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ORIGINAL RESEARCH

# Sex Differences in Cumulative Exposure to Metabolic Risk Factors Before Hypertension Onset: The Cohort of the Tehran Lipid and Glucose Study

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**BACKGROUND:** Previous studies have shown a sex difference in the association between hypertension and cardiovascular disease; however, the precise mechanism remains unclear. Because there are strong associations between metabolic risk factors (MRFs) and hypertension, a sex-specific analysis of MRFs before hypertension onset could offer new insights and expand our understanding of sex differences in cardiovascular disease. We evaluated cumulative exposure to major MRFs and rate of change of those factors, including body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol among individuals who did and did not develop hypertension at follow-up.

**METHODS AND RESULTS:** We included 5374 participants (2191 men) initially without hypertension with age range of 20–50 years at baseline who participated in the Tehran Lipid and Glucose Study, and had been examined at least 3 times during the study period (1999–2018). In both sexes, the cumulative exposure to all MRFs (except for fasting plasma glucose and high-density lipoprotein cholesterol in men) were higher in those who developed hypertension, compared with those who did not develop hypertension. However, women experienced greater cumulative exposure to major MRFs, compared with their male counterparts. Also, they experienced a faster increase in waist circumference, systolic blood pressure, diastolic blood pressure, and high-density lipoprotein cholesterol than men. Furthermore, rapid increase in systolic blood pressure began earlier in women than men, at the age of 30 years. We also found that those men who developed hypertension experienced unfavorable change in major MRFs during young adulthood (<50 years of age).

**CONCLUSIONS:** Women exhibited more metabolic disturbances than men before onset of hypertension, which may explain the stronger impact of hypertension for major types of cardiovascular disease in women, compared with men.

**Key Words:** burden ■ hypertension ■ metabolic ■ risk factor ■ trajectory

Hypertension is one of the most important risk factors for cardiovascular disease (CVD) morbidity and mortality worldwide.[1] In 2016, 40.5 million (71%) of worldwide deaths were from noncommunicable diseases. Of these, 17.9 million (44%) deaths were because of CVD, with hypertension as the leading risk factor.[2] Longitudinal studies in major industrialized countries have shown that systolic blood pressure (SBP) rises steadily with increasing age.[3,4] Thus, for much of the last century, a progressively increasing blood pressure (BP) was thought to be the consequence of the aging process.[5] However, little to no increase in SBP with aging has been observed in nonindustrialized countries.[3–5] This difference in the age-associated increase in SBP between populations in industrialized and nonindustrialized countries is

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## CLINICAL PERSPECTIVE

### What Is New?

- In this study, during a median follow-up of >15 years, those with incident hypertension had greater cumulative exposure and faster rates of change of major metabolic risk factors compared with those without incident hypertension.
- The differences in cumulative exposure to all metabolic risk factors except for total cholesterol, between those with and without incident hypertension, were significantly higher in women, compared with men.
- We found a faster change in waist circumference, systolic blood pressure, diastolic blood pressure, and high-density lipoprotein cholesterol in women with and without incident hypertension, compared with their male counterparts.

### What Are the Clinical Implications?

- The trajectory of metabolic risk factors may provide additional insight into the pathophysiology and treatment of hypertension.
- The higher cumulative exposure and rate of change of major metabolic risk factors before hypertension among women may explain the stronger impact of hypertension on cardiovascular disease in women compared with men.
- Prevention and management efforts for cardiovascular disease risk should focus on reducing the hypertension risk burden in women.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **FH-CVD** | family history of CVD |
| **FPG** | fasting plasma glucose |
| **IGC** | individual growth curve |
| **Ln-triglycerides** | log transformation of triglycerides |
| **MRFs** | metabolic risk factors |
| **PAL** | physical activity level |
| **TLGS** | Tehran Lipid and Glucose Study |
| **WC** | waist circumference |

generally attributed to environmental and lifestyle factors.[5] Overall, it has been shown that BP level is lower in women than in men during the reproductive years. Also, current studies have reported that at a younger age, women have a lower BP level and less hypertension than similarly aged men, whereas this reverses at older age.[6] Nevertheless, few studies have reported a greater burden of hypertension for women than men. For example, women with hypertension exhibit higher prevalence of arterial stiffness, heart failure with preserved ejection fraction, atrial fibrillation, and dementia at an older age compared with hypertensive men.[7,8] In the cohort study of UK Biobank, including 471 998 participants, women with hypertension had a 50% higher risk of myocardial infarction, compared with men with hypertension.[9] Also, in another study with 471 971 UK Biobank participants, hypertension was associated with a 36% higher risk of ischemic stroke in women than men.[10] A longitudinal cohort study in the United States among 26 461 participants demonstrated that the excess risk of stroke associated with hypertension was 7% greater in women than men.[11] The INTERHEART global case–control study including 27 098 participants from 52 countries showed that hypertension was associated with a 27% greater excess risk of myocardial infarction in women than men.[12]

The mechanisms of sex differences in CVD risk among individuals with hypertension remain unclear.[9,10] On the other hand, increasing evidence indicates a strong association between metabolic risk factors (MRFs) and hypertension[13,14] in both sexes. Investigation of these MRFs by sex among those who develop hypertension may have important implications for the design of more specific and effective interventions for both sexes. However, most previous studies have focused on these MRFs in a single or limited number of measurements,[15,16] ignoring the fact that single measures of MRFs may not reflect the cumulative or lifetime exposures to MRFs.[17,18] The trajectory analysis is an effective method that captures changes of risk factor over time. This method allow us to estimate cumulative exposure to MRFs based on their trajectories, which gives a more accurate estimate of the effects of these factors over years,[19] and may contribute to understanding of mechanisms leading to sex differences in hypertension and CVD risk.[20–22] To the best of our knowledge, no study has comprehensively examined the sex difference in cumulative exposure to major MRFs preceding hypertension among adults. We have recently found significant sex differences in the impact of different MRFs on development of hypertension using the single measurement of these factors.[14] The current study extended our previous work in 2 major ways. First, we used repeated measurement of major MRFs including body mass index (BMI), waist circumference (WC), SBP, diastolic BP (DBP), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides, and HDL-C (high-density lipoprotein cholesterol) from the TLGS (Tehran Lipid and Glucose Study). Second, using the trajectory of the MRFs among individuals free of hypertension at baseline, we estimated rate of change and cumulative exposure to MRFs in those who did and did not develop hypertension at follow-up.

# METHODS

## Transparency and Reproducibility

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Study Population

The TLGS is a prospective cohort study of a random sample of residents living in Tehran, capital of Iran, which was designed to understand the risk factors and outcomes for noncommunicable diseases.[23,24] The protocol of the TLGS was based on the World Health Organization–recommended model for field surveys of diabetes and other noncommunicable diseases.[25] The first phase of the TLGS was started in 1999 to 2001 in district No. 13, 1 of the 22 districts of Tehran. Age distribution and socioeconomic status of the population in this district was representative of the overall population of Tehran at the recruitment time.[26,27] Among 20 medical health centers in district No. 13, 3 health centers were chosen; then, a total of 15 005 individuals aged ≥3 years (response rate: 57.5%)[27] who were under the coverage of these 3 health centers were selected using the multistage cluster random sampling method. There was no significant different between responders and nonresponders.[27] Reexaminations were conducted in intervals of 3 years, and 3550 individuals were added in the second examination.[28] Until now, 6 examinations (phase) 1 (1999–2001), 2 (2002–2005), 3 (2005–2008), 4 (2009–2011), 5 (2012–2015), and 6 (2015–2018) have been conducted in TLGS (Data S1). For the present study, 9014 participants aged 20 to 50 years from the first (n=7133) and second (n=1881) phases were selected and followed until the end of the study (April 18, 2018). We excluded 908 individuals with prevalent hypertension at baseline, 245 people who had missing data on hypertension status at baseline, and 1430 individuals with no follow-up data after recruitment. Because at least 3 measurements of MRFs were required for studying the trajectory of MRFs, we further excluded 1057 people who did not participate at least 2 times before hypertension incidence or before the last participation for those who did not develop hypertension. Finally, 5374 adults (2191 men) formed the study population (Figure 1). At baseline, <5% of the study population had missing values for several MRFs and other covariates; thus, we chose not to exclude these individuals. The study populations participated 3 to 6 times during the study period (5 times on average). The number of participants who participated 3, 4, 5, and 6 times was 662, 872, 1667, and 2173, respectively. It should be noted that some individuals

