

# Associations between fruit consumption and home blood pressure in a randomly selected sample of the general Swedish population

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## Abstract

Frequent fruit consumption has been associated with lower office blood pressure. Less is known about associations between fruit consumption and home blood pressure. Our aim was to study the correlation between consumption of specific fruits and home blood pressure in a large randomly selected study population. The main outcome was systolic home blood pressure. Home blood pressure measurements were performed with calibrated oscillometric meters during seven consecutive days. Means for all available measurements were used. Validated food frequency questionnaires were used for estimating frequency of fruit consumption. The specified fruits were bananas, apples/pears and oranges/citrus fruit. Complete case analysis regarding fruit consumption, office- and home blood pressure measurements and other relevant variables was performed in 2283 study participants out of 2603 available. Multivariable linear regression analysis was performed. There were statistically significant associations between consumption of all fruit types and lower systolic home blood pressure unadjusted ( $p$  for trend; bananas, apples/pears and oranges/citrus fruit  $p < .001$ ). The numerical differences between most and least frequent consumption of fruit were for bananas  $-2.7$  mm Hg, apples/pears  $-3.9$  mm Hg and for oranges/citrus fruit  $-3.4$  mm Hg. When adjusted for covariates, both consumption of apples/pears and oranges/citrus fruit had an independent statistically significant association with lower blood pressure ( $p = .048$  resp.  $p = .009$ ). Future controlled interventional studies are needed to evaluate the effect of specific fruit on home blood pressure.

## KEYWORDS

ambulatory blood pressure/home blood pressure monitor, diet, epidemiology

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## 1 | INTRODUCTION

High fruit consumption has previously been shown to be associated with lower risk of hypertension and is recommended to patients with hypertension as a lifestyle intervention.<sup>1-3</sup> The prospective studies Nurses' Health Study and the Health Professionals Follow-up Study found lower risk of self-reported hypertension when eating fruit more often.<sup>1</sup> The randomized clinical trial Dietary Approach to Stop Hypertension (DASH) showed a decrease in both office- and ambulatory blood pressure by adding more fruit and vegetables to the diet.<sup>4</sup>

Home blood pressure levels have been shown to be a more accurate risk factor for cardiovascular disease than office blood pressure.<sup>5,6</sup> Accordingly, recent guidelines emphasize the importance of evaluating out-of-office blood pressure measurements for diagnosis and follow-up of patients with hypertension.<sup>3,7</sup> Less is known about associations between fruit consumption and home blood pressure.

The aim of this study was to assess the association between self-reported fruit consumption and home blood pressure in a large randomly selected study population.

## 2 | METHODS

### 2.1 | Study participants

For this cross-sectional study we used data from the Swedish CArdioPulmonary bioImage Study (SCAPIS). SCAPIS is an observational cohort study in which approximately 30 000 participants were selected randomly from the population registries of Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå, and Uppsala.<sup>8</sup> Inclusion criteria were 50–65 years of age and ability to understand the Swedish language. Out of the participants from the Linköping center ( $n = 5057$ ) we excluded 2774 participants with self-reported use of blood pressure medication during the last 2 weeks or with missing values of blood pressure measurement, self-reported fruit consumption and other relevant variables (Figure 1).

Venous blood samples were drawn in a fasting state as previously described.<sup>9</sup> The participants answered questions on health state, including a validated food frequency questionnaire.<sup>10</sup> For each of three types of specified fruits (bananas, apples/pears and oranges/citrus fruit), self-reported frequency of consumption was assessed. Answer alternatives were from consumption five times per day or more to 1–3 times per month or less. These alternatives were categorized into four groups ("not every week", "1–2 times per week", "3–4 times per week", "at least five times per week").

### 2.2 | Ethics

Data analysis was approved by the Regional Ethics Committee of Linköping and performed in accordance with the Declaration of Helsinki of 1975. The study was approved by the Regional

Ethical Review board in Umeå (# 2010-228-31 M) and in Linköping (#2018/478-31) All participants gave written informed consent for participation in the study.

