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Age and gender dependent associations of blood pressure and serum sodium and potassium-renal and extrarenal regulations

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ABSTRACT

Association analyses between blood pressure (BP) and serum sodium and potassium for 14657 men and 16977 women between ages 12 and 85 show that responses of BP to serum sodium and potassium are age and gender dependent. The data were from the National Health and Nutrition Examination Survey between 2003 and 2014. Associations between serum sodium and BP are positive only for advanced age groups and for serum sodium level above 139~140 mmol/l in less advanced groups. These positive associations can be explained by traditional renal-centered mechanism. Inverse associations between systolic BP and serum sodium exist when sodium is below 139 mmol/l in less advanced age groups (<60 for men and <70 for women). These inverse associations can partially be explained by the extrarenal regulatory mechanism in which sodium storage in negatively charged glycosaminoglycans in the interstitium may be involved. Associations of high serum potassium and low BP are consistent and exist in most age groups. Effect of potassium on systolic BP and diastolic BP are more prominent in less advanced age groups. Age dependent associations between sodium and BP support the theory that sodium homeostasis in the body may not be regulated by renal-centered responses alone. There might be regulation of an extrarenal system in which sodium attraction by negatively charged glycosaminoglycans plays a role.

1. Introduction

High blood pressure or hypertension is a growing public health challenge because of its strong association with cardiovascular diseases (CVD) and stroke. CVD is estimated to account for nearly 1 in every 3 deaths in adults in the US.[1] According to recent estimates, roughly 1/3 of US adults (~75 million) have high blood pressure.[2] The broad consensus is that dietary potassium intake is negatively associated with blood pressure (BP) and dietary sodium intake is positively associated with BP.[3,4] There are also calls for caution on the possible potential health risk of long-term low sodium intake (<2.3 or 1.5 g per day).[5,6] Increasing dietary sodium intake are generally believed to result in expansion of blood volume and increase in BP.[7] However, recent studies also suggested that there are water-independent sodium storage via regulated glycosaminoglycans in skin and other tissues.[8-10] Increased potassium, on the other hand, reduces BP through its ability in vasodilation and increased excretion of sodium.[11] Though large quantities of studies on association of BP and dietary intakes or urinary excretions of sodium and potassium have been reported[12,13], there are few studies on age and gender dependent association between BP and serum sodium and potassium. Lack of study in this aspect hinders the understanding of mechanism on how sodium and potassium affect BP and might compromise the effectiveness of long-term effort in combating CVD risk of targeted population.[14]

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) are two common readings for monitoring BP and cardiovascular risk. Significant amount of SBP, DBP, serum sodium and potassium data have been collected during the past two decades by the National Health and Nutrition Examination Survey (NHANES). NHANES is a program of studies intended

for assessing the health and nutritional status of adults and children in the US, administered by the National Center for Health Statistics of US Centers for Disease Control and Prevention (CDC). Large dataset of NHANES have made stratified analyses of association between SBP and DBP and serum sodium and potassium levels at varied age groups and detailed explanation of their association possible. Current study intends to examine whether associations between high BP and serum sodium and potassium are age and gender dependent in the general population using NHANES biochemical and BP datasets between 2003 and 2014. This study might be the first study, to the author's best knowledge, that this relationship is directly examined for multiple individual age groups.

2. Material and Methods

2.1. Data

SBP and DBP in mm of mercury (Hg) were obtained from the Blood Pressure files of NHANES between 2003 and 2014 for 20403 men and 23826 women participants. Serum sodium and potassium data in mmol/liter and blood osmolality in mmol/kg were obtained from the Standard Biochemistry Profile files of NHANES measured during the same period for 14657 men and 16977 women. The age and gender data were obtained from the demographic files in NHANES database. For SBP and DBP, because the first of the three readings in the NHANES BP data file has the most complete records, it was used in the analyses unless an individual data pair has apparent outliers (such as SBP or DBP being zero). This period between 2003 and 2014 includes measurements of 6 NHANES sampling cycles.

2.2. Statistical analyses

Because of the significant variations in responses of individual's BP to the serum sodium and potassium, age grouped average and moving average methods were used to extract the broad underlying trends (Figure 1). Both methods are well-established statistical means for reducing the high frequency variations of time series or ordered data series of a large dataset. [15,16] The "low passing filter" of moving average or group average method allows an underlying broad trend to be uncovered in an otherwise highly fluctuated large data series.[15] Advantage of trend analyses using the moving average approach over conventional scatter plot method based on individual data is apparent for large datasets (Figure 1)

Age grouped data was used for age vs. sodium, potassium, SBP, DBP and osmolality analyses because there are sufficient data in each age group to extract the broad trend line without loss of any age values. The differences among the trends extracted from age grouped average (moving average with varied interval spans) and moving average with fixed interval spans are not significant (Figure 1). Age grouped averages of SBP and DBP between ages 8 and 85 were shown in later sections for 20403 men and 23826 women. Age grouped averages of serum sodium, potassium and osmolality between ages 12 and 85 were shown for 14657 men and 16977 women.