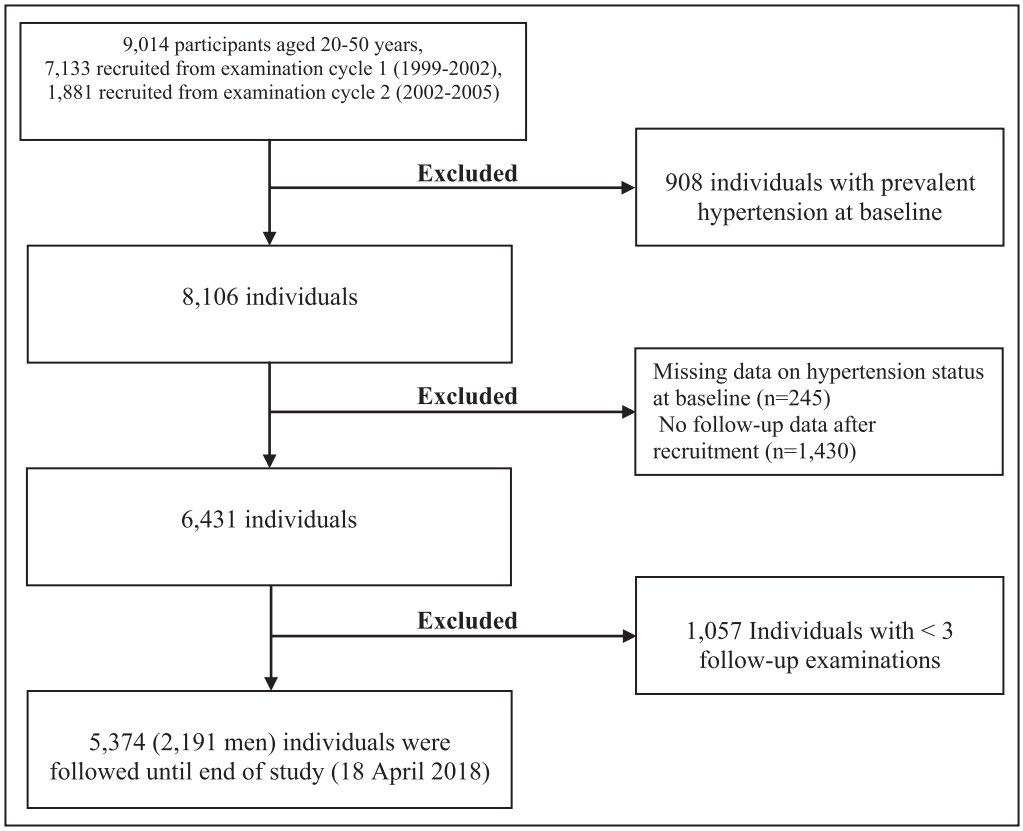


**Figure 1. Study sample selection flow chart, Tehran Lipid and Glucose Study.**

also had missing values in MRFs in a number of follow-up examinations. Therefore, the number of participations may not necessarily be equal to the number of measurements. This type of missing values for MRFs is not problematic, because the person-period data set does not include records for these unobserved phases in longitudinal analysis.[29] Second, <5% of MRFs values were missing in person-period format. In Table S1 we have presented detailed information about the data set. This study was approved by the ethical committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All participants provided written informed consent.

## Measurements

Information on age, smoking status, medication use, and family history of CVD (FH-CVD) was obtained using standardized questionnaires. At each phase, participants also underwent measurements of their anthropometric measures, BP, and biochemical measurements using standardized protocols and assays. Body weight was measured to the nearest 0.1 kg while the participants were wearing light clothing and no shoes. Body height was measured to the nearest 0.1 cm in a standing position. BMI was calculated as weight (kilograms) divided by height (meters) squared, and WC was measured to the nearest 0.1 cm with participants in a standing position. SBP and DBP were calculated as the average of 2 sequential measurements taken on the left arm of the seated participants who had been resting for at least 5 minutes using a standard mercury column sphygmomanometer with appropriate-sized cuff. Peripheral blood samples were collected in the morning after a 12-hour overnight fast for measurements of FPG, TC, triglycerides, and HDL-C.[24] In the first phase, the Lipid Research Clinics questionnaire[30] was used to measure the physical activity level (PAL). From the second phase, PAL was assessed by the Modifiable Activity Questionnaire.[31]

## Definition of Terms

Participants self-reported their smoking status as current smoker versus nonsmoker. A current smoker was a person who smoked cigarettes or other smoking implements daily or occasionally. Nonsmokers included never-smokers and ex-smokers. FH-CVD was defined as reports of coronary heart disease or stroke occurring in relatives before 55 years of age in male relatives and before 65 years of age in female relatives. We categorized PAL as low and high. In the first phase, low PAL was defined as doing exercise or labor <3 times a week, and in the second phase, it was defined as metabolic equivalent tasks minutes of <600 metabolic equivalent tasks per week.[32] Hypertension incidence was defined as a BP level ≥140/90 mm Hg or use of antihypertensive medication.

## Statistical Analysis

Because distribution of triglycerides was positively skewed, the natural log transformation of triglycerides (Ln-triglycerides) was used in all analysis. The characteristics of the study participants at the baseline are described as means for continuous variables and percentages for categorical variables, and were compared between those who did and did not develop hypertension. Also, we compared baseline characteristics between participants and nonparticipants. Nonparticipants included those with missing data on hypertension status at baseline, individuals without any follow-up data, and those with <3 times of participation in the study. The comparisons were done using the Student *t* test and Pearson $\chi^2$ test for continuous and categorical variables, respectively.

We defined hypertension onset as the first examination at which hypertension criteria were met. For each participant meeting hypertension criteria in a phase, all data after hypertension occurrence were truncated. The trajectories of MRFs were modeled separately in men and women using individual growth curve (IGC) analysis, as we have previously described.[33]

Conceptually, IGC models allow researchers to measure change over time in a phenomenon. The time in our study was defined as participant's age, and we assessed how a MRF varies as a function of age. IGC constructs growth curves of MRFs using the random-effects mixed model, which incorporates fixed and random effects. Fixed effects are the average change over time or age, and random effects are the individual differences around the fixed effects. In fact, IGC allows investigating 2 levels of variability of a response variable: level (1) within subjects, and level (2) between subjects. One of the advantages of this approach is that it allows for repeated measurements and different numbers of unequally spaced observations across individuals.[29,34] We followed the modeling strategy suggested by Mirman[34] and Singer[29] for IGC analysis. Three possible polynomial curves (linear, quadratic, and cubic) of the MRFs were fitted.

For example, to examine a quadratic growth form, the level 1 model could be written as follows:

$$y_{ij} = b_{0i} + b_{1i}(age_{ij}) + b_{2i}(age_{ij})^2 + e_{ij}$$

In this equation, $b_{0i}$ is intercept, $b_{1i}$ carries information about the linear effect of age, and $b_{2i}$ shows the quadratic effect of participant's age. All of these coefficients are the parameters of the IGC models that vary from individual to individual, and were estimated using the maximum likelihood method. The coefficient of $b_{1i}$

in an IGC model was defined as linear rate of change. For example, if $b_{1i}$=1.5 and $b_{2i}$=−0.04, because $b_{1i}$ is positive, the trajectory initially rises, but because $b_{2i}$ is negative, this increase does not persist.[29]

The goodness of fit of the models was assessed using likelihood ratio tests and Akaike information criterion. Age and its higher-order terms were included 1 by 1 in the models. We did not include higher-order terms of age if they were not significant, or made lower-order terms not significant, or did not improve the Akaike information criterion values. We centered the age at the grand mean age (41.5 years) to remove collinearity between age and its higher-order terms in IGC models.[29] We also divided the terms $age^2$ and $age^3$ by 10 and 20, respectively, to stabilize the variance terms.[19,29] The characteristics of models are presented in Tables S2 and S3. The cumulative exposure to MRFs was measured as the area under the curve (AUC) of growth curves using the integral of the growth curves for each individual from 20 to 70 years of age divided by 50 to get the annual cumulative exposure to each MRF.[19,33] The linear rate of changes of MRFs for each person was defined as the combined (fixed plus random) coefficients of age term in IGC models.

We used 2-way ANCOVA to test significant differences in the group means of MRFs, AUCs, rates of change, and intercepts. This method allowed us to investigate the simultaneous effects of hypertension status and sex on each MRF by including an interaction term of sex and hypertension status. Also, ANCOVA had an additional benefit of allowing us to adjust for the covariates. The differences in group means were adjusted for baseline age. Also, we further adjusted for FH-CVD, smoking status, and PAL to examine a significant interaction in the presence of potential confounders.[14]

The ANCOVA was applied by general linear model using the IBM SPSS Statistics for Windows, version 20, and IGC analysis was performed in R 3.6.2 using the nlme package[35] and a 2-sided *P* value <0.05 was considered statistically significant.

## RESULTS

The characteristics of the study population at the baseline are summarized in Table 1. Of the 5374 participants, (41%) were men, with the mean (SD) ages 33.8 (8.1) and 33.1 (8.1) years in men and women, respectively. In general, individuals without incident hypertension were younger, and had lower levels of BMI, WC, FPG, SBP, DBP, Ln-triglycerides, and TC, compared with individuals who developed hypertension. They were also less likely to have FH-CVD and to have low PAL. Baseline characteristics of participants and nonparticipants are presented in Table 2. Participants had lower levels of all MRFs except for TC, compared with nonparticipants. They were also less likely to smoke and more likely to have low PAL.

The median (interquartile range) follow-up of participants was 15.4 (12.5–16.5) years. Study sample included 1149 (491 men) new cases of hypertension. The mean (SD) age of onset of hypertension was 45.9 (8.3) and 47.8 (7.9) years in men and women, respectively.

