBP, among Iranian men comparing with women, in 2017 (Figure S1),[7] in which the sex gap increases with age. In addition, the cross-sectional effect was stronger than the aging effect on the PP of men older than 39 years old. In the case of women, the SBP of 30-39 and the PP of 40-49 years again witnessed a higher cohort effect. Besides, both CS and LO effects increased SBP, decreased DBP, and therefore, raised PP. This phenomenon is in line with other studies.[30] Moreover, earlier investigations indicate a higher CVD risk in the middle age and elderly, due to lowering DBP and stabilizing SBP, making an increase in PP. In fact, PP is being recognized as a stronger predictor of CVD, than SBP and DBP.[31-33]

Overall, BMI had positive effects on SBP, DBP, and PP, for all age groups and both sexes. The largest BMI effect was on the SBP in the 30-49 years old. As Figure 1 shows, adjusting for confounders weakened the effect of aging on SBP and DBP, in both sexes, and in the 20-49 years old. These attenuations were accompanied with increasing impact of WC in women, and decreasing effect of

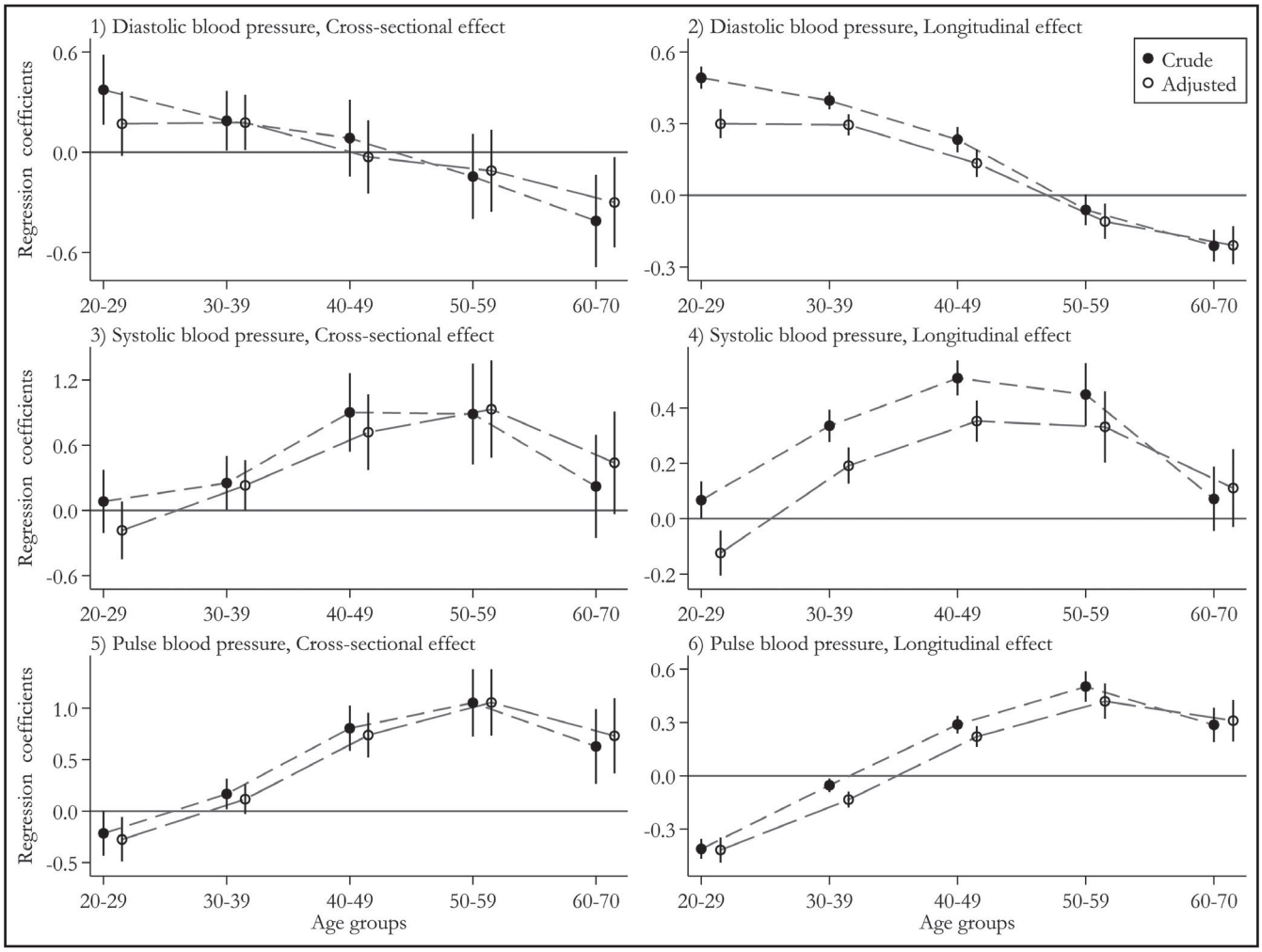

FIGURE 1 Fixed effects obtained from crude and adjusted models, for the men

smoking in men. Thus, the increases of SBP and DBP in the middle age were to a major part caused by confounders, and not only by the aging. Previous studies have also recognized obesity to be effective in increase in SBP withage,[34,35] and altering it could evidently lower the chance of BP progression to hypertension.[36,37] Furthermore, a recent meta-analysis of 57 cohort studies reports 1.49 (95%CI: 1.41, 1.58) and 1.27 (95%CI: 1.15, 1.39) relative risks of developing hypertension for a 5-unit increase of BMI and a 10-cm increase of WC, respectively.