For serum sodium and potassium vs. SBP and DBP data, the data were divided into 7 age groups: between ages of 12-19, 20-29, 30-39, 40-49, 50-59, 60-69 and 70-85. Each group has 1872 to 3069 subjects for men and 2347 to 4302 subjects for women. Moving average method was used to filter off the high frequency variations of all data in each age group after the SBP and DBP were sorted (i.e. ordered) either by their corresponding sodium level or potassium

level. After analyzed the interval spans of 300, 500 and 1000 data points, interval span of 1000 points was selected for the moving average calculation. This large interval span removed most of the high frequency variations that are likely associated with the non-sodium or potassium related cofactors and smoothed and kept the major trend of the data points for each age group (Figure 1). Iso-systolic blood pressure maps with serum potassium as x-axis and sodium as y-axis were plotted using a 2-D moving average interpolation method (Golden Software, Surfer v.11) after both serum potassium and sodium data were standardized. Iso-systolic pressure maps illustrate the age and gender associated serum potassium or sodium dominance on SBP that linear moving average trends of sodium or potassium vs. SBP cannot show.

3. Results

3.1. Age and gender varied trends of SBP, DBP and serum sodium, potassium and osmolality

SBP of both genders increase faster before age 20 and steadily afterwards (Figure 2). However, SBP of men are only above that of women after puberty (~12 years old) and before women's menopause age (~50 years old). Women's SBP catches on men's SBP after menopause and becomes higher than men's after approximately age 70. Plot of DBP vs. age has a parabolic shape for both genders with a peak DBP at about age 50 (Figure 2b). The gender gap of DBP narrows after age 50.

Parting of serum sodium levels in men and women occurs quickly after puberty with a sharp rise in men's serum sodium and a decline in women's serum sodium (Figure 2c). There is a decline of serum sodium for women before the age of approximately 26. Men's serum sodium levels are generally higher than women's before women's menopause. Women's serum

sodium increase after age 25 and surpasses men's after menopause and stays above men's serum sodium level for approximately 20 years between ages 50 and 70 years old. Potassium levels decline during the age of teen and early twenties and increase after age of approximately 26 for both genders. Men's potassium levels are consistently higher than women's, though the gap narrows after age 60. Both men and women's osmolality increase with age (Figure 2e,f). Increase of women's osmolality, somewhat similar to sodium, follows the aging patterns of estrogen. Linear regression of serum sodium with osmolality are apparent for both men and women in all age groups (R^2>0.955) except men's age group of 70-85.

3.2. Age and gender dependent dominances of serum sodium and serum potassium on SBP

The iso-systolic blood pressure maps illustrate the dominant effect of serum sodium on SBP in the advanced age group (70-85 years old) for both genders (Figure 3). Populations of this age group with low serum sodium and high serum potassium have apparent low SBP while populations with high serum sodium and low serum potassium have high SBP (Figure 3a, b). For populations under 70 years old, influence of serum potassium on SBP is more dominant than influence of serum sodium. It also needs to notice that low serum potassium and low serum sodium are associated with higher blood pressure in population of less advanced age groups (low left corners of Figure 3c,d,e). This inverse association between SBP and serum sodium will be more apparent in the linear moving average trends of less advanced age groups in the following section.

3.3. Age and gender dependent relationships of BP and serum sodium and potassium

Age dependent relationships of SBP and DBP and serum sodium and potassium are apparent (Figures 4- 5). Both SBP and DBP of men are generally higher than that of women at the same sodium or potassium levels for the same age group before women's menopause.

For men, there are apparent averaged upward trends in SBP vs. serum sodium plot for the advanced age groups of 60-69 and 70-85 (Figure 4). There are apparent declining trends of SBP in response to serum sodium rise for age groups of 12-19, 20-29, 30-39, and 50-59 at moderate and low serum sodium level (<139~140 mmol/l). There are also the upward tick (i.e., short) trends of SBP in response to rising serum sodium when serum sodium level is approximately above 139~140 mmol/l for age groups between 20 and 59. DBP increases in response to sodium levels are apparent for the advanced age group of 60-69 and less apparent for age group 70-85. DBP decreases in response to serum sodium increase for three age groups younger than 39 years old. Because there are large number of data points (between 873 and 2070 for men, 1348 and 2454 for women after filtering) in the extracted trends, all the slopes, either positive or negative, are statistically significant (all $p \approx 0.00$) when regression slopes of linear trends were tested.

