Hypothetical blood-pressure-lowering interventions and risk of stroke and dementia

Online Resources

Authors: L. Paloma Rojas-Saunero, MD1*; Saima Hilal PhD1,2,3*; Eleanor J. Murray Sc.D4,5; Roger W. Logan PhD4; M. Arfan Ikram PhD1; Sonja A. Swanson, Sc.D1,4

1. Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
2. Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
3. Saw Swee Hock School of Public Health, National University of Singapore, Singapore
4. Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA
5. Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

* These authors contributed equally to the manuscript

Correspondence:
L. Paloma Rojas-Saunero MD,
Department of Epidemiology, Erasmus MC University Medical Center
Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. P.O. Box 2040
E-mail address l.rojassaunero@erasusmc.nl,
Telephone number 010 704 34 88
### Table e-1: Target trial description

Emulation of a target trial of multiple and joint strategies to lower the risk of stroke among adults from 55 to 80 years old.

| Section                        | Target trial                                                                 | Emulation using observation data |
|--------------------------------|------------------------------------------------------------------------------|----------------------------------|
| Aim                            | To estimate the effect of joint interventions on 15-year risk of stroke among people at risk | Same                             |
| Eligibility criteria           | Individuals below 80 years old, with no prior history of stroke or transient ischemic attack, cognitive impairment, dementia diagnosis or Parkinson’s disease or Parkinsonism. | Same + MMSE above 26 at baseline. |
| Treatment strategies           | 1. Maintaining SBP below 120 mmHg                                            | Same                             |
|                                | 2. Maintaining SBP below 140 mmHg                                            |                                  |
|                                | 3. Reducing SBP by 10% if above 140 mmHg                                     |                                  |
|                                | 4. Reducing SBP by 20% if above 140 mmHg                                     |                                  |
|                                | 5. Quitting smoking                                                          |                                  |
|                                | 6. Joint 1 + 5                                                               |                                  |
|                                | 7. Joint 2 + 5                                                               |                                  |
|                                | 8. Joint 3 + 5                                                               |                                  |
|                                | 9. Joint 4 + 5                                                               |                                  |
| Comparison arm                 | Natural course                                                              | Same                             |
| Follow-up                      | Starts at first visit, ends after stroke diagnosis, death, lost to follow up or after 15 years since baseline, which ever happens first. Annual checkups during trial to assess adherence and adverse effects. | Same + simulate visit process    |
| Outcome                        | Stroke (Death as competing risk)                                            | Same                             |
| Causal contrast of interest    | What would have been observed if all individuals adhered to their assigned strategy over the 15 years of follow-up (Per protocol effect) | Same                             |
| Statistical analysis           | Comparison of 15 year-risk of stroke between groups that received each treatment strategy, adjusted for post-baseline confounders associated with adherence to the treatment strategies and lost to follow-up | Same as per-protocol effect + adjustment of baseline |
Measurements.

The information on covariates were also collected during each visit through several questionnaires, physical examination and blood samples. From each visit, we selected the following covariates: age, sex, education attained, BMI, Apolipoprotein E (APOE)-ε4 carrier status, alcohol intake (grams per day), cholesterol (mmol/dl) and hypertensive medication. Education attained was divided in three categories: 1) primary; 2) further: lower or intermediate general or vocational education, or higher general education; 3) higher: vocational education or university. BMI was computed by dividing the weight in kg by the square of the height in meters. APOE genotype was determined using polymerase chain reaction on coded DNA samples. Distribution of APOE genotype and allele frequencies was in the Hardy-Weinberg equilibrium. APOE-ε4 carrier status was defined by the presence of at least one ε4 allele. Alcohol intake was collected from a validated semiquantitative food-frequency questionnaire and units were harmonized to grams/day, based on the assumption that one unit (glass) of alcoholic beverage equals 10 grams of alcohol. Hypertensive medication was categorized by the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification as antihypertensives (c02), diuretics (c03), beta blockers (c07), calcium channel blockers (c08), and renin-angiotensin-aldosterone system modifying agents (c09). History of heart disease and diabetes was collected at baseline. Heart disease was defined as the history of myocardial infarction, atrial fibrillation and cardiac intervention such as angioplasty, coronary artery bypass grafting and other coronary revascularization procedures.

Additionally, the occurrence of incident heart diseases and cardiac interventions, incident diabetes, transient ischemic attack, Parkinson disease, Parkinsonism, and cancer diagnosis were recorded independent from the visit process. The specific date of diagnosis was obtained through an automated follow-up system that integrates data from different sources as was performed for stroke and dementia.