### 2.3 | Blood pressure measurements

As described in detail previously, both office- and home blood pressure measurements were performed in the Linköping cohort.<sup>9</sup> Semi-automatic oscillometric blood pressure meters (Omron m10-IT, Omron, Kyoto, Kyoto Prefecture, Japan) were used. As recommended in a recent consensus document, home blood pressure measurements were performed both in the morning and in the evening for seven consecutive days (except for the first day when only the evening measurements were performed).<sup>11</sup> Study participants were instructed to measure their blood pressure in a resting seated position. On each occasion, measurements were performed in triplicate and the mean value was noted by the study participant. The means of all available measurements were used in this study.

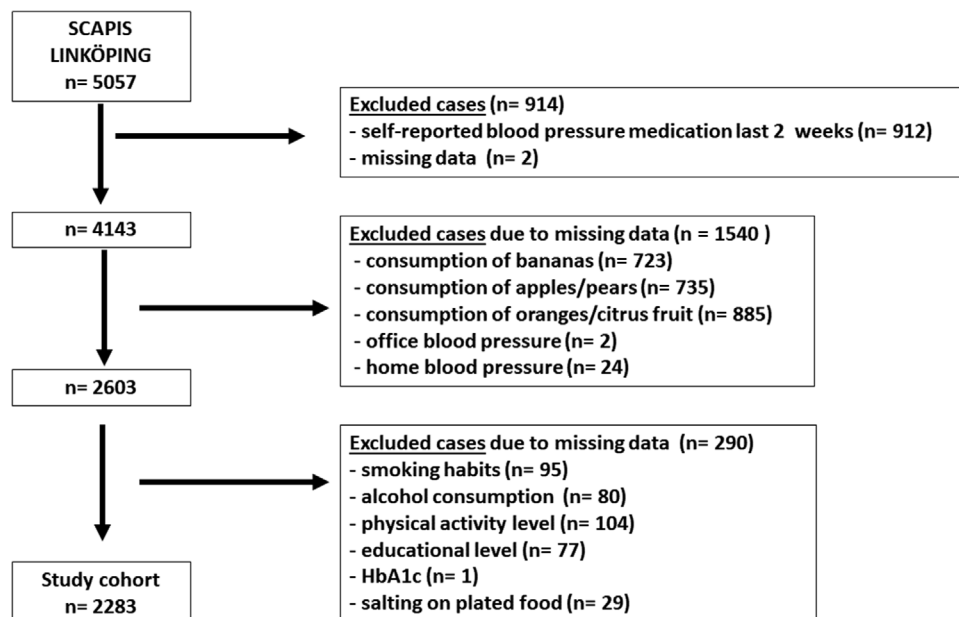
### 2.4 | Statistics

Between-group differences were tested for statistical significance with analysis of variance (ANOVA) for continuous variables and Chi-Square tests for categorical variables. For each type of fruit, trends for differences in blood pressure levels across groups were tested for statistical significance with multivariable linear regression analysis, overall and divided by sex, with and without adjustment for the following covariates: age, sex, BMI, smoking habits, frequency of alcohol consumption, educational level, physical activity, salting on plated food, cholesterol, HbA1c and creatinine levels. Strengths of correlations between continuous variables were assessed with Pearson's correlation coefficient. Two-sided  $p$  values  $< .05$  were considered statistically significant. One-way analysis of co-variance (ANCOVA) was used to test between-group differences for statistical significance after adjustment for potential confounders. Statistical analyses were performed in SPSS version 28 (IBM Corporation, Somers, New York, USA).