The mean of MRFs adjusted for baseline age in ANCOVA model are shown in Table 3. Among men and women, levels of BMI, WC, SBP, DBP, TC, and Ln-triglycerides were higher in those who developed hypertension than those who did not develop it. Furthermore, among those who developed hypertension, women had higher levels of BMI and HDL-C, but lower level of SBP and Ln-triglycerides than their male

**Table 1. Baseline Characteristics of Men and Women by Hypertension Status at Follow-Up**

| | Men | | Women | |
|---|---|---|---|---|
| | Without hypertension n=1700 | With hypertension n=491 | Without hypertension n=2525 | With hypertension n=658 |
| Age, y | 33.2 (8.1) | 35.8 (7.9) | 31.9 (8.0) | 37.7 (7.6) |
| BMI, kg/m$^2$ | 24.7 (3.9) | 26.4 (3.8) | 25.5 (4.4) | 28.7 (4.7) |
| WC, cm | 85.5 (10.7) | 89.2 (10.2) | 81.5 (11.2) | 89.4 (11.4) |
| FPG, mmol/L | 5.0 (0.9) | 5.1 (1.1) | 4.8 (0.7) | 5.1 (1.4) |
| SBP, mm Hg | 110.0 (9.8) | 116.5 (9.5) | 106.4 (9.9) | 115.2 (9.9) |
| DBP, mm Hg | 72.2 (7.8) | 77.5 (7.2) | 71.3 (7.96) | 77.9 (6.5) |
| HDL-C, mmol/L | 0.9 (0.2) | 0.9 (0.2) | 1.2 (0.2) | 1.1 (0.2) |
| Ln-triglycerides, mmol/L | 0.4 (0.5) | 0.6 (0.5) | 0.2 (0.5) | 0.5 (0.5) |
| TC, mmol/L | 4.9 (1.1) | 5.3 (1.1) | 4.8 (1.0) | 5.2 (1.0) |
| Smokers | 611 (36.0) | 141 (29.0) | 105 (4.2) | 21 (3.2) |
| Family history of CVD (yes) | 230 (13.5) | 93 (18.9) | 350 (13.9) | 127 (19.3) |
| Physical activity (low) | 1144 (70.8) | 389 (81.2) | 1631 (68.8) | 477 (74.4) |

Continuous variables are expressed as mean (SD), and categorical data are presented as frequency (%).

BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Ln-triglycerides, natural log of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

**Table 2. Baseline Characteristics of Participants and Nonparticipants***

| | Nonparticipants n=2732 | Participants n=5374 | *P* value* |
|---|---|---|---|
| Men | 1228 (44.9) | 2191 (40.8) | <0.001 |
| Age, y | 33.3 (8.7) | 33.4 (8.2) | 0.756 |
| BMI, kg/m$^2$ | 26.1 (4.8) | 25.7 (4.4) | 0.001 |
| WC, cm | 85.6 (12.2) | 84.5 (11.4) | <0.001 |
| FPG, mmol/L | 5.1 (1.3) | 4.9 (0.9) | <0.001 |
| SBP, mm Hg | 111.4 (11.3) | 109.6 (10.5) | <0.001 |
| DBP, mm Hg | 74.6 (8.4) | 73.0 (8.1) | <0.001 |
| HDL-C, mmol/L | 1.7 (0.3) | 1.1 (0.3) | 0.011 |
| Ln-triglycerides, mmol/L | 0.4 (0.5) | 0.3 (0.5) | 0.001 |
| TC, mmol/L | 4.9 (1.1) | 4.9 (1.1) | 0.510 |
| Smokers | 581 (23.0) | 878 (16.4) | <0.001 |
| Family history of CVD (yes) | 390 (14.3) | 800 (14.9) | 0.486 |
| Physical activity (low) | 1640 (68.5) | 3641 (71.3) | 0.016 |

Values present mean (SD) for continuous variables and frequency (%) for categorical variables. *P* values show statistical differences based on *t* test and $\chi^2$ test for continuous and categorical variables, respectively. BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Ln-triglycerides, natural log of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

*Nonparticipants included those with missing data on hypertension status at baseline, individuals without any follow-up data, and those with <3 times of participation in the study.

counterparts. Among individuals without incident hypertension, women had significantly higher BMI and HDL-C, but lower level of WC, FPG, SBP, DBP, and Ln-triglycerides, compared with their male counterparts (Table 3). There was a significant interaction between sex and hypertension status regarding baseline characteristic, so that the differences between individuals with and without incident hypertension were greater in women than in men for baseline levels of BMI, WC, FPG, SBP, and Ln-triglycerides. The interaction remained significant after further adjustment for smoking status, PAL, and FH-CVD (Table 3).

The parameters of the final IGC models for each MRF are presented in Tables S4 and S5. Also, in Figure S1, we have shown the means of predicted values of each MRF among men and women. For easier comparison, in Figure 2, the smoothed curves of each MRF across age are depicted.

The AUC values of MRFs are shown in Table 4. Among women, the age-adjusted AUC of all MRFs except for HDL-C were significantly higher in those with incident hypertension, compared with those without incident hypertension. Also, men who developed hypertension had higher AUC for all MRFs except for HDL-C and FPG. We found that among those with and without incident hypertension, women had

**Table 3. The Adjusted Mean of Metabolic Risk Factors at Baseline Among Individuals Who Did and Did Not Develop Hypertension**

| | Men (n=2191) | | | Women (n=3183) | | | *P* for sex difference | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Without hypertension (n=1700) | With hypertension (n=491) | *P* value* | Without hypertension (n=2525) | With hypertension (n=658) | *P* value* | Without hypertension | With hypertension | *P* interaction† | *P* interaction‡ |
| BMI, kg/m$^2$ | 24.8 (0.1) | 26.1 (0.2) | <0.001 | 25.7 (0.1) | 28.1 (0.1) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| WC, cm | 85.6 (0.2) | 88.2 (0.4) | <0.001 | 82.2 (0.4) | 87.5 (0.4) | <0.001 | <0.001 | 0.273 | <0.001 | <0.001 |
| FPG, mmol/L | 5.03 (0.02) | 5.07 (0.04) | 0.359 | 4.89 (0.01) | 5.08 (0.03) | <0.001 | <0.001 | 0.894 | 0.023 | 0.025 |
| SBP, mm Hg | 110.1 (0.2) | 116.3 (0.4) | <0.001 | 106.5 (0.1) | 115.0 (0.3) | <0.001 | <0.001 | 0.020 | 0.001 | 0.001 |
| DBP, mm Hg | 72.2 (0.1) | 77.3 (0.3) | <0.001 | 71.5 (0.1) | 77.4 (0.3) | <0.001 | 0.002 | 0.677 | 0.067 | 0.056 |
| HDL-C, mmol/L | 0.97 (0.01) | 0.96 (0.01) | 0.503 | 1.17 (0.01) | 1.12 (0.01) | <0.001 | <0.001 | <0.001 | 0.073 | 0.051 |
| Ln-triglycerides, mmol/L | 0.46 (0.01) | 0.57 (0.02) | <0.001 | 0.21 (0.01) | 0.40 (0.02) | <0.001 | <0.001 | <0.001 | 0.032 | 0.069 |
| TC, mmol/L | 4.96 (0.02) | 5.17 (0.04) | <0.001 | 4.95 (0.02) | 5.10 (0.04) | 0.001 | 0.735 | 0.277 | 0.422 | 0.292 |

Values show the mean (SE) adjusted for baseline age in ANCOVA model. BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Ln-triglycerides, natural logarithm of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

*P values were adjusted by Bonferroni method and show the statistical difference between those with and without hypertension.

†P value shows the significance of interaction term of sex by hypertension status in ANCOVA model adjusted for baseline age.

‡P value shows the significance of interaction term of sex by hypertension status in ANCOVA model adjusted for baseline age, smoking status, physical activity level, and family history of cardiovascular disease.