For women, SBP decreases in response to increasing sodium at low to moderate levels (<139 mmol/l) for almost all age groups except age groups 30-39 and 70-85 (Figure 4). SBP increases in response to increasing serum sodium at high serum sodium level (> 139 ~140 mmol/l) for almost all age groups as well except for age groups 60-69 and 20-29 (Figure 4b). DBP increases in response to sodium increase for three age groups: 20-29, 70-85 and 30-39. DBP decreases in response to sodium increase for age groups of 40-49 and 50-59.

Both men and women's SBP decrease with increasing serum potassium except in the age group of 30-39 (Figure 5). This inverse relationship is more significant (shown by steeper slopes) in age groups of 50-59 and 60-69 for both genders. Decrease of DBP in response to serum potassium increase is more apparent for men than for women (Figure 5c, d). DBP increases in response to serum potassium increase for two age groups 20-29 and 30-39 for women.

4. Discussion

4.1. Age and gender dependent trends of BP vs. serum sodium and potassium

SBP increases with age. DBP increases with age before 50 and decreases afterwards for both men and women (Figure 3). These trends reflect the progressive stiffness of large elastic arteries in cardiothoracic circulation and slow narrowing of blood vessels with age.[17,18] Progressively decreasing glomerular filtration rate, reducing renal flow rate and increasing blood osmolality with age also contribute to increased blood pressure in advanced ages.[19]

Changes of relative levels of SBP and DBP in plots of SBP and DBP vs. ages for men and women before puberty and after women's menopause are expected at least partially to be related to the gender differences in estrogen and androgen levels. Women's estrogen (E2) affects the regulatory mechanism of blood pressure via upregulation of nitric oxide (NO) production and different expression levels of angiotensin and endothelin receptors.[19] E2 increases NO production and decreases angiotensin II activities and angiotensin converting enzymes.[20,21] Hence, faster increases of women's SBP after menopause may at least partially be related to loss of beneficial effects of estrogen.[22] Aging trends of women's serum sodium may

also likely be related to the enhancing or blunting of pressure-natriuresis relationship resulting from increase or decrease in estrogen.[23,24] Aging trends of osmolality have similar patterns as that of sodium. Declining total body water and blood volume and loss of urinary concentrating ability might be part of the reasons for the continuing increase of osmolality with age.

Trends of serum potassium vs. age in both genders likely correspond more to the growth need of body-bone mass than hormones. Progressive declines of serum potassium before age 26 for both genders are related to the growth need of potassium in tissues and bones during this period.[26,27] Once the growth need subsides, serum potassium increases with age corresponding to the decline in total body potassium as a result of gradual decline in muscle mass. Gender difference in potassium is related to the different needs of total body potassium in the fat free body mass of men and women.[27,2825] In addition, age and gender differences in electrolyte intakes and drinking behaviors may also contribute to trends observed here.[20]

4.2. Regulations of serum sodium by renal and extrarenal mechanisms, age and gender dependence

Associations of increasing serum sodium with SBP and DBP elevation are apparent for age groups 60-69 and 70-85 for men and for age group 70-85 for women. Up-tick of SBP in response to rising serum sodium in less advanced age groups of both genders when serum sodium exceeds 139~140 mmol/l may indicate a critical triggering level of renal system response. Positive association of serum sodium and SBP can be explained by the traditional

renal centered regulation through anti-diuretic hormone (ADH), rein-angiotensin-aldosterone system (RAAS) and atrial natriuretic peptide (ANP) mechanism.[29]

SBP decrease in response to serum sodium increase in less advanced age groups at moderate and lower sodium levels (<139~140 mmol/l) may imply an extrarenal mechanism for regulation of sodium homeostasis. The groups with serum sodium less than 140 mmol/l encompass majority of the data in the less advanced age groups (~51% of men and 57.8% of women in the studied population younger than 70 years old). Recent studies shown that sodium homeostasis may also be regulated by negatively charged glycosaminoglycans in the interstitium in skin and other tissues (endothelial surface layer and muscle).[8-10] In addition, the authors think that the sodium attracted onto the negatively charged glycosaminoglycan sites may attract polar water molecules and create a loose double layer. The sodium and water loose double layer, though does not change the total extra cellular fluid (ECF), may shift plasma fluid into the interstitial fluid and reduce the blood volume and blood pressure. Only when serum sodium reaches a critical level or the interstitium charge sites are satisfied, further increase of serum sodium can trigger the increase of blood volume and blood pressure in less advanced age groups.