## 3 | RESULTS

### 3.1 | Study participant characteristics

Out of the 5057 participants in the Linköping SCAPIS population, 2283 matched the inclusion- and exclusion criteria for this analysis (Figure 1). Their demographic and clinical characteristics are presented in Table 1. Table 2 shows the different variables by apples/pears consumption. Tables S1 and S2 show the same variables by consumption of bananas and oranges/citrus fruit. For all types of fruit there were significant differences in smoking habits and physical activity (Table 2, Tables S1 and S2). In the apples/pears and oranges/citrus fruit groups



**FIGURE 1** Study flowchart

there were statistically significant differences regarding age, sex, and creatinine levels.

In males, there were significant differences regarding physical activity level for all fruit groups (Tables S3–S5) so that more frequent fruit consumption was associated with higher level of physical activity. Frequent consumption of apples/pears or oranges/citrus fruit were associated with older age. Current smoking was associated with less frequent consumption of apples/pears.

Females with more frequent consumption of bananas tended to be younger whereas females with more frequent consumption of apples/pears or citrus fruits tended to be older (Tables S6–S8). For all fruit groups, more frequent consumption was associated with lower likelihood of being a current smoker, and with a higher likelihood of exercising and training regularly.

The correlation coefficients for office blood pressure and home blood pressure were 0.77 ( $p < .001$ ) for the systolic blood pressure and 0.74 ( $p < .001$ ) for the diastolic blood pressure. The correlation coefficients between the average of the six morning readings and the average of the seven evening readings for home blood pressure in the total study population were 0.89 ( $p < .001$ ) for the systolic blood pressure and 0.87 ( $p < .001$ ) for the diastolic blood pressure, respectively.

### 3.2 | Home blood pressure and fruit consumption

More frequent fruit consumption was associated with significantly lower systolic home blood pressure levels in all fruit groups (Table 3). These associations remained statistically significant for consumption of both apple/pear and oranges/citrus fruit after adjustments. The numerically largest difference in systolic home blood pressure was for apples/pears with  $-3.9$  mm Hg (Table 3).

The trend of lower diastolic home blood pressure with higher fruit consumption was statistically significant unadjusted for all fruit types (Table 3). After adjustments the statistical significance remained for apples/pears and oranges/citrus fruit. The largest numerical difference was  $-2.6$  mm Hg between most and least frequent apples/pears consumption.

In men, the only statistically significant association between fruit consumption and home blood pressure levels was observed for more frequent consumption of apples/pears, which was associated with lower home diastolic blood pressure (Table S9). However, this association did not remain statistically significant after adjustment.

In females, there were statistically significant associations between lower home diastolic blood pressure levels and more frequent fruit consumption, for all fruit types, and these associations remained statistically significant after adjustment (Table S10). Systolic home blood pressure levels, on the other hand, were significantly lower in those women who ate bananas more frequently unadjusted, but not after adjustments. Similar findings were observed in those women who ate oranges/citrus fruits more frequently after adjustment.

Adjusted home blood pressure means according to ANCOVA are presented in Table S11.

### 3.3 | Office blood pressure and fruit consumption

More frequent fruit consumption was associated with lower systolic office blood pressure ( $-2.8$  mm Hg) only for oranges/citrus fruit and this difference remained statistically significant after adjustment (Figures 2 and 3, Table 3).

Diastolic office blood pressure was significantly lower in those who consumed apples/pears or oranges/citrus fruit more often ( $-2.1$  mm Hg

**TABLE 1** Baseline characteristics of the study population ( $n = 2283$ ). Data presented as mean  $\pm$  standard deviation for continuous variables. For categorical variables counts and percentages are given