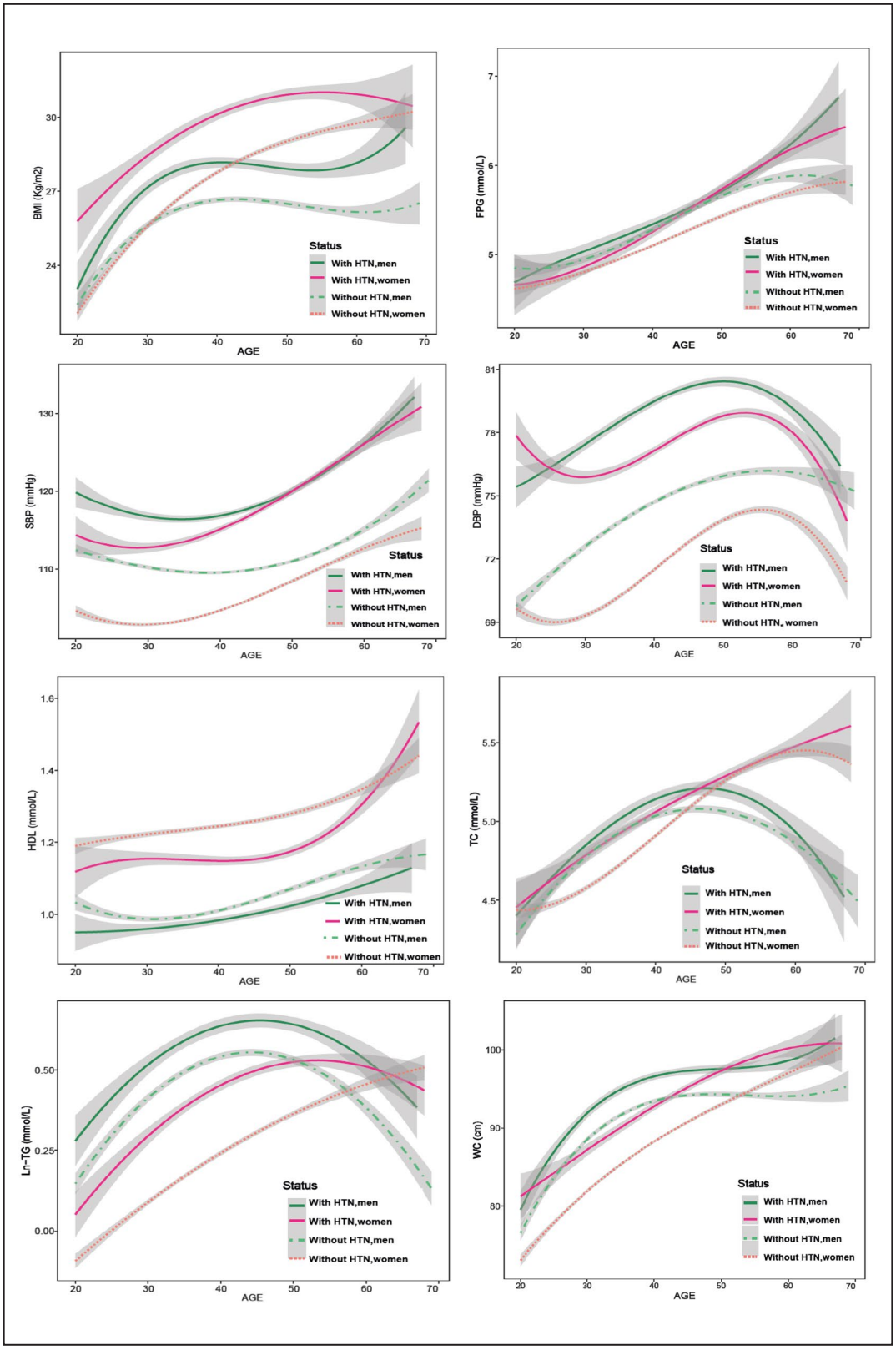


**Figure 2. Smoothed curves of predicted value for metabolic risk factors by sex and hypertension status.**

Gray shading indicates ±SE. BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HTN, hypertension; Ln-triglycerides, natural logarithm of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

significantly higher AUC of BMI, HDL-C, and TC than men. There were significant interactions between sex and hypertension status regarding AUC of all MRFs except for TC, so that the magnitude of difference between those with and without incident hypertension were remarkably higher in women, compared with men, which remained significant after further adjustment for confounders.

The average of rates of change of MRFs adjusted for age are shown in Table 5. We found that for the positive values for rates of change all MRFs in both sexes, the larger its value, the more rapid the change. Accordingly, men who developed hypertension had faster rates of change in BMI, SBP, Ln-triglycerides, and TC, compared with men who did not develop it. Among women, those who developed hypertension had significantly faster rates of change in all MRFs except for BMI and Ln-triglycerides, compared with women who did not develop it. Testing for sex difference showed that women had a higher rate of change in all MRFs except for FPG compared with men among both groups of individuals with and without incident hypertension.

We found significant interaction between sex and hypertension status in rates of change of MRFs, so that the differences in rates of change in BMI, Ln-TG, and TC between individuals with and without incident hypertension were greater in men, compared with women, even after adjustment for confounders. However, the differences in rate of change of WC, SBP, DBP, and HDL-C were higher between women with and without incident hypertension, compared with their male counterparts.

The combined intercepts in each IGC are shown in Figure 3. Because we centered age at 41.5 years, the values show the mean of each MRF at the age of 41.5 years. The differences in mean of BMI, FPG, SBP, DBP, and Ln-triglycerides between those with and without incident hypertension were greater in women, compared with their male counterparts at the age of 41.5 years.

## DISCUSSION

To our knowledge, this is the first study to report rate of change and cumulative exposure to MRFs preceding hypertension, over a long period. Our results from >5000 Iranian adults, with repeated measurements of MRFs, showed that in both sexes, those with incident hypertension had greater cumulative exposure and faster rates of change of major MRFs compared with those without incident hypertension. However, differences between those with and without incident hypertension were greater in women than men for cumulative exposure to all MRFs except for TC, and for rate of change of WC, SBP, DBP, and HDL-C.

**Table 4. Adjusted Mean of AUC of Metabolic Risk Factors Among Individuals Who Did and Did Not Develop Hypertension**

| | Men (n=2191) | | | Women (n=3183) | | | *P* for sex difference | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Without hypertension (n=1700) | With hypertension (n=491) | *P* value* | Without hypertension (n=2525) | With hypertension (n=658) | *P* value* | Without hypertension | With hypertension | *P* interaction† | *P* interaction‡ |
| AUC measures (∫) | | | | | | | | | | |
| BMI, kg/m$^2$ | 26.3 (0.1) | 27.8 (0.2) | <0.001 | 27.8 (0.2) | 30.3 (0.1) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| WC, cm | 92.5 (0.2) | 96.2 (0.4) | <0.001 | 90.2 (0.2) | 95.9 (0.3) | <0.001 | <0.001 | 0.578 | <0.001 | <0.001 |
| FPG, mmol/L | 5.6 (0.02) | 5.6 (0.04) | 0.074 | 5.3 (0.01) | 5.5 (0.03) | <0.001 | <0.001 | 0.087 | 0.007 | 0.009 |
| SBP, mm Hg | 113.6 (0.2) | 121.3 (0.3) | <0.001 | 109.2 (0.1) | 121.0 (0.3) | <0.001 | <0.001 | 0.525 | <0.001 | <0.001 |
| DBP, mm Hg | 74.9 (0.1) | 79.7 (0.2) | <0.001 | 72.2 (0.1) | 78.2 (0.1) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| HDL-C, mmol/L | 1.1 (0.01) | 1.1 (0.01) | 0.232 | 1.3 (0.01) | 1.2 (0.01) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Ln-triglycerides, mmol/L | 0.4 (0.01) | 0.5 (0.01) | <0.001 | 0.2 (0.01) | 0.4 (0.01) | <0.001 | <0.001 | <0.001 | 0.003 | 0.006 |
| TC, mmol/L | 4.81 (0.01) | 4.89 (0.02) | 0.012 | 4.96 (0.01) | 5.04 (0.02) | 0.003 | <0.001 | <0.001 | 0.957 | 0.882 |

Values were adjusted for baseline age in ANCOVA model. BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Ln-triglycerides, natural logarithm of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

*P values were adjusted by Bonferroni method and show the statistical difference between those with and without hypertension.

†P value shows the significance of interaction term of sex by hypertension status in ANCOVA model adjusted for baseline age.

‡P value shows the significance of interaction term of sex by hypertension status in ANCOVA model adjusted for baseline age, smoking status, physical activity level and family history of CVD.

The sex difference in trajectory BP measures during life course has been recently shown in a multicohort study with a multiethnic population.[36] The study included 32 833 participants (54% women) aged 18–85 years from 4 community cohorts. The trajectory analysis showed a sharper increase in SBP in women, compared with men, which began in the third decade and continued through the life course. In agreement with this study and a number of other studies in industrialized countries,[3,4] we found that BP elevation in women begins at the age of 30 years, indicating that among women, the accelerated rise in BP measures begins before they are likely thinking about their risk for heart disease.[20] We further found that women with incident hypertension, compared with men, experienced greater changes in the cumulative exposure and faster rates of change of BP measures over time. Trajectory patterns showed that although women with incident hypertension had lower level of SBP than in men during young adulthood, their SBP rose faster than that of the men, beginning at age 30 years and increased steadily until the age of 50 years, where BP values diverged in men and women.

Such overt sex differences in trajectory of BP elevation may be because of the variety of underlying mechanisms, including variable associations with other MRFs, which are also known to differ between men and women.[6,18] We observed that women with incident hypertension, compared with men, experienced greater cumulative exposure to BMI and faster rate of change of WC over time. Previous studies have reported that obesity increases BP in both sexes, but the stronger relation has been established in women,[6,37,38] so that a comparable increase in BMI causes a greater increase in SBP in women than in men.[6,39] Also, a 3-fold higher risk of hypertension has been reported for obese premenopausal women than for lean women.[6] In our study, the higher cumulative exposure to BMI in women may contribute to the greater change in their BP measures, compared with men. The earlier and steeper BP trajectory and the higher exposure to BMI in women may explain the greater impact of hypertension on major types of CVD including stroke,[10,11,40] myocardial infarction,[9,12] and heart failure[41] in women than men.