1. Ott, A. et al. Education and the incidence of dementia in a large population-based study: The Rotterdam Study. Neurology 52, 663 LP-663 (1999).
2. Ruitenberg, A. et al. Alcohol consumption and risk of dementia: The Rotterdam Study. Lancet 359, 281–286 (2002).
3. Leening, M. J. G. et al. Methods of data collection and definitions of cardiac outcomes in the Rotterdam Study. Eur. J. Epidemiol. (2012). doi:10.1007/s10654-012-9668-8
Table e-2. Characteristics of included and excluded (missing covariates) participants

| Characteristics                  | Included (n = 4930) | Excluded (n = 263) |
|----------------------------------|--------------------|--------------------|
| Age in years, mean (SD)          | 66.23 (6.6)        | 69.00 (6.9)        |
| Women (%)                        | 2824 (57.3)        | 155 (58.9)         |
| Apoe 4 carrier                   | 1322 (28.1)        | 59 (30.7)          |
| Education                        |                    |                    |
| Primary                          | 2378 (48.6)        | 122 (56.5)         |
| Further                          | 2044 (41.8)        | 78 (36.1)          |
| Higher                           | 472 (9.6)          | 16 (7.4)           |
| Prevalent heart disease          | 368 (7.7)          | 22 (13.3)          |
| Prevalent diabetes               | 432 (12.9)         | 16 (16.3)          |
| Prevalent cancer                 | 20 (0.4)           | 1 (0.4)            |
### Table e-3

| Time-fixed covariates                          | Assessed  | Functional form when used as predictor | Categories |
|------------------------------------------------|-----------|----------------------------------------|------------|
| Age at baseline                                | 1st visit | 4 categories                           | Higher (4) |
| Education at baseline                          | 1st visit |                                        | Further (3)|
|                                                |           |                                        | Primary (2) |
|                                                |           |                                        | Missing (1) |
| Sex                                            | 1st visit | 2 categories                           | Female, male |
| Apoe 4 carrier                                 | 1st visit | 3 categories                           | Non carrier (3)|
|                                                |           |                                        | Carrier (2) |
|                                                |           |                                        | Missing (1) |
| History of diabetes at baseline                | 1st visit | Indicator                              | Yes/No     |
| History of heart disease diagnosis at baseline | 1st visit | Indicator                              | Yes/No     |

| Time-varying covariates                        | Assessed  | Functional form when used as predictor | Categories |
|------------------------------------------------|-----------|----------------------------------------|------------|
| Second visit                                   | Between year 1 and year 5 | Indicator and time since switch | N/A        |
| Third visit                                    | Between year 5 and year 9 and only if visit 2 happened | Indicator and time since switch | N/A        |
| Fourth visit                                   | Between year 5 and year 14 and only if visit 3 happened | Indicator and time since switch | N/A        |
| Smoking status                                 | 1st - 4th visit | 3 categories                           | Current (3)|
|                                                |           |                                        | Former (2) |
|                                                |           |                                        | Never (1)  |
| Alcohol intake (g/day)                         | 1st - 4th visit | 5 categories                           | >= 10 g/day (5)|
|                                                |           |                                        | 5 - 10 g/day (4)|
|                                                |           |                                        | 1 - 5 (3)  |
|                                                |           |                                        | < 1 (2)    |
|                                                |           |                                        | Missing (1) |
| Systolic blood pressure (mmHg)                 | 1st - 4th visit | Continuous                             |            |
| Body mass index                                | 1st - 4th visit | Continuous                             | Splines in 18.5 20 25 30 |
| Hypertension medication                        | 1st - 4th visit | Indicator                              | Yes/No     |
| Total Cholesterol                              | 1st visit | 4 Categories                           |            |
| Diagnosis of diabetes type 2                   | Year of diagnosis | Indicator and time since switch |            |
| Diagnosis of heart disease                     | Year of diagnosis | Indicator and time since switch |            |
| Diagnosis of Parkinson’s Disease or Parkinsonism | Year of diagnosis | Indicator and time since switch |            |
| Diagnosis of transient ischemic attack         | Year of diagnosis | Indicator and time since switch |            |
| Diagnosis of stroke                            | Year of diagnosis | Indicator and time since switch |            |
| Diagnosis of cancer                            | Year of diagnosis | Indicator and time since switch |            |
| Diagnosis of dementia                          | Year of diagnosis | Indicator and time since switch |            |
Figure e-1.