Variables	Men $n = 1084$	Women $n = 1199$
Age	57.0 $\pm$ 4.4	57.1 $\pm$ 4.4
BMI (kg/m <sup>2</sup> )	26.7 $\pm$ 3.4	25.8 $\pm$ 4.2
Office SBP (mm Hg)	132.2 $\pm$ 16.5	127.7 $\pm$ 17.1
Office DBP (mm Hg)	82.6 $\pm$ 10.0	81.4 $\pm$ 9.9
Home SBP (mm Hg)	123.4 $\pm$ 12.4	113.9 $\pm$ 12.7
Home DBP (mm Hg)	78.4 $\pm$ 8.3	75.0 $\pm$ 8.3
HbA1c (mmol/mol)	35.5 $\pm$ 6.7	35.2 $\pm$ 4.3
T-cholesterol (mmol/l)	5.4 $\pm$ 1.0	5.7 $\pm$ 1.0
S-creatinine ( $\mu$ mol/l)	88.9 $\pm$ 11.1	72.2 $\pm$ 10.2
Current smoker $n$ (%)	86 (7.9%)	105 (8.8%)
Salting on plated food $n$ (%)	214 (19.7%)	194 (16.2%)
Self-reported myocardial infarction $n$ (%) $n$ missing = 14	17 (1.6%)	5 (0.4%)
Self-reported stroke $n$ (%) $n$ missing = 14	14 (1.3%)	9 (0.8%)
Self-reported diabetes $n$ (%) $n$ missing = 14	27 (2.5%)	17 (1.4%)
Frequency of alcohol consumption $n$ (%)		
Once per month or less often	136 (12.5%)	209 (17.4%)
2–4 times per month	500 (46.1%)	592 (49.4%)
2–3 times per week	380 (35.1%)	363 (30.3%)
$\geq$ Four times per week	68 (6.3%)	35 (2.9%)
Physical activity level $n$ (%)		
Sedentary life-style	90 (8.3%)	79 (6.6%)
Moderate exercise in spare time	443 (40.9%)	548 (45.7%)
Moderate and regular exercise	357 (32.9%)	446 (37.2%)
Regular exercise and training	194 (17.9%)	126 (10.5%)
University educational level $n$ (%)	483 (44.6%)	603 (50.3%)

for both, Table 3). After adjustment these differences remained statistically significant.

In males, there were no statistically significant associations between systolic or diastolic office blood pressure levels and fruit consumption (Table S9). In females, more frequent fruit consumption was associated with statistically significant lower systolic office blood pressure levels only for oranges/citrus fruit, and only after adjustment (Table S10).

Diastolic office blood pressure was significantly lower in women who ate oranges/citrus fruit more frequently, and this association remained statistically significant after adjustments. In women who ate apples and pears more often, diastolic blood pressure levels were significantly lower after adjustments.

Adjusted office blood pressure means according to ANCOVA are presented in Table S11.

## 4 | DISCUSSION

In this cross-sectional study there were significant associations between more frequent fruit consumption and lower home blood pressure levels, and these associations were observed mostly in women. When adjustment for different covariates by use of multivariable linear regression was performed, these associations remained statistically significant both for consumption of apples/pears and for consumption of oranges/citrus fruit. When subgroup analyses were performed according to sex, the associations remained significant for oranges/citrus fruit consumption in females.

The explanations for the observed sex disparities remain to be elucidated. In this regard, we find it noteworthy that for all fruit types, women who consumed fruits more frequently were significantly less likely to be current smokers, whereas in men such a relationship was observed for apples/pears only. This suggests that frequent fruit consumption may be more closely associated with other healthy lifestyle patterns in women than in men. However, it should also be acknowledged that there were numerically fewer men than women who reported consuming fruits at least five times per week, and therefore, the statistical power to demonstrate significant differences was probably lower among men than among women.

Although the prognostic importance has been reported to shift from diastolic to systolic blood pressure with increasing age<sup>12</sup>, the independent and highly statistically significant associations between more frequent fruit consumption and lower home diastolic blood pressure levels that were observed in women is of potential clinical interest. Indeed, many of the participants in the current study were of an age in which diastolic blood pressure levels may be as strongly predictive of future coronary heart disease as systolic blood pressure levels.<sup>12</sup>

Plausible mechanisms that would explain this association include electrolytes such as potassium and nutrients such as vitamin C.<sup>13–16</sup> The cross-sectional Ohasama study found higher home blood pressure and prevalence of home hypertension with low fruit intake.<sup>17</sup> A follow-up study showed lower likelihood of incident home hypertension during four years when eating fruit more often.<sup>15</sup> Both intake of vitamin C and potassium were positively correlated with lower risk of hypertension. Oranges and other citrus fruits are relatively rich in these nutrients and bananas have a high potassium content<sup>18</sup>.