Though serum sodium level does not reflect the dietary intake of sodium, increased dietary intake of sodium may subsequently increase serum sodium levels.[30,31] Increased serum sodium level is associated with decreasing SBP in this study for sodium level below ~140 mmol/l in less advanced age groups. Increased urinary excretion of sodium, considered as the marker for dietary sodium intake, has been associated with SBP increase consistently.[3,4] The extrarenal

third compartment sodium storage in the negatively charged glycosaminoglycans may help explain this discrepancy. In less advanced age groups, increased intake of sodium will need to satisfy the interstitium negative charge sites before an increase in urinary sodium excretion can be observed. It is only after the interstitium charge sites are satisfied and balanced with Na^+ ions in ECF that further increase of sodium intake can trigger the renal-centered system response and result in the concurrent increases of urinary excretion of sodium, blood volume and SBP. In the advanced age group because of increased osmolality, diminished interstitial fluid and reduced interstitium charge sites, increasing intake of sodium can trigger a quick response of renal centered system, and a quick increase in the blood volume and blood pressure.

Previous studies, when age and gender were not separated, indicated that either a highly significant inverse correlation,[32] or no correlation between serum sodium and SBP and DBP,[33] or a positive correlation between hypertension risk and serum Na concentration over 140 mmol/l.[34] These results are largely similar to results of this study: 1) inverse correlation between serum sodium and SBP when averaged serum sodium is under 140 mmol/l for majority of study points; 2) positive correlation exists between serum sodium and increasing SBP in advanced age groups and when serum sodium is larger than 140 mmol/l in less advanced age groups.

4.3. Age and gender dependent associations of blood pressure and serum potassium

Associations of high serum potassium with low SBP and DBP exist in most age groups for both genders. Dominance of potassium over sodium on SBP is also apparent in less advanced

age groups for both genders (Figure 2). High flexibility of arterial walls in younger body, potassium ions as vasodilators and relationships of high potassium with increased excretion of sodium were postulated as the main reason for this association.[4,7,35] Associations of increasing potassium and low SBP and DBP become more significant for people ages 50 and older for both genders when stiffness of artery and loss of flexibility of renal tubule become prominent. [20] Relatively lower amount of potassium in ECF and lower affinity of potassium to interstitium charge sites than sodium may be the reason that renal system regulation dominates the consistent relationships of SBP and serum potassium.

Inverse correlations of increasing serum potassium and lowering SBP are apparent, but more significant for the general population after age 50 in both genders. The result in this study is consistent with a previous work reported that serum potassium is negatively associated with SBP in men.[32] However, one recent study on Chinese population also suggested excessive serum potassium (over 4.85 mmol/l) may imply a hypertension risk perhaps because of an impaired renal function or an unknown factor.[33]

Change of the dominance on SBP from serum potassium in less advanced age groups to serum sodium in advanced age groups is apparent (Figure 3). Increased salt sensitivity with aging hearts, reduced total body fluid, progressive decline in glomerular filtration rate and renal blood flow rate may be reasons for the dominant positive associations of serum sodium and BP in advanced age groups.[17-18]

4.4. Limitation of the study

Disorders of sodium are generally related more to water than to sodium metabolism[34]. Relationships between BP and serum sodium may not reflect the relationship of BP and dietary intakes of sodium. Future studies will be needed to further examine the mechanism of extrarenal regulation.[36] Many other factors such as body mass index and illness, including CVD can affect the BP. Because results here are based on statistics of large dataset and moving average trends, association of SBP and DBP and serum sodium and potassium levels of an individual or a small group can deviate significantly from the averaged relationship of a large group, which is a common fallacy in ecological studies.