Difference between mean predicted values and mean observed values
Outcome: stroke

| Alcohol intake | BMI | Cancer diagnosis | Cholesterol |
|---------------|-----|------------------|-------------|
|               |     |                  |             |

| Cigarette smoking | Dementia diagnosis | Diabetes diagnosis | Heart disease diagnosis |
|-------------------|--------------------|--------------------|-------------------------|
|                   |                    |                    |                         |

| Hipertension medication | Parkinson/Parkinsonism | Systolic blood pressure | TIA |
|-------------------------|------------------------|-------------------------|-----|
|                         |                        |                         |     |

| Visit 2 | Visit 3 | Visit 4 |
|---------|---------|---------|
|         |         |         |

Years

0 5 10 15

-2 -1 0 1 2
Figure e-2

Difference between mean predicted values and mean observed values

Outcome: dementia

|                | Alcohol intake | BMI | Cancer diagnosis | Cholesterol |
|----------------|----------------|-----|------------------|-------------|
| Difference     |                |     |                  |             |
| 0              |                |     |                  |             |
| -1             |                |     |                  |             |
| -2             |                |     |                  |             |

|                | Cigarette smoking | Diabetes diagnosis | Heart disease diagnosis | Hypertension medication |
|----------------|--------------------|--------------------|-------------------------|-------------------------|
| Difference     |                    |                    |                         |                         |
| 0              |                    |                    |                         |                         |
| -1             |                    |                    |                         |                         |
| -2             |                    |                    |                         |                         |

|                | Parkinson/Parkinsonism | Stroke diagnosis | Systolic blood pressure | TIA |
|----------------|------------------------|-----------------|-------------------------|-----|
| Difference     |                        |                 |                         |     |
| 0              |                        |                 |                         |     |
| -1             |                        |                 |                         |     |
| -2             |                        |                 |                         |     |

|                | Visit 2 | Visit 3 | Visit 4 |
|----------------|---------|---------|---------|
| Difference     |         |         |         |
| 0              |         |         |         |
| -1             |         |         |         |
| -2             |         |         |         |

Years

0 5 10 15
Table e-4

1. Stroke

1.1. Death as censored.
The observed risk at 15 years is **12.0%**.

| No | Intervention                        | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|-------------------------------------|----------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                      | 14 (12.4, 16.1)           | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg      | 12.6 (10.1, 15.3)         | 0.9 (0.75, 1.03)   | -1.4 (-3.5, 0.4)       | 97.8                 |
| 2  | Maintaining SBP below 140 mmHg      | 12.7 (11, 14.8)           | 0.91 (0.83, 0.98)  | -1.3 (-2.4, -0.3)      | 83.5                 |
| 3  | Reducing SBP by 10% if above 140 mmHg | 12.7 (10.8, 14.8)       | 0.91 (0.82, 0.99)  | -1.3 (-2.6, -0.2)      | 82.7                 |
| 4  | Reducing SBP by 20% if above 140 mmHg | 12.7 (10.4, 15)         | 0.91 (0.78, 1.01)  | -1.3 (-3, 0.1)         | 82.7                 |
| 5  | Quitting smoking                    | 12.7 (11.2, 14.6)        | 0.9 (0.86, 0.94)   | -1.4 (-2, -0.8)        | 25.9                 |
| 6  | Joint 1 + 5                         | 11.3 (9.1, 13.7)         | 0.8 (0.67, 0.93)   | -2.8 (-4.7, -0.9)      | 98.7                 |
| 7  | Joint 2 + 5                         | 11.6 (9.9, 13.4)         | 0.83 (0.74, 0.9)   | -2.4 (-3.8, -1.5)      | 88.6                 |
| 8  | Joint 3 + 5                         | 11.4 (9.6, 13.3)         | 0.81 (0.72, 0.9)   | -2.6 (-4, -1.4)        | 88.2                 |
| 9  | Joint 4 + 5                         | 11.5 (9.3, 13.4)         | 0.82 (0.7, 0.92)   | -2.6 (-4.3, -1.1)      | 88.2                 |
1.2. Stroke and death as combined outcome
The observed risk at 15 years is 36.4%.