The randomized interventional DASH study showed a decrease of 2.8 mm Hg in office blood pressure with a diet containing more fruit and vegetables compared to the control diet.<sup>4</sup> However, when also substituting dairy products for low-fat alternatives and reducing total and saturated fat content of the diet the systolic office blood pressure was significantly lowered compared to control (-5.5 mm Hg) and the fruit/vegetables group (-2.7 mm Hg). Interestingly, there was no significant decrease in blood pressure in a subgroup analysis for non-hypertensives randomized to the fruit/vegetables group compared to controls. Later studies have confirmed the results of the original trial for office blood pressure with a meta-analysis concluding a mean decrease in office blood pressure by -4.5/-2.6 mm Hg by using the DASH diet.<sup>19</sup> A subgroup analysis in the original study of ambulatory blood pressure was also performed showing greater decrease in the

**TABLE 2** Clinical and demographic characteristics by frequency of apple and pear consumption in total population (n = 2283)

Variables	Not every week n = 510	1–2 times per week n = 761	3–4 times per week n = 448	At least five times per week n = 564	p-value
Age	56.7 ±4.4	56.7 ±4.3	57.2 ±4.3	57.7 ±4.4	<.001
Sex (men) n (%)	310 (60.8%)	388 (51.0%)	180 (40.2%)	206 (36.5%)	<.001
BMI	26.3 ±3.8	26.3 ±4.0	26.3 ±3.8	26.0 ±3.9	.536
Office SBP (mm Hg)	131.8 ±17.7	128.9 ±16.7	130.5 ±16.4	129.0 ±17.0	.011
Office DBP (mm Hg)	83.1 ±10.6	81.5 ±9.7	82.5 ±9.9	81.0 ±9.5	.002
Home SBP (mm Hg)	120.9 ±13.8	118.1 ±13.1	118.1 ±12.9	117.0 ±13.6	<.001
Home DBP (mm Hg)	78.0 ±8.7	76.6 ±8.3	76.6 ±8.6	75.4 ±8.2	<.001
HbA1c (mmol/mol)	35.2 ±5.4	35.2 ±5.8	35.4 ±6.0	35.6 ±5.1	.512
T-cholesterol (mmol/l)	5.6 ±1.1	5.6 ±1.0	5.5 ±1.0	5.5 ±1.0	.721
S-creatinine (μmol/l)	82.3 ±13.6	80.7 ±14.6	79.1 ±13.4	78.3 ±13.3	<.001
Current smoker n (%)	70 (13.7%)	61 (8.0%)	32 (7.1%)	28 (5.0%)	<.001
Salting on plated food n (%)	94 (18.4%)	145 (19.1%)	79 (17.6%)	90 (16.0%)	.520
Self-reported myocardial infarction n (%) n missing = 14	6 (1.2%)	7 (0.9%)	6 (1.3%)	3 (0.5%)	N/A
Self-reported stroke n (%) n missing = 14	5 (1.0%)	4 (0.5%)	7 (1.6%)	7 (1.2%)	N/A
Self-reported diabetes n (%) n missing = 14	8 (1.6%)	12 (1.6%)	7 (1.6%)	17 (3.0%)	.198
Frequency of alcohol consumption n (%)					.113
Once per month or less often	80 (15.7%)	106 (13.9%)	63 (14.1%)	96 (17.0%)	
2–4 times per month	235 (46.1%)	365 (48.0%)	217 (48.4%)	275 (48.8%)	
2–3 times per week	159 (31.2%)	261 (34.3%)	150 (33.5%)	173 (30.7%)	
≥ Four times per week	36 (7.1%)	29 (3.8%)	18 (4.0%)	20 (3.5%)	
Physical activity level n (%)					<.001
Sedentary life-style	52 (10.2%)	62 (8.1%)	30 (6.7%)	25 (4.4%)	
Moderate exercise in spare time	233 (45.7%)	337 (44.3%)	197 (44.0%)	224 (39.7%)	
Moderate and regular exercise	154 (30.2%)	256 (33.6%)	173 (38.6%)	220 (39.0%)	
Regular exercise and training	71 (13.9%)	106 (13.9%)	48 (10.7%)	95 (16.8%)	
University educational level n (%)	221 (43.3%)	354 (46.5%)	227 (50.7%)	284 (50.4%)	.058