Conclusions

The results show that age and gender dependent associations between the blood pressure and serum sodium and potassium are regulated mainly by renal centered mechanism but may also be affected by the extrarenal system. Increasing serum sodium have a clear positive association with blood pressure elevation for age groups approximately over 60 in men and approximately over 70 in women at all sodium levels and in less advanced age group (<50) when sodium level is high (>140 mmol/l). The positive associations can be explained by the renal centered mechanism of ADH-RAAS-ANP responses. However, associations of decreasing SBP and DBP with increasing serum sodium in less advanced age groups when serum sodium levels are below ~140 mmol/l support the existence of an extrarenal regulatory mechanism as well. Sodium could be stored in the negatively charged glycosaminoglycans in the interstitium without commensurate water retention in ECF (except the possible shift of interstitial and plasma fluid) until serum sodium reaches a critical level (~>140 mmol/l) and glycosaminoglycan

charge sites are satisfied. In comparison, associations of increasing serum potassium and decreasing blood pressure are more consistent and are regulated by traditional renal centered mechanism because of its lower ECF concentration and low affinity to the interstitium charge sites. The inverse association of potassium and SBP exist for most age groups and their significance increases after age 50 for both genders. The dominance on SBP changes from serum potassium in less advanced age group to serum sodium in advanced age group.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Figure 1. Comparison of original unfiltered (left panels, original unfiltered and filtered lines together) and filtered (right panels, only filtered lines) data trends of blood pressure, blood (serum) sodium vs. age and blood pressure vs. blood(serum) potassium. 300, 500 or 1000 points in legends indicate the data interval spans used for the moving average calculation.

