Mildly elevated diastolic blood pressure increases subsequent risk of breast cancer in postmenopausal women in the Health Examinees-Gem study

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### Supplementary Table 1. Baseline characteristics of the HEXA-G study population by menopausal status

| Variable                                      | Premenopausal | Postmenopausal | p value<sup>a</sup> |
|-----------------------------------------------|---------------|---------------|---------------------|
| Number of participants                        | 30,131        | 42,900        | <0.01               |
| Person-years                                  | 279,617       | 392,291       |                     |
| Follow-up time, median years                  | 9.22          | 9.13          |                     |
| Breast cancer cases                           | 425           | 433           | <0.01               |
| SBP (mmHg, mean ± SD)                         | 116.9±14.11   | 123.27±14.96  | <0.01               |
| DBP (mmHg, mean ± SD)                         | 72.88±9.47    | 75.95±9.41    | <0.01               |
| Age (years, mean ± SD)                        | 45.5±4.19     | 57.12±5.83    | <0.01               |
| Age at baseline, years                        | <0.01         |               |                     |
| 40-49                                         | 24,122        | 3,591         | 12.96               |
| 50±59                                         | 6,009         | 24,390        | 80.37               |
| >60                                           | NA            | 14,919        | 99.66               |
| BMI (kg/m², mean ± SD)                        | 23.07±2.90    | 23.98±2.90    | <0.01               |
| Education                                     | <0.01         |               |                     |
| ≤Middle school                                | 4,646         | 21,306        | 82.1                |
| High School or College                        | 16,051        | 16,292        | 50.37               |
| Bachelor or higher                            | 9,431         | 5,302         | 35.98               |
| Smoking status                                | <0.01         |               |                     |
| Never                                         | 29,049        | 41,679        | 58.93               |
| Ever                                          | 1,082         | 1,221         | 53.02               |
| Alcohol drinking status                       | <0.01         |               |                     |
| Never                                         | 17,257        | 31,628        | 64.7                |
| Ever                                          | 12,874        | 11,272        | 46.68               |
| Physical activity                             | <0.01         |               |                     |
| Yes                                           | 14,778        | 22,679        | 60.55               |
| No                                            | 15,353        | 20,221        | 56.84               |
| Familiar history of breast cancer             | 0.07          |               |                     |
| Yes                                           | 134           | 154           | 53.47               |
| No                                            | 29,997        | 42,746        | 58.76               |
| Age at menarche                               | <0.01         |               |                     |
| <9 to 14 years                                | 7,065         | 20,402        | 74.28               |
| 15 years                                      | 7,661         | 10,194        | 57.09               |
| 16 or more                                    | 15,405        | 12,304        | 44.4                |
| Age at first pregnancy                        | <0.01         |               |                     |
| No pregnancy*                                 | 1,543         | 1,077         | 41.11               |
| <25 years                                     | 18,686        | 20,711        | 52.57               |
| >=25 years                                    | 9,902         | 21,112        | 68.07               |
| Breastfeeding                                 | <0.01         |               |                     |
| Yes                                           | 22,450        | 37,204        | 62.37               |
| No                                            | 7,681         | 5,696         | 42.58               |
| Hormone replaced treatment use                | <0.01         |               |                     |
| Never                                         | 30,131        | 31,726        | 51.29               |
| Former use                                    | NA            | 8,299         | 100                 |
| Current use                                   | NA            | 2,875         | 100                 |
| Self-reported hypertension                    | <0.01         |               |                     |
| No                                            | 27,358        | 31,002        | 53.12               |
| Yes                                           | 2,773         | 11,898        | 81.10               |
| Family history of hypertension                | <0.01         |               |                     |
| No                                            | 19,616        | 29,469        | 60.04               |
| Yes                                           | 10,515        | 13,431        | 56.09               |

HEXA-G, Health Examinees Study-Gem; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SD, standard deviation; NA, no applicable

Variable distributions are reported as n(%) unless otherwise specified.