Data presented as mean ± standard deviation for continuous variables. For categorical variables counts and percentages are given. *p* values are from ANOVA tests or from Chi square tests.

combination diet for systolic blood pressure (-4.5 mm Hg) than in the fruit/vegetables group (-3.1 mm Hg) compared to control.<sup>44</sup>

The difficulty in evaluating the efficacy of fruit consumption on blood pressure is the fact that most interventional studies, such as the DASH study, also adds vegetables and changes the composition of other food groups in the intervention diets. The advice of increased fruit consumption with other dietary interventions have showed conflicting results on office blood pressure.<sup>20,21</sup>

Varying fruit consumption might be associated with different lifestyle habits and socioeconomic factors. A meta-analysis concluded that high fruit consumption was associated with low prevalence of smoking, high prevalence of university level education and high level

of physical activity.<sup>22</sup> In a cross-sectional study there were higher fruit consumption in females and those with high educational level.<sup>23</sup> Both for apples/pears- and oranges/citrus fruit consumption there were significant differences in sex distribution with seemingly higher fruit consumption in females. In all fruit groups there were an association between smoking habits and physical activity. Only in the oranges/citrus fruit group a statistically significant difference persisted in systolic home blood pressure after adjustments for relevant covariates.

A limitation of the current study is that only the frequency of fruit consumption, and not the consumed amount, was assessed. Furthermore, we did not have information regarding circulating- or

**TABLE 3** Office and home blood pressure according to reported frequency of fruit consumption in total population ( $n = 2283$ )

		Banana consumption		Apple/pear consumption		Oranges/citrus fruit consumption	
		Mean $\pm$ SD	Count	Mean $\pm$ SD	Count	Mean $\pm$ SD	Count
Office SBP	Not every week	130.0 $\pm$ 17.2	601	131.8 $\pm$ 17.7	510	130.6 $\pm$ 17.1	634
	1–2 times per week	130.2 $\pm$ 17.0	752	128.9 $\pm$ 16.7	761	130.8 $\pm$ 16.9	767
	3–4 times per week	130.2 $\pm$ 16.9	442	130.5 $\pm$ 16.4	448	129.4 $\pm$ 17.0	406
	At least five times per week	129.0 $\pm$ 16.6	488	129.0 $\pm$ 17.0	564	127.8 $\pm$ 16.6	476
	<i>p</i> value (unadjusted/adjusted)	.340 / .560		.050 / .095		.003 / <.001	
Office DBP	Not every week	82.1 $\pm$ 10.3	601	83.1 $\pm$ 10.6	510	82.6 $\pm$ 10.5	634
	1–2 times per week	82.1 $\pm$ 9.9	752	81.5 $\pm$ 9.7	761	82.3 $\pm$ 9.8	767
	3–4 times per week	82.1 $\pm$ 9.9	442	82.5 $\pm$ 9.9	448	81.9 $\pm$ 10.1	406
	At least five times per week	81.3 $\pm$ 9.6	488	81.0 $\pm$ 9.5	564	80.5 $\pm$ 9.2	476
	<i>p</i> value (unadjusted/adjusted)	.176 / .935		.007 / .013		<.001 / <.001	
Home SBP	Not every week	119.5 $\pm$ 13.6	601	120.9 $\pm$ 13.8	510	119.7 $\pm$ 13.5	634
	1–2 times per week	118.7 $\pm$ 13.5	752	118.1 $\pm$ 13.1	761	119.2 $\pm$ 13.1	767
	3–4 times per week	118.2 $\pm$ 13.2	442	118.1 $\pm$ 12.9	448	117.4 $\pm$ 13.3	406
	At least five times per week	116.8 $\pm$ 13.1	488	117.0 $\pm$ 13.6	564	116.3 $\pm$ 13.5	476
	<i>p</i> value (unadjusted/adjusted)	<.001 / .224		<.001 / .048		<.001 / .009	
Home DBP	Not every week	77.4 $\pm$ 8.5	601	78.0 $\pm$ 8.7	510	77.5 $\pm$ 8.5	634
	1–2 times per week	76.7 $\pm$ 8.5	752	76.6 $\pm$ 8.3	761	77.0 $\pm$ 8.4	767
	3–4 times per week	76.7 $\pm$ 8.5	442	76.6 $\pm$ 8.6	448	76.2 $\pm$ 8.7	406
	At least five times per week	75.5 $\pm$ 8.3	488	75.4 $\pm$ 8.2	564	75.1 $\pm$ 8.2	476
	<i>p</i> value (unadjusted/adjusted)	<.001 / .135		<.001 / .003		<.001 / <.001	