Also, it is well established that obese women develop more obesity-related comorbidities such as hyperlipidemia, insulin resistance, and diabetes than men.[6] In line with current evidence, we found a higher change in triglycerides, HDL-C, and FPG in women with incident hypertension, compared with men, which may be related to the higher cumulative exposure to BMI in women than men. We observed that among men who developed hypertension, BMI and WC increased rapidly from a low level to their peaks at the age of 40 years, whereas their female counterparts started

**Table 5. Adjusted Mean of Rate of Change of Metabolic Risk Factors Among Individuals Who Did and Did Not Develop Hypertension**

| | Men | | | Women | | | *P* for sex difference | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Without hypertension (n=1700) | With hypertension (n=491) | *P* value* | Without hypertension (n=2525) | With hypertension (n=658) | *P* value* | Without hypertension | With hypertension | *P* interaction† | *P* interaction‡ |
| Rate of change | | | | | | | | | | |
| BMI, kg/m$^2$ | 0.10 (0.001) | 0.13 (0.002) | <0.001 | 0.19 (0.001) | 0.19 (0.002) | 0.926 | <0.001 | <0.001 | <0.001 | <0.001 |
| WC, cm | 0.52 (0.002) | 0.52 (0.005) | 0.631 | 0.70 (0.002) | 0.75 (0.004) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| FPG, mmol/L | 0.04 (0.003) | 0.05 (0.006) | 0.138 | 0.03 (0.003) | 0.05 (0.005) | 0.048 | 0.258 | 0.728 | 0.827 | 0.837 |
| SBP, mm Hg | 0.19 (0.004) | 0.35 (0.008) | <0.001 | 0.28 (0.003) | 0.56 (0.007) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| DBP, mm Hg | 0.29 (0.001) | 0.29 (0.001) | 0.336 | 0.30 (0.001) | 0.35 (0.001) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| HDL-C, mmol/L§ | 0.010 (0.000) | 0.010 (0.000) | 0.109 | 0.012 (0.000) | 0.011 (0.000) | <0.001 | <0.001 | <0.001 | 0.011 | 0.004 |
| Ln-triglycerides, mmol/L§ | 0.002 (0.000) | 0.001 (0.000) | <0.001 | 0.010 (0.000) | 0.010 (0.000) | 0.887 | <0.001 | 0.001 | 0.001 | <0.001 |
| TC, mmol/L§ | 0.003 (0.000) | 0.001 (0.000) | <0.001 | 0.024 (0.000) | 0.024 (0.000) | 0.027 | <0.001 | <0.001 | <0.001 | <0.001 |

Values show the mean (SE) adjusted for baseline age in ANCOVA model. BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Ln-triglycerides, natural logarithm of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

*P values were adjusted by Bonferroni method and show the statistical difference between those with and without hypertension.

†P value shows the significance of interaction term of sex by hypertension status in ANCOVA model adjusted for baseline age.

‡P value shows the significance of interaction term of sex by hypertension status in ANCOVA model adjusted for baseline age, smoking status, physical activity level, and family history of cardiovascular disease.

§Maximum 3 digits have been shown after the decimal point for SE.

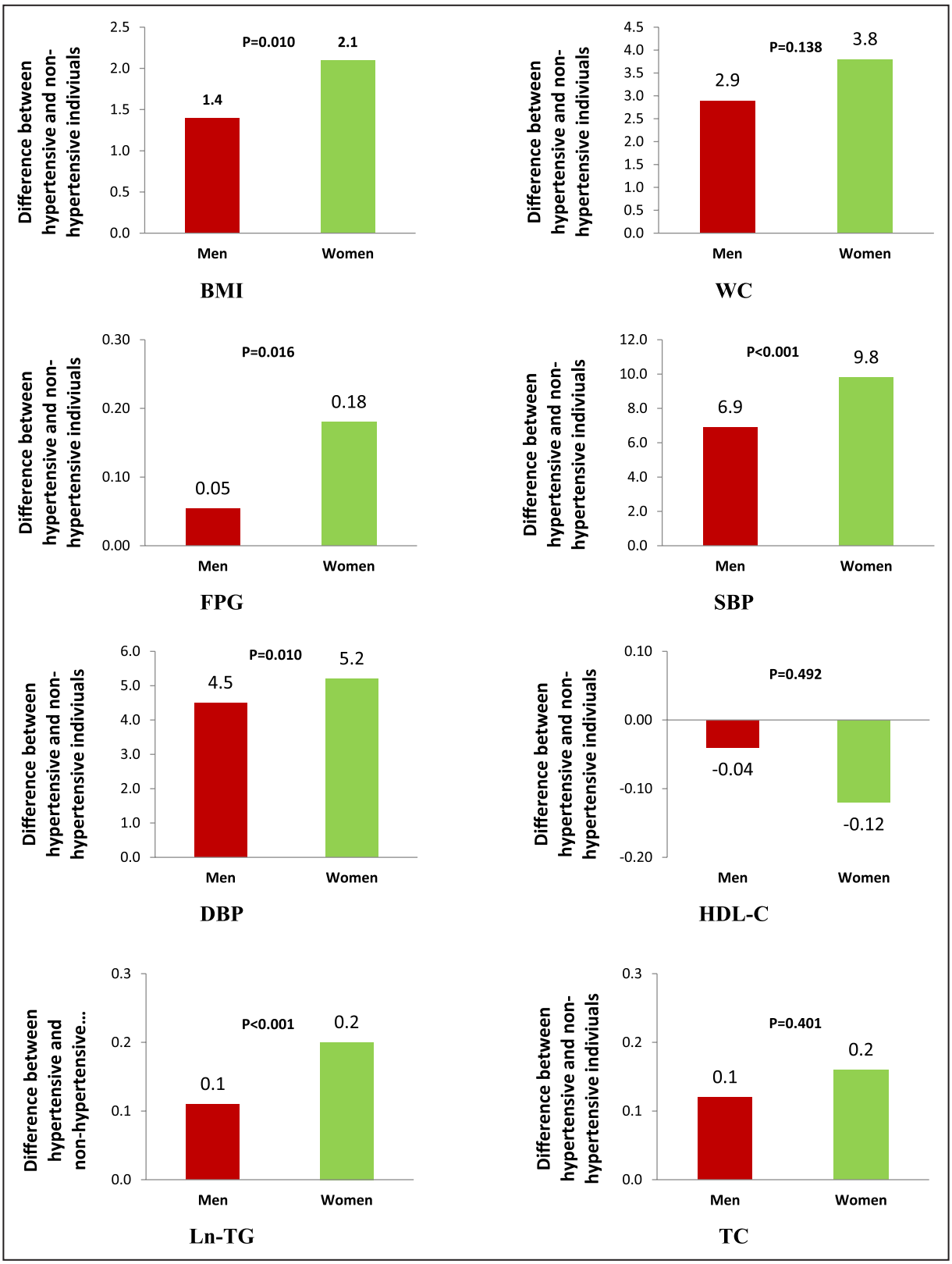


**Figure 3. Differences in age-adjusted mean values of metabolic risk factors at the age of 45.1 years among hypertensive and nonhypertensive individuals; *P* values show the statistical significance of interactions of sex by hypertension status.**

BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Ln-TG, natural logarithm of triglyceride; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

out at a higher level of BMI and WC, and an accelerated rise in BMI and WC continued beyond the menopausal transition. Also, the peaks of the triglycerides and TC trajectories occurred at earlier ages (around age 45 years) in men who developed hypertension, compared with women, and then started to decline. The rapid increase in BMI and lipids levels among men before the age of 45 years may contribute to the higher prevalence of hypertension in men, compared with women, during young adulthood.[6,42] Closely related was the finding that the mean age of hypertension incidence was lower in men than in women (45.9 versus 47.8) in our study.

We further found that women who did not develop hypertension tended to have a higher cumulative exposure to BMI and TC, and faster rates of change in all MRFs except for FPG, than men. Given that obesity has more deleterious effects on cardiovascular health in women compared with men,[6,43] and cardioprotection normally observed in premenopausal women is lost by the presence of obesity,[6] development of weight management interventions may improve hypertension and CVD outcomes among Iranian women, considering the higher prevalence of obesity and physical inactivity among them.[44]

On the other hand, men who did not develop hypertension had higher cumulative exposure to SBP, DBP, triglycerides, and lower exposure to HDL-C than their female counterparts, and also, the peaks of BMI, WC, triglycerides, and TC occurred between the ages of 40 and 50 years, indicating that Iranian men may be at higher risk of premature CVD than women.[45] Thus, more tailored interventions should be implemented early in life to prevent hypertension and CVD among Iranian men.

The key strength of our study was a relatively large sample with up to 6 repeated measurements during a 20-year period. We used direct measurements of weight, height, WC, and MRFs in each follow-up. Our study also had several limitations. First, ≈32% of eligible participants at baseline were excluded from the analysis (nonparticipants). The statistically but not clinically important differences were observed between the participants versus nonparticipants in some baseline variables. Because participants were generally healthier than nonparticipants, the results may be biased toward an underestimation of incidence of hypertension and thus AUC of MRFs. Second, our findings are subject to residual confounding by other lifestyle factors such as dietary intake. Third, PALs were measured by 2 different questionnaires in the first and second phases. Although we defined a categorical variable (low and high) for PAL, the measurement error because of self-reported PAL may remain. Additionally, self-reported smoking status may be less accurate, especially among women, because of increased awareness of the social undesirability of smoking. Finally, our results were obtained from the population of the Tehran urban area. Because complex cultural, economic, and social factors lead to differences in the lived experience between men and women that can also affect physiology and vascular biology,[36] our findings may not be generalizable to other countries and also other rural areas of Iran.

## CONCLUSIONS

We observed that women who developed hypertension, compared with men, experienced more metabolic disturbances before onset of hypertension, which may explain the greater impact of hypertension on major types of CVD including stroke, myocardial infarction, and heart failure in women than in men. Moreover, men in our study experienced unfavorable change of major MRFs during young adulthood, which will set the stage for development of premature CVD in men. The trajectory of MRFs may provide additional insight into the pathophysiology and treatment of hypertension and optimize prevention and management efforts in both women and men.

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### Disclosures

None.