| No | Intervention                                 | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|----------------------------------------------|---------------------------|--------------------|------------------------|----------------------|
| 0  | Natural course                               | 38.8 (37.2, 40.5)         | 1 (1, 1)           | 0 (0, 0)               | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg               | 39.3 (37.5, 42.3)         | 1.01 (0.97, 1.08)  | 0.5 (-1.2, 2.9)        | 97.8                 |
| 2  | Maintaining SBP below 140 mmHg              | 38.2 (36.5, 40)           | 0.99 (0.96, 1.01)  | -0.5 (-1.4, 0.5)       | 83.5                 |
| 3  | Reducing SBP by 10% if above 140 mmHg       | 38.4 (36.9, 40.5)         | 0.99 (0.97, 1.02)  | -0.3 (-1.4, 0.9)       | 82.7                 |
| 4  | Reducing SBP by 20% if above 140 mmHg       | 39.1 (37.4, 41.2)         | 1.01 (0.97, 1.05)  | 0.4 (-1.1, 2)          | 82.7                 |
| 5  | Quitting smoking                             | 35.8 (34.2, 37.6)         | 0.92 (0.91, 0.94)  | -2.9 (-3.6, -2.3)      | 25.9                 |
| 6  | Joint 1 + 5                                  | 36.6 (34.3, 39.2)         | 0.94 (0.9, 1)      | -2.2 (-3.9, -0.1)      | 98.7                 |
| 7  | Joint 2 + 5                                  | 34.9 (33.8, 37)           | 0.9 (0.88, 0.94)   | -3.8 (-4.8, -2.1)      | 88.6                 |
| 8  | Joint 3 + 5                                  | 35.5 (34, 37.4)           | 0.92 (0.89, 0.95)  | -3.2 (-4.5, -2)        | 88.2                 |
| 9  | Joint 4 + 5                                  | 36.3 (34.4, 38.2)         | 0.94 (0.9, 0.97)   | -2.5 (-4, -1.1)        | 88.2                 |
### Table e-6

1.3. Under 65 years subgroup
The observed risk at 15 years is 6.1%.

| No | Intervention                                      | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                    | 6.3 (5, 7.9)              | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                    | 5.8 (3.9, 7.9)            | 0.91 (0.64, 1.16)  | -0.5 (-2.4, 1)          | 97.6                 |
| 2  | Maintaining SBP below 140 mmHg                    | 5.5 (4.2, 7)              | 0.87 (0.72, 0.98)  | -0.8 (-1.8, -0.2)       | 78.5                 |
| 3  | Reducing SBP by 10% if above 140 mmHg             | 5.4 (4.1, 7.2)            | 0.86 (0.7, 0.99)   | -0.9 (-1.9, -0.1)       | 78.9                 |
| 4  | Reducing SBP by 20% if above 140 mmHg             | 5.5 (4.2, 7.8)            | 0.88 (0.67, 1.07)  | -0.8 (-2.1, 0.4)        | 78.9                 |
| 5  | Quitting smoking                                  | 5.4 (4.3, 6.8)            | 0.85 (0.76, 0.96)  | -0.9 (-1.6, -0.2)       | 30.9                 |
| 6  | Joint 1 + 5                                       | 4.8 (3.2, 6.9)            | 0.77 (0.53, 1.04)  | -1.4 (-2.8, 0.2)        | 98.1                 |
| 7  | Joint 2 + 5                                       | 4.6 (3.4, 5.9)            | 0.73 (0.61, 0.88)  | -1.7 (-2.7, -0.8)       | 86.5                 |
| 8  | Joint 3 + 5                                       | 4.6 (3.4, 5.9)            | 0.73 (0.58, 0.89)  | -1.7 (-2.8, -0.7)       | 85.8                 |
| 9  | Joint 4 + 5                                       | 4.7 (3.3, 6.4)            | 0.75 (0.56, 0.98)  | -1.6 (-2.7, -0.2)       | 85.8                 |
1.4. Above 65 years and below 80 years subgroup
The observed risk at 15 years is 14.0%.

| No | Intervention                                      | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                    | 14 (12.6, 15.8)           | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                   | 12.1 (9.3, 15.3)          | 0.86 (0.69, 1.03)  | -2 (-4.3, 0.4)          | 98.8                 |
| 2  | Maintaining SBP below 140 mmHg                   | 12.6 (11.1, 14.9)         | 0.9 (0.81, 1)      | -1.5 (-2.8, 0)          | 87.3                 |
| 3  | Reducing SBP by 10% if above 140 mmHg            | 12.8 (10.8, 14.9)         | 0.91 (0.79, 1)     | -1.3 (-3.2, 0)          | 87.0                 |
| 4  | Reducing SBP by 20% if above 140 mmHg            | 12.4 (10.2, 15)           | 0.88 (0.74, 1.01)  | -1.6 (-3.7, 0.1)        | 87.0                 |
| 5  | Quitting smoking                                 | 13.5 (11.7, 15.2)         | 0.96 (0.91, 1)     | -0.6 (-1.4, 0.1)        | 22.1                 |
| 6  | Joint 1 + 5                                      | 11.6 (8.9, 14.9)          | 0.83 (0.64, 1.02)  | -2.5 (-5.4, 0.2)        | 98.8                 |
| 7  | Joint 2 + 5                                      | 12.2 (10.4, 14.4)         | 0.87 (0.75, 0.97)  | -1.8 (-3.5, -0.5)       | 91.5                 |
| 8  | Joint 3 + 5                                      | 12.2 (10.1, 14.3)         | 0.87 (0.75, 0.97)  | -1.8 (-3.8, -0.5)       | 90.3                 |
| 9  | Joint 4 + 5                                      | 11.9 (9.6, 14.5)          | 0.85 (0.71, 1)     | -2.2 (-4.3, 0)          | 90.3                 |
### Table e-8