Data presented as mean and standard deviation with *p* for trend from linear regression. Adjusted for age, sex, BMI, smoking habits, frequency of alcohol consumption, salt consumption, educational level, physical activity, cholesterol, HbA1c and creatinine levels.

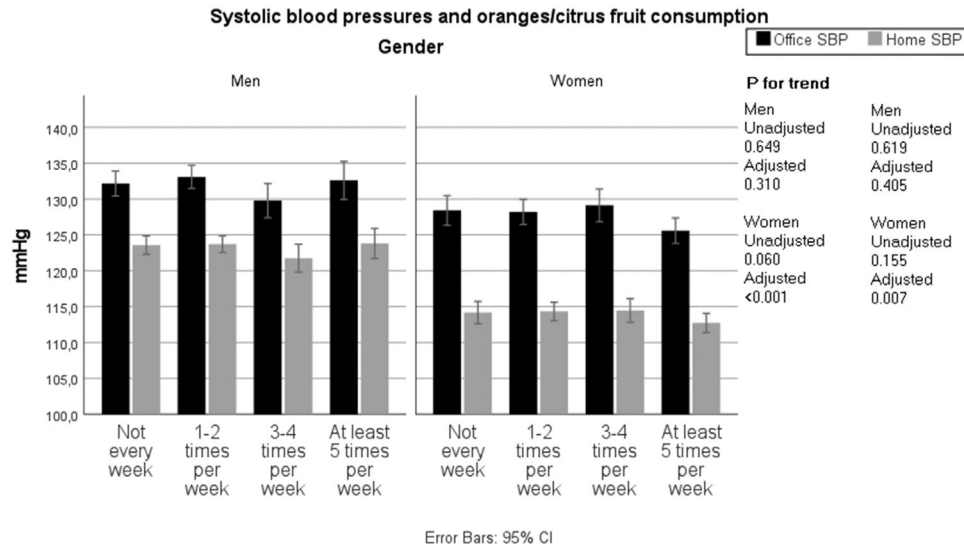
urinary levels of electrolytes. The cross-sectional study design limits the findings to associations without possible evaluations of causality. Study strengths include randomly selected study participants, use of calibrated home blood pressure measurements and validated food frequency questionnaires.