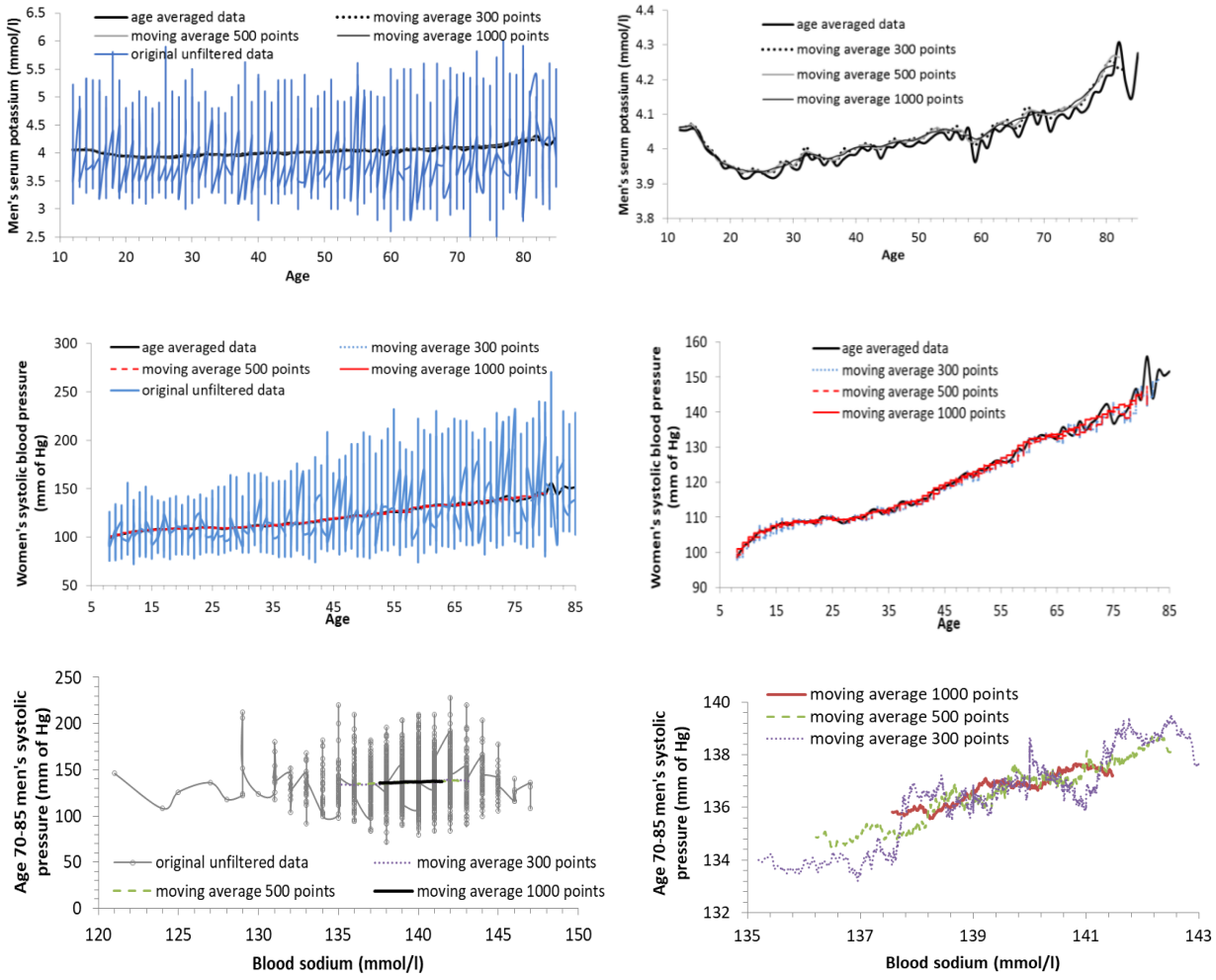

Figure 2. Age averaged trends of a), systolic and b), diastolic blood pressures of 20403 men and 23826 women between ages 12 and 85; age averaged trends of blood(serum) c), sodium, d), potassium and e) osmolality, and f) trend lines of blood (serum) sodium vs. osmolality of varied age groups for 14657 men and 16977 women between ages 12 and 85. All data were collected between 2003 and 2014.

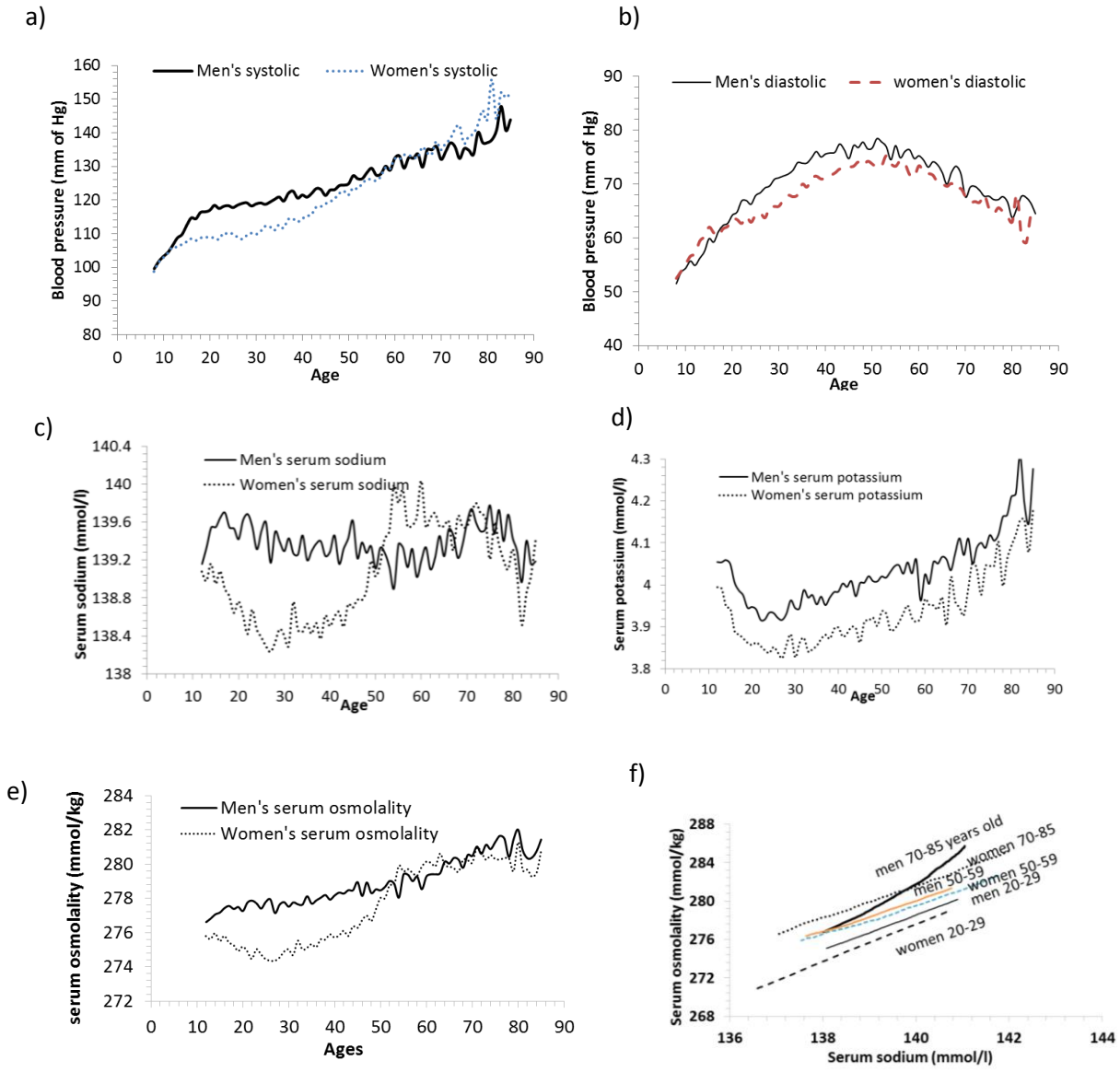

Figure 3. Iso-systolic blood pressure (mm of Hg) maps of blood(serum) sodium and potassium for men (left panels) and women (right panels), ages between a-b), 70 and 85, c-d), 60 and 69, e-f) 30 and 39 years old. Moving average interpolation method was used for map data interpolation. Participants in each age group range from 1872 to 3069 for men and from 2347 to 4302 for women. Scale bars on the right of side of each panel are color scales of SBP (in mm of Hg) of the corresponding age group.