<sup>a</sup> Student’s t-test for continuous variables; Chi-square test for categorical variables
| Variables (cases/participants) | <130 | 130 - 139 | 140 - 159 | ≥160 | p for trend<sup>a</sup> |
|--------------------------------|------|-----------|-----------|------|----------------------|
| **All women (858/73,031)**    |      |           |           |      |                      |
| Number of Participants         | 51,956 | 13,309 | 6,702 | 1,064 |                      |
| Breast cancer cases            | 623   | 141      | 81      | 13   |                      |
| Person-years                   | 479,035 | 121,483 | 61,421 | 9,969 |                      |
| HR (95% CI) Model 1            | ref   | 0.93 (0.78 - 1.12) | 1.08 (0.87 - 1.37) | 1.06 (0.61 - 1.84) | 0.83 |
| HR (95% CI) Model 2            | ref   | 0.96 (0.80 - 1.16) | 1.12 (0.88 - 1.42) | 1.10 (0.63 - 1.92) | 0.57 |
| HR (95% CI) Model 3            | ref   | 0.95 (0.78 - 1.14) | 1.09 (0.85 - 1.39) | 1.06 (0.61 - 1.85) | 0.78 |
| **Premenopausal (433/30,131)** |      |           |           |      |                      |
| Number of Participants         | 24,314 | 3,920     | 1,601    | 296  |                      |
| Breast cancer cases            | 354   | 44       | 32       | NR<sup>b</sup> |        |
| Person-years                   | 226,155 | 35,995  | 14,675  | 2,792 |                      |
| HR (95% CI) Model 1            | ref   | 0.78 (0.57 - 1.07) | 1.39 (0.97 - 2.00) | 0.69 (0.22 - 2.17) | 0.96 |
| HR (95% CI) Model 2            | ref   | 0.79 (0.58 - 1.09) | 1.44 (0.99 - 2.08) | 0.72 (0.23 - 2.25) | 0.82 |
| HR (95% CI) Model 3            | ref   | 0.79 (0.57 - 1.09) | 1.43 (0.98 - 2.09) | 0.71 (0.23 - 2.23) | 0.87 |
| **Postmenopausal (425/42,900)**|      |           |           |      |                      |
| Number of Participants         | 27,642 | 9,389     | 5,101    | 768  |                      |
| Breast cancer cases            | 269   | 97       | 49       | 10   |                      |
| Person-years                   | 252,880 | 85,488  | 46,746  | 7,177 |                      |
| HR (95% CI) Model 1            | ref   | 1.05 (0.83 - 1.33) | 0.97 (0.71 - 1.32) | 1.29 (0.68 - 2.42) | 0.70 |
| HR (95% CI) Model 2            | ref   | 1.07 (0.84 - 1.35) | 0.99 (0.72 - 2.08) | 1.34 (0.71 - 2.54) | 0.58 |
| HR (95% CI) Model 3            | ref   | 1.05 (0.82 - 1.33) | 0.95 (0.69 - 1.30) | 1.28 (0.68 - 2.43) | 0.78 |

Model 1: unadjusted
Model 2: adjusted for family history of breast cancer, body mass index, parity, age at birth of a first child, age at menopause, breastfeeding, physical activity, alcohol consumption, smoking status. In postmenopausal additionally adjusted by hormone replaced therapy use.
Model 3: adjusted for model 2 variables and self-reported history of hypertension.

<sup>a</sup>p-trend values were calculated with linear-by-linear association tests.

<sup>b</sup>Frequencies less than 5 are not reported
Supplementary Table 3. Hazard ratios and 95% confidence intervals of breast cancer risk according SBP and DBP dichotomous stratification

| Variables (cases/participants) | Systolic Blood Pressure (mm Hg) | Diastolic Blood Pressure (mm Hg) |
|-------------------------------|---------------------------------|----------------------------------|
|                               | <130 | ≥130 | <85 | ≥ 85 |
| All women (858/73031)         |      |      |     |      |
| Number of Participants        | 51,956 | 21,075 | 62,693 | 10,338 |
| Breast cancer cases           | 623 | 235 | 716 | 142 |
| Person- years                 | 479,035 | 192,873 | 575,653 | 96,255 |
| HR (95% CI) Model 1           | ref | 0.99 (0.85 - 1.15) | ref | 1.23 (1.03 - 1.48) |
| HR (95% CI) Model 2           | ref | 1.02 (0.87 - 1.19) | ref | 1.26 (1.05 - 1.51) |
| HR (95% CI) Model 3           | ref | 0.99 (0.85 - 1.17) | ref | 1.23 (1.03 - 1.49) |
| Premenopausal (433/30,131)    |      |      |     |      |
| Number of Participants        | 24,314 | 5,817 | 26,966 | 3,165 |
| Breast cancer cases           | 354 | 79 | 387 | 46 |
| Person- years                 | 226,155 | 53,462 | 250,144 | 29,473 |
| HR (95% CI) Model 1           | ref | 0.94 (0.74 - 1.21) | ref | 1.01 (0.74 - 1.37) |
| HR (95% CI) Model 2           | ref | 0.96 (0.75 - 1.24) | ref | 1.03 (0.75 - 1.40) |
| HR (95% CI) Model 3           | ref | 0.95 (0.74 - 1.23) | ref | 1.02 (0.74 - 1.40) |
| Postmenopausal (425/42,900)   |      |      |     |      |
| Number of Participants        | 27,642 | 15,258 | 35,727 | 7,173 |
| Breast cancer cases           | 269 | 156 | 329 | 96 |
| Person- years                 | 252,880 | 139,411 | 325,509 | 66,782 |
| HR (95% CI) Model 1           | ref | 1.04 (0.85 - 1.26) | ref | 1.41 (1.12 - 1.77) |
| HR (95% CI) Model 2           | ref | 1.05 (0.86 - 1.29) | ref | 1.43 (1.14 - 1.80) |
| HR (95% CI) Model 3           | ref | 1.03 (0.83 - 1.26) | ref | 1.40 (1.11 - 1.79) |