Further studies are needed to evaluate the relationship between consumption of specific fruits and home blood pressure. For inference analysis randomized controlled trials of high quality with sufficient time of follow-up are needed. Our data suggests that when such interventional trials are planned, it would be important to specify fruit consumption with an estimate of consumed amount in addition to frequency.

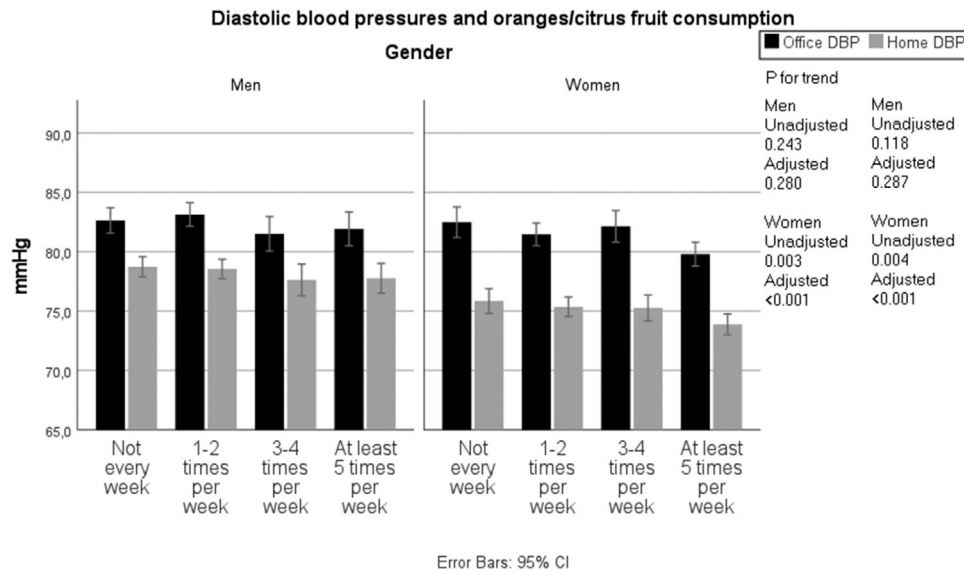
## 5 | CONCLUSIONS

This study showed an association between high frequency of fruit consumption and lower home blood pressure in people who did not report using antihypertensive drugs. Both apples/pears and oranges/citrus fruit consumption remained significantly associated with lower systolic home blood pressure after adjustments with relevant covariates. For all fruit types, home diastolic blood pressure levels were significantly and independently lower in women who consumed fruits more frequently. Further studies are needed, preferably randomized controlled trials, to study the effect of consumption of specific fruits on home blood pressure levels.





**FIGURE 2** Systolic blood pressures and oranges/citrus fruit consumption by sex. Bar chart presenting means and 95% confidence intervals of systolic blood pressure levels ordered by increasing frequency of oranges/citrus fruit consumption. P-values from linear regression models



**FIGURE 3** Diastolic blood pressures and oranges/citrus fruit consumption by sex. Bar chart presenting means and 95% confidence intervals of diastolic blood pressure levels ordered by increasing frequency of oranges/citrus fruit consumption. P-values from linear regression models

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## AUTHOR CONTRIBUTIONS

Carl Johan Östgren led the SCAPIS Linköping cohort recruitment. Fredrik H. Nystrom organized and financed the home blood pressure measurements in SCAPIS Linköping. Edvin Ström performed the statistical analyses and wrote the first draft of the manuscript. All authors provided data interpretation and meaningful contributions to the revision of the manuscript, and read and approved the final version of the manuscript.

## CONFLICTS OF INTEREST

Magnus O. Wijkman has served on advisory boards or lectured for MSD, Lilly, Novo Nordisk and Sanofi, and has organized a professional regional meeting sponsored by Lilly, Rubin Medical, Sanofi, Novartis and Novo Nordisk. Fredrik H. Nystrom has lectured on behalf of AstraZeneca, Lilly, Sanofi and MSD. Edvin Ström and Carl Johan Östgren report no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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