1.5. Women subgroup
The observed risk at 15 years is **9.2%**.

| No | Intervention                                      | Absolute Risk (%) Cl(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|-------------------------|-----------------------|
| 0  | Natural course                                    | 9.3 (8.1, 10.9)           | 1 (1, 1)           | 0 (0, 0)                | 0.0                   |
| 1  | Maintaining SBP below 120 mmHg                    | 8.3 (6.4, 11.3)           | 0.9 (0.72, 1.13)   | -0.9 (-2.7, 1.3)       | 97.2                  |
| 2  | Maintaining SBP below 140 mmHg                    | 8.4 (7.4, 10.4)           | 0.91 (0.82, 1.03)  | -0.8 (-1.8, 0.2)       | 83.6                  |
| 3  | Reducing SBP by 10% if above 140 mmHg             | 8.4 (7.2, 10.6)           | 0.9 (0.8, 1.07)    | -0.9 (-2, 0.7)         | 82.6                  |
| 4  | Reducing SBP by 20% if above 140 mmHg             | 8.4 (6.8, 10.9)           | 0.9 (0.77, 1.09)   | -0.9 (-2.2, 0.9)       | 82.6                  |
| 5  | Quitting smoking                                  | 8.6 (7.5, 10.4)           | 0.93 (0.86, 0.98)  | -0.7 (-1.4, -0.2)      | 23.4                  |
| 6  | Joint 1 + 5                                       | 7.7 (6, 10.7)             | 0.83 (0.66, 1.04)  | -1.6 (-3.3, 0.4)       | 98.8                  |
| 7  | Joint 2 + 5                                       | 7.9 (6.8, 9.9)            | 0.85 (0.76, 0.99)  | -1.4 (-2.6, -0.1)      | 88.4                  |
| 8  | Joint 3 + 5                                       | 7.7 (6.5, 9.9)            | 0.83 (0.73, 1)     | -1.6 (-2.8, 0)         | 88.0                  |
| 9  | Joint 4 + 5                                       | 7.7 (6.1, 10.3)           | 0.83 (0.71, 1.02)  | -1.6 (-2.9, 0.3)       | 88.0                  |
Table e-9

1.6. Men subgroup
The observed risk at 15 years is 11.6%.

| No | Intervention                                      | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|--------------------------------------------------|---------------------------|--------------------|-------------------------|-----------------------|
| 0  | Natural course                                   | 11.6 (10.2, 13.5)         | 1 (1, 1)           | 0 (0, 0)                | 0.0                   |
| 1  | Maintaining SBP below 120 mmHg                   | 10 (7.3, 13.2)            | 0.86 (0.69, 1.05)  | -1.6 (-3.7, 0.5)        | 98.8                  |
| 2  | Maintaining SBP below 140 mmHg                   | 10.2 (8.6, 12.2)          | 0.88 (0.77, 1)     | -1.4 (-2.5, 0)          | 84.8                  |
| 3  | Reducing SBP by 10% if above 140 mmHg            | 10.2 (8.5, 12.5)          | 0.87 (0.76, 1.01)  | -1.5 (-2.8, 0.1)        | 83.4                  |
| 4  | Reducing SBP by 20% if above 140 mmHg            | 10.1 (7.9, 12.8)          | 0.87 (0.71, 1.03)  | -1.6 (-3.2, 0.4)        | 83.4                  |
| 5  | Quitting smoking                                 | 10.9 (9.4, 13)            | 0.94 (0.87, 1.02)  | -0.7 (-1.7, 0.3)        | 30.9                  |
| 6  | Joint 1 + 5                                      | 9.5 (6.9, 12.5)           | 0.81 (0.63, 1.04)  | -2.2 (-4.5, 0.5)        | 99.5                  |
| 7  | Joint 2 + 5                                      | 9.6 (8, 11.7)             | 0.83 (0.72, 0.96)  | -2 (-3.4, -0.4)         | 89.7                  |
| 8  | Joint 3 + 5                                      | 9.5 (7.8, 12)             | 0.82 (0.71, 0.97)  | -2.1 (-3.5, -0.4)       | 88.9                  |
| 9  | Joint 4 + 5                                      | 9.4 (7.5, 12.3)           | 0.81 (0.67, 1.01)  | -2.2 (-4, 0.1)          | 88.9                  |
### Table e-10