Model 1: unadjusted
Model 2: adjusted for family history of breast cancer, body mass index, parity, age at birth of a first child, age at menopause, breastfeeding, physical activity, alcohol consumption, smoking status. In postmenopausal additionally adjusted by hormone replaced therapy use.
Model 3: adjusted for model 2 variables and self-reported history of hypertension.
Supplementary Table 4. Subgroup and sensitivity analysis of breast cancer risk according to systolic blood pressure categories

| Variables                          | Participants | BC cases | <130 | 130 - 139 | 140 - 159 | ≥160 | p for interaction | p for trend |
|------------------------------------|--------------|----------|------|-----------|-----------|------|------------------|------------|
| Systolic Blood Pressure (mm Hg)    |              |          |      |           |           |      |                  |            |
| Body mass index (Kg/m²)            |              |          |      |           |           |      |                  |            |
| < 23.0                             | 33,095       | 402      | ref  | 1.05 (0.78 - 1.41) | 0.98 (0.63 - 1.54) | 1.69 (0.75 - 3.84) | 0.52       |
| 23.0 - 25.0                        | 19,418       | 209      | ref  | 0.86 (0.59 - 1.27) | 0.97 (0.58 - 1.62) | 0.81 (0.20 - 3.32) | 0.51       |
| ≥25.0                              | 20,518       | 247      | ref  | 0.90 (0.65 - 1.24) | 1.21 (0.85 - 1.73) | 0.80 (0.33 - 1.96) | 0.79       |
| Age at baseline (years)            |              |          |      |           |           |      |                  |            |
| 40 - 49                            | 27,713       | 390      | ref  | 0.95 (0.69 - 1.32) | 1.27 (0.81 - 2.01) | 0.67 (0.17 - 2.71) | 0.84       |
| 50 - 59                            | 30,348       | 329      | ref  | 0.89 (0.66 - 1.20) | 1.37 (0.97 - 1.92) | 1.19 (0.52 - 2.70) | 0.88       |
| 60 - 69                            | 14,970       | 139      | ref  | 1.05 (0.72 - 1.55) | 0.65 (0.38 - 1.11) | 1.23 (0.49 - 3.08) | 0.43       |
| Physical activity                  |              |          |      |           |           |      |                  |            |
| Yes                                | 37,457       | 442      | ref  | 0.82 (0.62 - 1.08) | 1.11 (0.80 - 1.54) | 1.49 (0.78 - 2.82) | 0.60       |
| No                                 | 35,574       | 416      | ref  | 1.09 (0.84 - 1.41) | 1.06 (0.73 - 1.52) | 0.54 (0.17 - 1.69) | 0.99       |
| History of cardiovascular disease  |              |          |      |           |           |      |                  |            |
| Yes                                | 1,854        | 18       | ref  | 0.78 (0.22 - 2.85) | 1.27 (0.34 - 4.81) | 1.09 (0.63 - 1.90) | 0.54       |
| No                                 | 71,177       | 840      | ref  | 0.95 (0.78 - 1.15) | 1.08 (0.84 - 1.38) | 1.09 (0.63 - 1.90) | 0.77       |
| History of diabetes mellitus       |              |          |      |           |           |      |                  |            |
| Yes                                | 3,660        | 31       | ref  | 1.28 (0.56 - 2.83) | 0.34 (0.08 - 1.51) | 1.02 (0.13 - 7.94) | 0.67       |
| No                                 | 69,371       | 827      | ref  | 0.92 (0.76 - 1.12) | 1.15 (0.90 - 1.47) | 1.07 (0.60 - 1.91) | 0.42       |
| Family history of hypertension     |              |          |      |           |           |      |                  |            |
| Yes                                | 23,946       | 298      | ref  | 1.09 (0.82 - 1.47) | 1.03 (0.70 - 1.52) | 1.03 (0.45 - 2.36) | 0.85       |
| No                                 | 49,085       | 560      | ref  | 0.86 (0.67 - 1.10) | 1.15 (0.84 - 1.57) | 1.08 (0.51 - 2.30) | 0.73       |
| Sensitivity analysis               |              |          |      |           |           |      |                  |            |
| Two years lag -time                | 72,899       | 726      | ref  | 0.93 (0.76 - 1.15) | 1.05 (0.80 - 1.36) | 0.66 (0.31 - 1.39) | 0.51       |
| Excluded self-reported HTN         | 60,733       | 715      | ref  | 0.95 (0.76 - 1.18) | 1.33 (1.01 - 1.77) | 0.67 (0.25 - 1.8)  | 0.57       |

HR, hazard ratio; CI, confidence intervals; HTN, hypertension
a Adjusted by family history of breast cancer, parity, age at birth of the first child, age at menarche, breastfeeding, hormone replaced therapy use, physical activity, alcohol consumption, smoking status, self-reported history of hypertension.

b Interaction was calculated using Wald test of cross-product terms.
Supplementary Figure 1. Systolic and diastolic blood pressure and breast cancer risk excluding first two years of follow-up (N=72,899) and self-reported history of hypertension (N=60,733) by menopausal status