### Supplementary Material

Data S1
Tables S1–S5
Figure S1

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# SUPPLEMENTAL MATERIAL

**Data S1. Supplemental Methods**

**Study Population**

The Tehran Lipid and Glucose Study (TLGS) is a prospective cohort study was first designed in 1997 and implemented in 1999 in a west-Asian developing country, the Islamic republic of Iran (23). The protocol of the TLGS was based on the WHO-recommended model for field surveys of diabetes and other non-communicable diseases (NCDs) and the WHO-MONICA protocol (25) for population surveys (27). The main goal of the TLGS was understanding the risk factors and outcomes of NCDs in a representative sample of residents of Tehran, capital of Iran. Tehran city covers an area of 1500 $km^2$ and consists of 22 districts with a total population of over ten million people. In 1999, Tehran was composed of 20 urban districts and made up a population of 6.7 million. Study samples were chosen from the urban District 13 of Tehran, because city-wide data showed a high rate of stability in that district. Also, the age distribution in district 13 was representative of the overall population in Tehran (26). This district is under the coverage of Shahid Beheshti University of Medical Sciences and Health Services and have 20 medical health centers. All medical health centers in this district have the filed data of almost all covered families (over 90%) (24). TLGS consists of several phases, the phase 1 (1999-2001) was a cross-sectional, in which from the 20 medical health centers in district 13, three health centers of Lailatolghadr, Mohammadian, and Salavati were selected. Then, a multi-stage stratified cluster random sampling technique was used to select study sample. The selected subjects were contacted, invited, and then recruited to participate in the study and were referred to one of the three chosen medical health centers for the measurements. More than 15000 people aged $\geq$ 3 years participated in phase 1, with crude response rate of about 57.5%. However, preliminary data revealed there was no significant different between responders and non-responders. Following baseline collection of data in phase 1, the prospective follow up studies were conducted in phases 2 (2002-2005), 3 (2005-2008), 4 (2009-2011), 5 (2012-2015), and 6 (2015-2018) by means of about 3 years intervals

between assessments. Moreover, during the phases 2, about 3550 new participants were recruited and were followed in next phases.

In all phases, participants, after signing informed written consent, were studied by trained social workers and physicians according to a uniform protocol. Demographic, lifestyle information, medical history and clinical examination were obtained by the use of a standard and validated questionnaire. Blood pressure, and anthropometrical measurements were taken according to the standard protocol. For biochemical measurements, a blood sample was drawn between 7:00 and 9:00 AM into vacutainer tubes from all study participants after 12-14 hours overnight fasting. All laboratory kits were supplied by Pars Azmon Inc., Iran. Physical activity level (PAL) was assessed using Lipid Research Clinic (LRC) questionnaire in the first phase of the TLGS. Since the LRC questionnaire assesses PAL of the participant qualitatively and the questions are fully subjective, the Steering Committee of the TLGS replaced the questionnaire by Modifiable Activity Questionnaire (MAQ) and a Persian translated form of that was used to assess PAL in the TLGS participants. This questionnaire measures all three forms of activities including leisure time, job, and household activities in the past year (31).

For the present study, 9014 participants aged 20-50 years from the first (n=7133) and second (n=1881) phases were selected and followed until the end of the study (18 April 2018). We excluded 908 individuals with prevalent hypertension at baseline, 245 people who had missing data on hypertension status at baseline, and 1430 individuals with no follow-up data after recruitment. Because at least three measurements of metabolic risk factors (MRFs) were required for studying trajectory of MRFs, we further excluded 1057 people who did not participate at least two times before hypertension incidence or before the last participation for those who did not develop hypertension. Finally, 5374 adults (2191 men) formed the study population (Figure S1). At baseline, less than 5% of study population had missing values for several MRFs and other covariates; thus, we chose not to exclude these individuals. The

study populations were participated 3-6 times during the study period (5 times on average). The number of participants who were participated 3, 4, 5 and 6 times was 662, 872, 1667 and 2173, respectively. It should be noted that some individuals had also missing values in MRFs in a number of follow-up examinations. Therefore, the number of participations may not be necessarily equal to the number of measurements. This case's missing values are unproblematic; because, the person-period data set does not include records for these unobserved phases in longitudinal analysis (29). Second, <5% of MRFs values were missing in person-period format. In Table S1, we have presented the detailed information about dataset. This study was approved by the ethical committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All participants provided written informed consent.

**Table S1. Information about data in person-period format, 1999-2018.**

| Variable | Men | | Women | |
|---|---|---|---|---|
| | Number of observations | Number of excluded records (%) | Number of observations | Number of excluded records (%) |
| Age | 10115 | 0 (0) | 15355 | 0 (0) |
| BMI | 9906 | 209(2) | 14834 | 521 (3) |
| WC | 9904 | 211(2) | 14799 | 556 (4) |
| FPG | 9936 | 179(2) | 15184 | 171 (1) |
| SBP | 9973 | 142(1) | 15206 | 149 (1) |
| DBP | 9973 | 142(1) | 15206 | 149 (1) |
| HDL-C | 9933 | 182(2) | 15178 | 177 (1) |
| Ln-TG | 9938 | 177(2) | 15186 | 169 (1) |
| TC | 9941 | 174(2) | 15185 | 170 (1) |

In the person-period dataset, each person has multiple records according to the number of participation in the study; for example, if a man had participated 4 times in the study, he had 4 records in the dataset. Therefore, if he had missing value for one of the variables in one examination, that record was excluded, and three other records remained for the longitudinal analysis.

**BMI:** body mass index; WC: waist circumference; **FPG:** fasting plasma glucose; **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure; **HDL-C:** high-density lipoprotein cholesterol; **Ln-TG:** natural log of triglyceride; **TC:** total cholesterol; **SD:** standard deviation

## Table S2. Characteristics of final growth models for metabolic risk factors in men.

| | Type of model | Models | Residual heteroscedasticity | Residual correlation structure |
|---|---|---|---|---|
| BMI (kg/m$^2$) | Cubic growth model with the intercept and slopes variability | Level 1: $BMI_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + b_3Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2 + u_{2i}$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times \lvert Age \rvert^{2\delta}$ | First-Order Autoregressive |
| WC (cm) | Cubic unconditional growth model | Level 1: $WC_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + b_3Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| FPG (mmol/L) | Cubic growth model with the intercept and slope variability | Level 1: $FPG_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + b_3Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| SBP (mmHg) | Quadratic growth model with the int ercept and slope v ariability | Level 1: $SBP_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$ | $\sigma^2 \times \lvert Age \rvert^{2\delta}$ | First-Order Autoregressive |
| DBP (mmHg) | Cubic unconditional growth model | Level 1: $DBP_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + b_3Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| HDL-C (mmol/L) | Cubic growth model with the intercept and slopes variability | Level 1: $HDL_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + b_3Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2 + u_{2i}$<br>Level 2: $b_{3i} = \beta_3$ | - | - |
| Ln-TG (mmol/L) | Quadratic growth model with the intercept and slope variability | Level 1: $Ln\text{-}TG_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + b_3Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2 + u_{2i}$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| TC (mmol/L) | Quadratic growth model with the intercept and slope variability | Level 1: $TC_{ij} = b_{oi} + b_1Age_{ij} + b_2Age^2_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$ | - | First-Order Autoregressive |

**$\sigma^2 \times |Age|^{2\delta}$:** Variance proportional to the absolute value of Age raised to a constant power

**$\sigma^2 \times e^{2\delta \times Age}$:** variance proportional to the exponential of Age multiplied by a constant

**BMI:** body mass index; WC: waist circumference; **FPG:** fasting plasma glucose; **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure; **HDL-C:** high-density lipoprotein cholesterol; **Ln-TG:** natural log of triglyceride; **TC:** total cholesterol.

## Table S3. Characteristics of final growth models for metabolic risk factors in women.

| | Type of model | Models | Residual heteroscedasticity | Residual correlation structure |
|---|---|---|---|---|
| BMI (kg/m$^2$) | Quadratic unconditional growth model | Level 1: $BMI_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1$<br>Level 2: $b_{2i} = \beta_2$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| WC (cm) | Quadratic conditional growth model | Level 1: $WC_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| FPG (mmol/L) | Cubic growth model with the intercept and slope variability | Level 1: $FPG_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + b_3 Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| SBP (mmHg) | Quadratic growth model with the intercept and slope variability | Level 1: $SBP_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2 + u_{2i}$ | Was not adjusted fo r variance structure | Compound Symmetry |
| DBP (mmHg) | Cubic growth model with the intercept and slope variability | Level 1: $DBP_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + b_3 Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | - | - |
| HDL-C (mmol/L) | Quadratic conditional growth model | Level 1: $HDL\text{-}C_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + b_3 Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | Compound Symmetry |
| Ln-TG (mmol/L) | Cubic growth model with the intercept and slope variability | Level 1: $Ln\text{-}TG_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + b_3 Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1 + u_{1i}$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | $\sigma^2 \times e^{2\delta \times Age}$ | First-Order Autoregressive |
| TC (mmol/L) | Cubic unconditional growth model | Level 1: $TC_{ij} = b_{oi} + b_1 Age_{ij} + b_2 Age^2_{ij} + b_3 Age^3_{ij} + e_{ij}$<br>Level 2: $b_{oi} = \beta_0 + u_{0i}$<br>Level 2: $b_{1i} = \beta_1$<br>Level 2: $b_{2i} = \beta_2$<br>Level 2: $b_{3i} = \beta_3$ | - | First-Order Autoregressive |

**$\sigma^2 \times |Age|^{2\delta}$:** Variance proportional to the absolute value of Age raised to a constant power

**$\sigma^2 \times e^{2\delta \times Age}$:** variance proportional to the exponential of Age multiplied by a constant

**BMI:** body mass index; WC: waist circumference; **FPG:** fasting plasma glucose; **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure; **HDL-C:** high-density lipoprotein cholesterol; **Ln-TG:** natural log of triglyceride; **TC:** total cholesterol.