1.7. Without hypertension medication at baseline subgroup
The observed risk at 15 years is **8.8%**.

| No | Intervention                                   | Absolute Risk (%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|------------------------------------------------|-------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                 | 9.1 (8.2, 10.6)   | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                 | 7.8 (6.1, 9.3)    | 0.85 (0.68, 1)     | -1.3 (-2.7, 0)          | 97.8                 |
| 2  | Maintaining SBP below 140 mmHg                 | 8.1 (6.8, 9.4)    | 0.89 (0.79, 0.96)  | -1 (-1.8, -0.4)         | 82.1                 |
| 3  | Reducing SBP by 10% if above 140 mmHg          | 8 (6.6, 9.3)      | 0.87 (0.77, 0.96)  | -1.1 (-2, -0.3)         | 81.3                 |
| 4  | Reducing SBP by 20% if above 140 mmHg          | 7.9 (6.3, 9.2)    | 0.86 (0.72, 0.99)  | -1.2 (-2.4, -0.1)       | 81.3                 |
| 5  | Quitting smoking                               | 8.2 (7.2, 9.6)    | 0.89 (0.85, 0.95)  | -1 (-1.4, -0.4)         | 28.8                 |
| 6  | Joint 1 + 5                                    | 6.9 (5.1, 8.6)    | 0.76 (0.6, 0.93)   | -2.2 (-3.4, -0.6)       | 98.5                 |
| 7  | Joint 2 + 5                                    | 7.2 (6, 8.4)      | 0.79 (0.71, 0.87)  | -1.9 (-2.7, -1.1)       | 87.8                 |
| 8  | Joint 3 + 5                                    | 7.1 (5.7, 8.5)    | 0.78 (0.69, 0.88)  | -2 (-2.8, -1.1)         | 87.9                 |
| 9  | Joint 4 + 5                                    | 7 (5.3, 8.4)      | 0.77 (0.64, 0.9)   | -2.1 (-3.1, -0.9)       | 87.9                 |
1.8. No history of heart disease at baseline subgroup
The observed risk at 15 years is **9.9%**.

| No | Intervention                                | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------|----------------------------|--------------------|------------------------|-----------------------|
| 0  | Natural course                             | 9.9 (9.1, 10.9)           | 1 (1, 1)           | 0 (0, 0)               | 0.0                   |
| 1  | Maintaining SBP below 120 mmHg             | 8.7 (7.2, 10.9)           | 0.88 (0.72, 1.05)  | -1.2 (-2.7, 0.6)       | 98.1                  |
| 2  | Maintaining SBP below 140 mmHg             | 8.9 (8.1, 10.4)           | 0.9 (0.84, 1)      | -1 (-1.6, 0)           | 82.4                  |
| 3  | Reducing SBP by 10% if above 140 mmHg      | 9.0 (7.8, 10.4)           | 0.91 (0.82, 1.01)  | -0.9 (-1.8, 0.2)       | 82.8                  |
| 4  | Reducing SBP by 20% if above 140 mmHg      | 8.9 (7.5, 10.6)           | 0.9 (0.77, 1.04)   | -1 (-2.2, 0.4)         | 82.8                  |
| 5  | Quitting smoking                           | 9.2 (8.3, 10.2)           | 0.93 (0.89, 0.99)  | -0.7 (-1.1, -0.1)      | 26.3                  |
| 6  | Joint 1 + 5                                | 8.6 (6.3, 10.3)           | 0.81 (0.66, 0.99)  | -1.9 (-3.3, -0.1)      | 98.8                  |
| 7  | Joint 2 + 5                                | 8.4 (7.3, 9.8)            | 0.85 (0.76, 0.94)  | -1.4 (-2.3, -0.6)      | 88.7                  |
| 8  | Joint 3 + 5                                | 8.3 (7.3, 9.8)            | 0.84 (0.75, 0.95)  | -1.5 (-2.4, -0.5)      | 88.5                  |
| 9  | Joint 4 + 5                                | 8.2 (6.8, 10.1)           | 0.83 (0.7, 0.99)   | -1.6 (-2.9, -0.1)      | 88.5                  |
Table e-12