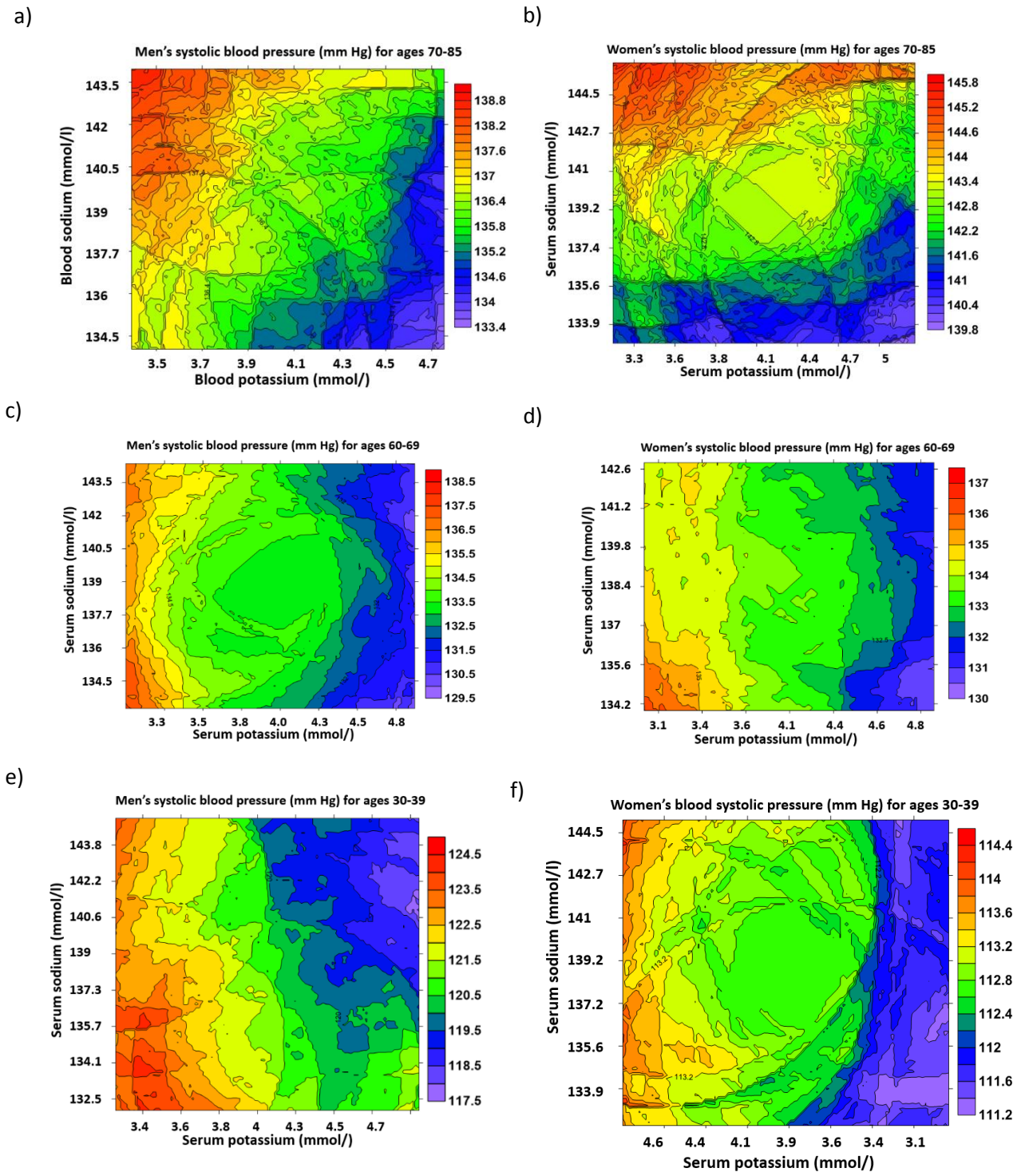

Figure 4. Trend lines of men and women's a-b) systolic blood pressure (SBP) and c- d) diastolic blood pressure (DBP) vs. blood (serum) sodium for each age group. Participants in each age group range from 1872 to 3069 for men and from 2347 to 4302 for women. The interval span of moving average filter for extracting the trend line was 1000 data points.