**Table S4. Parameters of final growth models for metabolic risk factors in men.**

| | | Intercept | Age | Age $^2$ | Age $^3$ | Variance of random intercept | Variance of random Age term | Variance of random Age$^2$ term |
|---|---|---|---|---|---|---|---|---|
| | Type of model | $\beta_0$ | $\beta_1$ | $\beta_2$ | $\beta_3$ | $\sigma^2 u_0$ | $\sigma^2 u_1$ | $\sigma^2 u_2$ |
| BMI (kg/m$^2$) | Cubic | 27.3 (0.08) | 0.11 (0.004) | -0.05 (0.002) | 0.002 (0.0003) | 15.16 (0.49) | 0.01 (0.001) | 0.001 (0.0003) |
| WC (cm) | Cubic | 94.86 (0.22) | 0.51(0.01) | -0.19 (0.006) | 0.007(0.0007) | 89.86 (3.40) | - | - |
| FPG (mmol/L) | Cubic | 5.35 (0.02) | 0.05 (0.002) | 0.005 (0.001) | -0.0005 (0.0001) | 0.84 (0.03) | 0.003 (0.0001) | - |
| SBP (mmHg) | Quadratic | 111.4 (0.2) | 0.22 (0.01) | 0.14 (0.01) | - | 61.49 (3.1) | 0.10 (0.03) | - |
| DBP (mmHg) | Cubic | 76.1 (0.1) | 0.29 (0.01) | -0.038 (0.006) | -0.003 (0.001) | 26.0 (1.3) | - | - |
| HDL-C (mmol/L) | Cubic | 1.01 (0.004) | 0.01 (0.0004) | 0.002 (0.0001) | -0.0001 (0.00002) | 0.04 (0.002) | 0.00003 (0.000006) | 0.000002 (0.000001) |
| Ln-TG (mmol/L) | Quadratic | 0.56 (0.01) | 0.001 (0.0006) | -0.006 (0.0003) | - | 0.17 (0.006) | 0.00009 (0.00002) | - |
| TC (mmol/L) | Quadratic | 5.07 (0.01) | 0.002 (0.001) | -0.011 (0.0007) | - | 0.57 (0.02) | 0.0005 (0.0001) | - |

Values show parameter and standard error (SE).

**BMI:** body mass index; WC: waist circumference; **FPG:** fasting plasma glucose; **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure; **HDL-C:** high-density lipoprotein cholesterol; **Ln-TG:** natural log of triglyceride; **TC:** total cholesterol

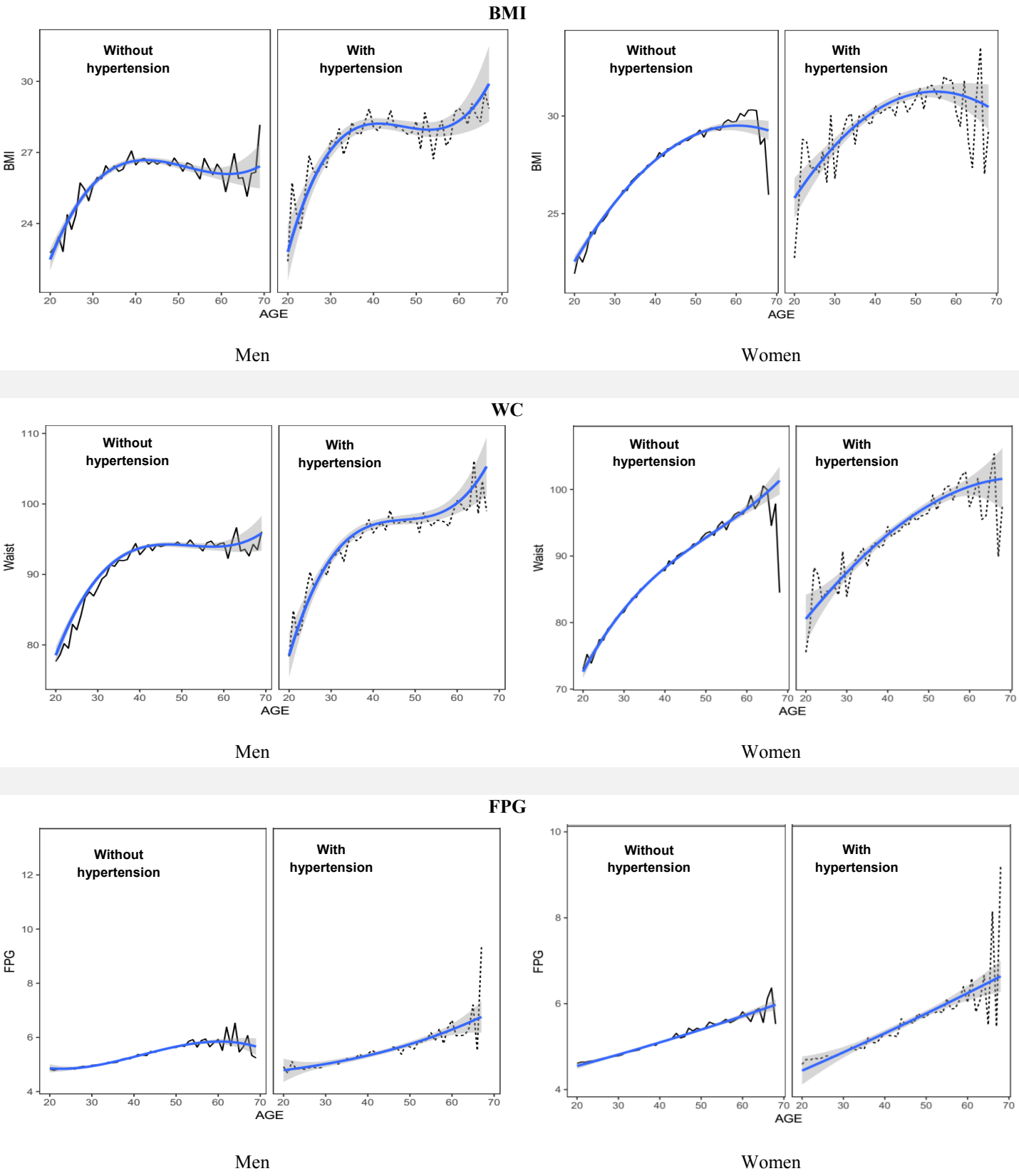
**Table S5. Parameters of final growth models for metabolic risk factors in women.**

| | | Intercept | Age | Age $^2$ | Age $^3$ | Variance of random intercept | Variance of random Age term | Variance of random Age$^2$ term |
|---|---|---|---|---|---|---|---|---|
| | Type of model | $\beta_0$ | $\beta_1$ | $\beta_2$ | $\beta_3$ | $\sigma^2 u_0$ | $\sigma^2 u_1$ | $\sigma^2 u_2$ |
| BMI (kg/m$^2$) | Quadratic | 28.45 (0.07) | 0.19 (0.003) | -0.04 (0.001) | - | 16.82 (0.48) | - | - |
| WC (cm) | Quadratic | 90.11 (0.18) | 0.71 (0.01) | -0.05 (0.006) | - | 85.07 (2.53) | 0.07 (0.009) | - |
| FPG (mmol/L) | Cubic | 5.18 (0.02) | 0.03 (0.001) | 0.003 (0.0009) | -0.0002 (0.0001) | 0.69 (0.02) | 0.001 (0.0001) | - |
| SBP (mmHg) | Quadratic | 107.1 (0.2) | 0.33 (0.01) | 0.15 (0.009) | - | 78.3 (2.4) | 0.14 (0.01) | 0.022 (0.006) |
| DBP (mmHg) | Cubic | 72.9 (0.12) | 0.30 (0.01) | 0.011 (0.005) | -0.007 (0.0008) | 27.2 (1.01) | 0.02 (0.005) | - |
| HDL-C (mmol/L) | Quadratic | 1.23 (0.005) | 0.012 (0.0002) | 0.002 (0.0001) | - | 0.07 (0.001) | 0.00003 (0.000006) | - |
| Ln-TG (mmol/L) | Cubic | 0.30 (0.01) | 0.01 (0.001) | -0.002 (0.0002) | -0.0002 (0.00004) | 0.14 (0.004) | 0.00003 (0.00001) | - |
| TC (mmol/L) | Cubic | 4.97 (0.01) | 0.02 (0.001) | -0.001 (0.0006) | -0.0005 (0.00008) | 0.44 (0.01) | - | - |

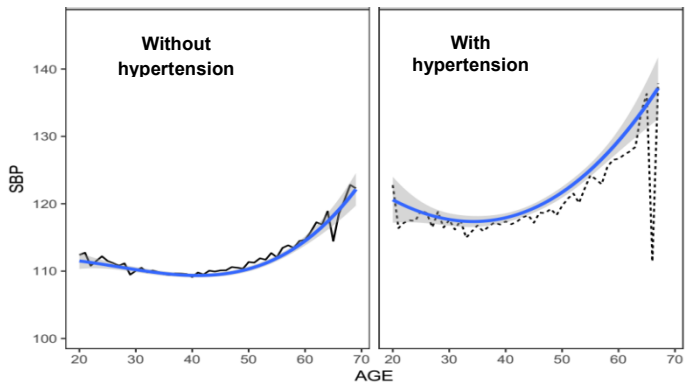
Values show parameter and standard error (SE).