[38] As well, the population attributable fraction of hypertension due to obesity is estimated to be 17.9 and 18.8% for male and female residents of Tehran, respectively.[39] Lately, a causal analysis showed that adjusted for sex, smoking, BMI, and a few more important confounders, aging leads to elevated BP, mediated through arterial stiffness.[12]

The strengths of our work include benefitting from a large cohort, with a remarkable number of repeated measurements, and a lengthy follow-up. We considered sex, age groups, antihypertensive drug use, diabetes, smoking, and obesity in both general and abdominal form, and utilized a sophisticated modeling approach able to capture the longitudinal nature of the data. Finally, we assessed BP in three various forms, systolic, diastolic, and pulse. Our findings are generalizable to the urban residents of Tehran. As a limitation, we do not include physical activity in the final analyses, despite the reported impact of physical fitness on decreasing BP.[40,41] While in the first Phase of TLGS, physical activity was measured using the Lipid Research Clinic questionnaire,[42] the tool changed to metabolic equivalent task-minutes per week[43] since the second Phase, which effectively altered the measurements,[44] and it avoided us to use this covariate. Another limitation was the lack of information on the hypertension duration and hypertension control, for the patients on the treatment, and on the information awareness.

4 | CONCLUSION

In a population-based study, in the Middle East and North Africa region for the first time, we examined the cross-sectional versus longitudinal effects of age on BP, during more than 15 years of follow-up. Accordingly, we generally showed the higher impact of cross-sectional effect of age on BP. Moreover, the longitudinal impacts of