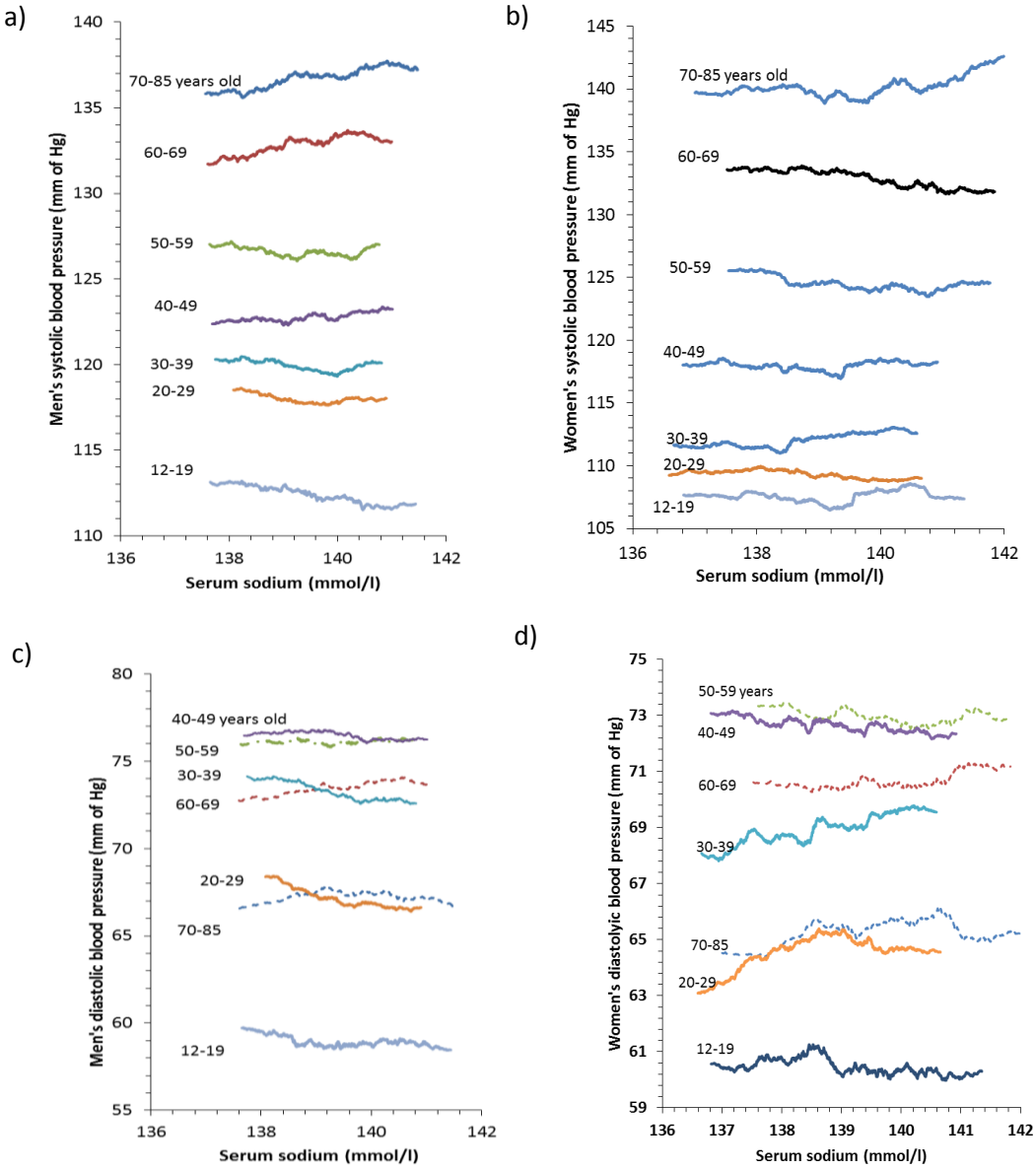

Figure 5. Trend lines of men and women's a-b) systolic blood pressure (SBP), and c-d) diastolic blood pressure (DBP) vs. blood (serum) potassium. Participants in each age group range from 1872 to 3069 for men and from 2347 to 4302 for women. The interval span of moving average filter for extracting the trend line was 1000 data points.