2. Dementia

2.1. Death as censored.
The observed risk at 15 years is **10.8%**.

| No | Intervention                               | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|-------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                            | 13.1 (11.7, 14.8)         | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg            | 13.9 (11.7, 17.1)         | 1.07 (0.92, 1.26)  | 0.9 (-1, 3.6)           | 98.2                 |
| 2  | Maintaining SBP below 140 mmHg            | 13 (11.4, 15.2)           | 1 (0.92, 1.09)     | 0 (-1, 1.3)             | 83.0                 |
| 3  | Reducing SBP by 10% if above 140 mmHg     | 13.3 (11.5, 15.6)         | 1.01 (0.93, 1.12)  | 0.2 (-1.1, 1.6)         | 83.3                 |
| 4  | Reducing SBP by 20% if above 140 mmHg     | 13.7 (11.8, 16.6)         | 1.05 (0.92, 1.2)   | 0.7 (-1, 2.6)           | 83.3                 |
| 5  | Quitting smoking                          | 12.8 (11.6, 14.5)         | 0.98 (0.95, 1.02)  | -0.3 (-0.8, 0.2)        | 25.9                 |
| 6  | Joint 1 + 5                               | 13.8 (11.4, 16.7)         | 1.05 (0.89, 1.23)  | 0.7 (-1.4, 3.2)         | 98.8                 |
| 7  | Joint 2 + 5                               | 12.8 (11.1, 14.9)         | 0.98 (0.89, 1.09)  | -0.2 (-1.3, 1.2)        | 88.2                 |
| 8  | Joint 3 + 5                               | 13 (11.2, 15.2)           | 0.99 (0.9, 1.11)   | -0.1 (-1.4, 1.4)        | 88.6                 |
| 9  | Joint 4 + 5                               | 13.4 (11.4, 16.1)         | 1.03 (0.9, 1.16)   | 0.4 (-1.4, 2.2)         | 88.6                 |
### Table e-13

#### 2.2. Dementia and death as combined outcome

The observed risk at 15 years is **36.7%**.

| No | Intervention                                      | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|------------------------|-----------------------|
| 0  | Natural course                                    | 38.9 (37, 40.4)           | 1 (1, 1)           | 0 (0, 0)               | 0.0                   |
| 1  | Maintaining SBP below 120 mmHg                    | 40.2 (38.4, 42.9)         | 1.03 (0.99, 1.1)   | 1.3 (-0.2, 3.8)        | 98.2                  |
| 2  | Maintaining SBP below 140 mmHg                    | 38.6 (37.1, 40.7)         | 0.99 (0.98, 1.04)  | -0.3 (-0.7, 1.6)       | 83.0                  |
| 3  | Reducing SBP by 10% if above 140 mmHg             | 39.5 (37.2, 41.2)         | 1.02 (0.99, 1.05)  | 0.6 (-0.6, 2)          | 83.3                  |
| 4  | Reducing SBP by 20% if above 140 mmHg             | 40.3 (37.8, 42.1)         | 1.04 (0.99, 1.07)  | 1.4 (-0.2, 2.8)        | 83.3                  |
| 5  | Quitting smoking                                  | 36.4 (34.3, 37.7)         | 0.93 (0.91, 0.94)  | -2.5 (-3.6, -2.1)      | 25.9                  |
| 6  | Joint 1 + 5                                       | 37.6 (35.6, 40.1)         | 0.97 (0.93, 1.04)  | -1.3 (-2.8, 1.4)       | 98.8                  |
| 7  | Joint 2 + 5                                       | 36.1 (34.6, 38.2)         | 0.93 (0.91, 0.97)  | -2.8 (-3.6, -1)        | 88.2                  |
| 8  | Joint 3 + 5                                       | 36.9 (34.8, 38.2)         | 0.95 (0.91, 0.99)  | -2 (-3.4, -0.6)        | 88.6                  |
| 9  | Joint 4 + 5                                       | 37.6 (35.2, 39.2)         | 0.97 (0.92, 1)     | -1.3 (-3, 0.2)         | 88.6                  |
Table e-14

2.3. Under 65 years subgroup

The observed risk at 15 years is \textbf{3.2\%}.