**BMI:** body mass index; WC: waist circumference; **FPG:** fasting plasma glucose; **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure; **HDL-C:** high-density lipoprotein cholesterol; **Ln-TG:** natural log of triglyceride; **TC:** total cholesterol

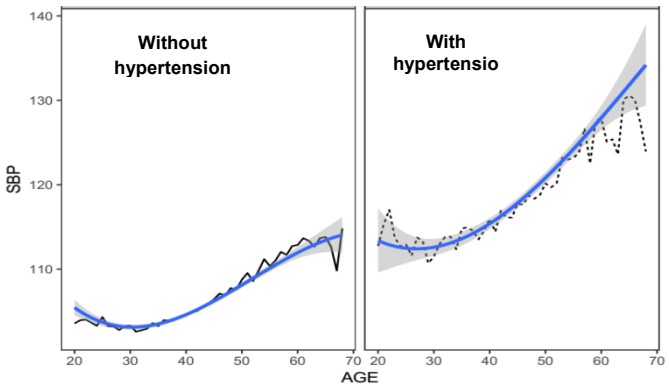
**Figure S1. Mean of predicted value for metabolic risk factors from the final models for men and women.**



**SBP**

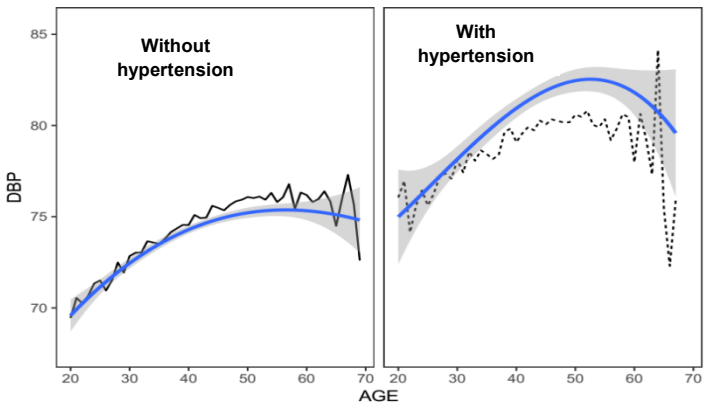



Men

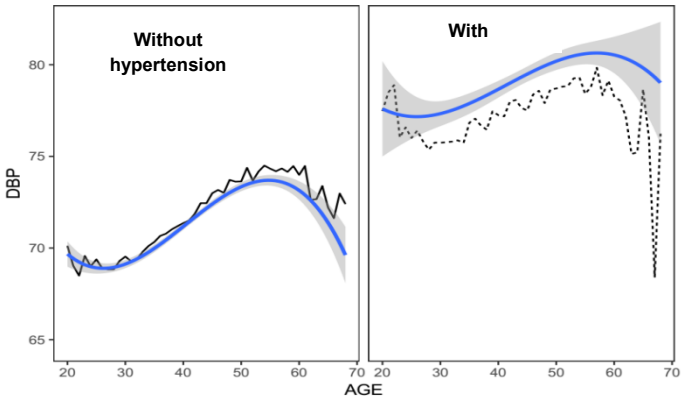



Women

**DBP**

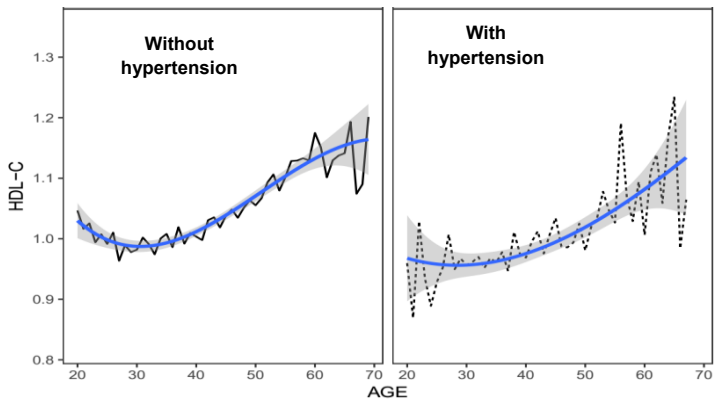



Men

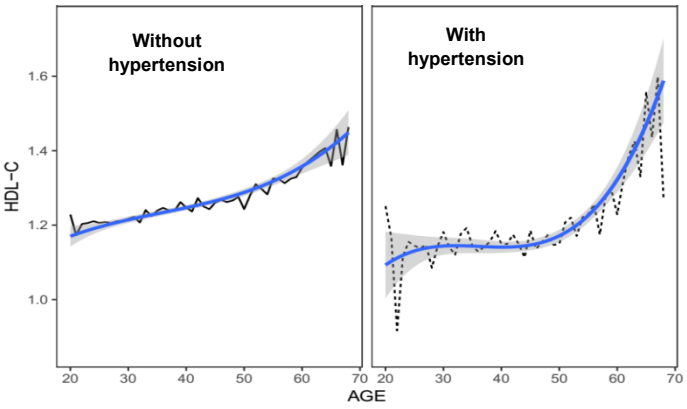



Women

**HDL-C**

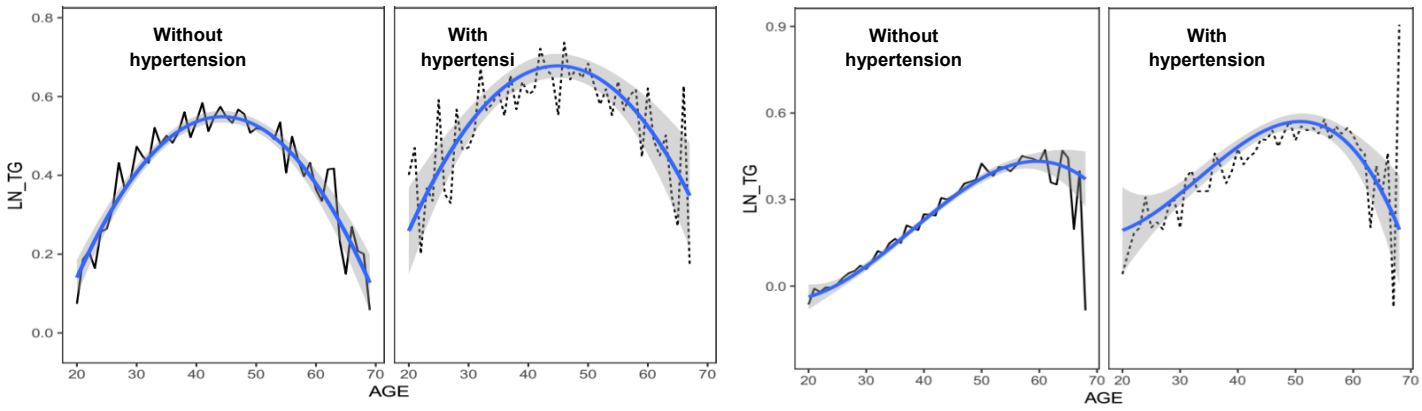



Men



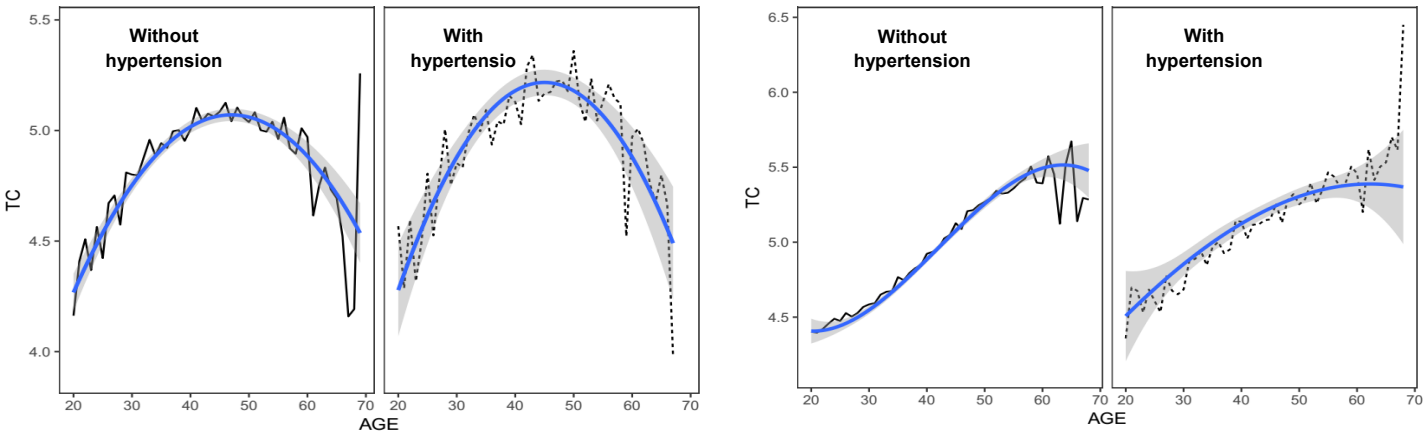

Women

**TG**




Men Women

**TC**




Men Women

In each graph, age is represented on the horizontal axis, and changes of MRFs are shown as a function of age, age$^2$, and age$^3$

**BMI:** body mass index; **WC:** waist circumference; **FPG:** fasting plasma glucose; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **HDL-C:** high-density lipoprotein cholesterol; **TG**: triglyceride; **TC**: total cholesterol; **MRFs**: metabolic risk factors