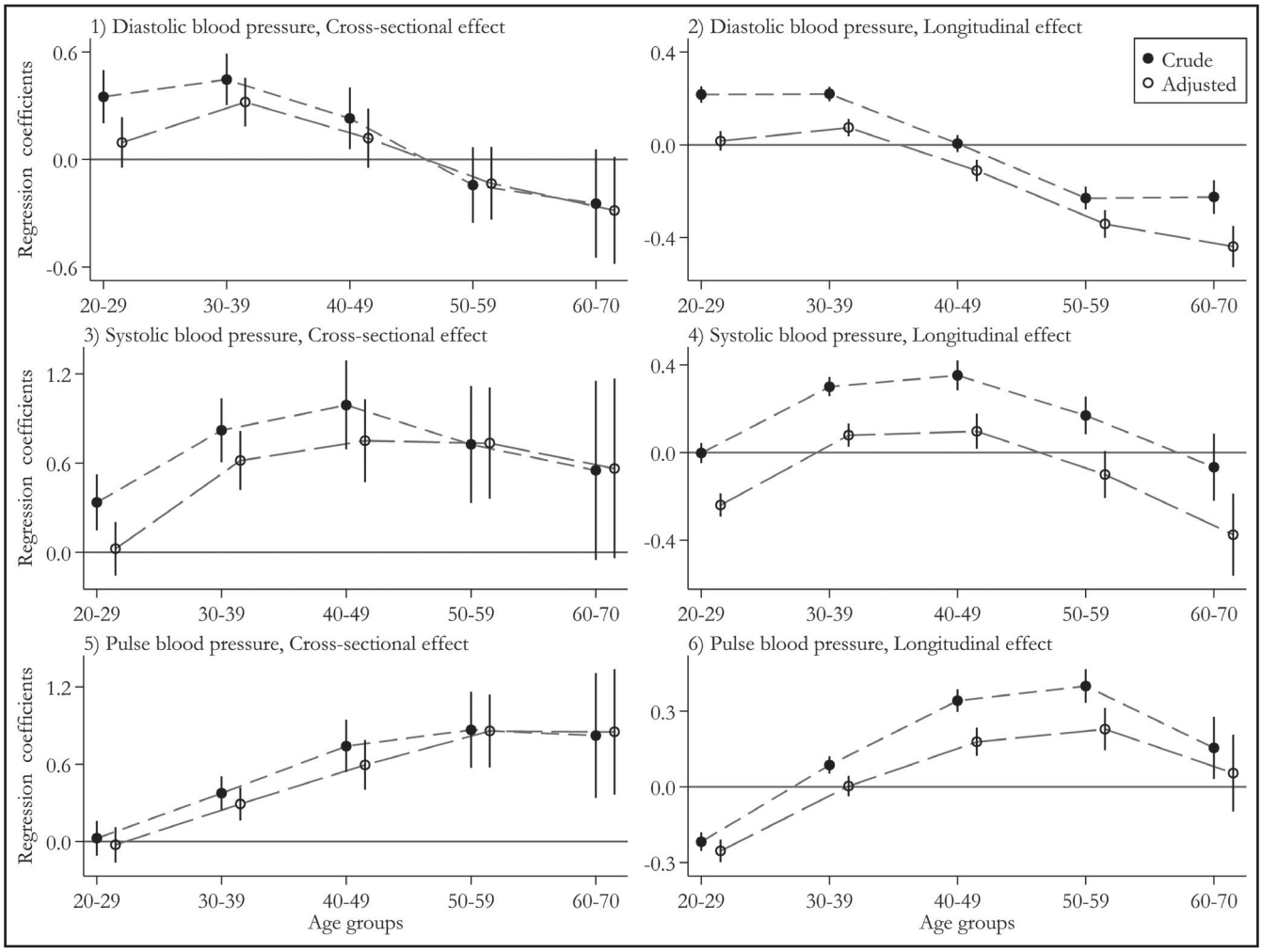

FIGURE 2 Fixed effects obtained from crude and adjusted models, for the women

age on BP were significantly larger in men and among the participants less than 50 years old. Interestingly, these low impacts of aging on BP of the premenopausal women are coincident with the increasing effects of general and central adiposity. Finally, adjusting for adiposity remarkably declined the impact of aging on BP, for the 20-49 years old population. Thus, a reasonable intervention program could manage the elevated BP in this age group through multicomponent strategies including diet and physical activity for targeting obesity.

CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

AK, FZ, and FH designed the study. AK, FZ, and FH contributed to the analysis and interpretation of data. AK and FH drafted the manuscript. AR, AN, and FA critically revised the manuscript. All authors approved the final draft.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Khajavi A, Zayeri F, Ramezankhani A, Nazari A, Azizi F, Hadaegh F. Age and aging effects on blood pressure: 15 years follow-up of Tehran lipid and glucose study. *J Clin Hypertens*. 2021;23:1205–1211. https://doi.org/10.1111/jch.14238