| No | Intervention                                           | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|--------------------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                         | 4 (3.2, 5.7)              | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                        | 4.3 (2.7, 6.7)            | 1.06 (0.75, 1.5)   | 0.2 (-1.1, 2.2)         | 97.3                 |
| 2  | Maintaining SBP below 140 mmHg                        | 3.9 (3.1, 5.6)            | 0.97 (0.79, 1.18)  | -0.1 (-0.8, 0.6)        | 79.2                 |
| 3  | Reducing SBP by 10\% if above 140 mmHg                | 4 (2.9, 5.8)              | 0.99 (0.78, 1.22)  | 0 (-1, 0.8)             | 79.0                 |
| 4  | Reducing SBP by 20\% if above 140 mmHg                | 4.2 (2.9, 6.2)            | 1.04 (0.77, 1.39)  | 0.2 (-1.1, 1.5)         | 79.0                 |
| 5  | Quitting smoking                                       | 4.1 (3.1, 5.8)            | 1.01 (0.89, 1.12)  | 0 (-0.4, 0.4)           | 30.7                 |
| 6  | Joint 1 + 5                                            | 4.2 (2.9, 6.5)            | 1.05 (0.71, 1.48)  | 0.2 (-1.2, 2)           | 98.3                 |
| 7  | Joint 2 + 5                                            | 4 (3.5, 8)                | 0.99 (0.8, 1.19)   | 0 (-0.9, 0.8)           | 86.2                 |
| 8  | Joint 3 + 5                                            | 4 (3.1, 5.8)              | 0.99 (0.81, 1.21)  | 0 (-0.8, 0.9)           | 85.5                 |
| 9  | Joint 4 + 5                                            | 4.2 (3, 6.1)              | 1.04 (0.73, 1.37)  | 0.2 (-1, 1.4)           | 85.5                 |
Table e-15

2.4. Above 65 years and below 80 years subgroup
The observed risk at 15 years is **14.1%**.

| No | Intervention                                      | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                    | 13.8 (12.4, 15.6)         | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                    | 14.4 (11.8, 17.5)         | 1.04 (0.85, 1.2)   | 0.6 (-2.2, 2.8)         | 98.8                 |
| 2  | Maintaining SBP below 140 mmHg                    | 13.6 (12, 15.8)           | 0.99 (0.9, 1.08)   | -0.2 (-1.3, 1.1)        | 87.7                 |
| 3  | Reducing SBP by 10% if above 140 mmHg             | 13.7 (11.8, 16.2)         | 0.99 (0.9, 1.1)    | -0.1 (-1.5, 1.4)        | 87.1                 |
| 4  | Reducing SBP by 20% if above 140 mmHg             | 13.9 (11.7, 16.9)         | 1.01 (0.88, 1.14)  | 0.2 (-1.9, 2)           | 87.1                 |
| 5  | Quitting smoking                                  | 14 (12.7, 15.9)           | 1.02 (0.97, 1.06)  | 0.2 (-0.5, 0.9)         | 21.6                 |
| 6  | Joint 1 + 5                                       | 14.5 (11.8, 18.1)         | 1.05 (0.83, 1.26)  | 0.7 (-2.2, 3.6)         | 99.1                 |
| 7  | Joint 2 + 5                                       | 13.8 (12.1, 16.5)         | 1 (0.91, 1.11)     | 0 (-1.4, 1.6)           | 90.9                 |
| 8  | Joint 3 + 5                                       | 13.9 (12.1, 16.7)         | 1.01 (0.9, 1.12)   | 0.1 (-1.5, 1.8)         | 90.6                 |
| 9  | Joint 4 + 5                                       | 14.2 (12, 17.3)           | 1.03 (0.87, 1.2)   | 0.4 (-1.8, 2.9)         | 90.6                 |
Table e-16

2.5. Women subgroup
The observed risk at 15 years is **10.7%**.

| No | Intervention                                      | Absolute Risk (%) CI(95%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                    | 11.2 (9.7, 12.7)          | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                    | 10.3 (8.3, 12.6)          | 0.93 (0.7, 1.1)    | -0.8 (-3.6, 1.1)        | 98.3                 |
| 2  | Maintaining SBP below 140 mmHg                    | 10.2 (8.8, 11.9)          | 0.91 (0.82, 1)     | -1 (-2.3, 0)            | 84.4                 |
| 3  | Reducing SBP by 10% if above 140 mmHg            | 10.2 (8.8, 11.8)          | 0.91 (0.79, 1.02)  | -1 (-2.6, 0.2)          | 82.9                 |
| 4  | Reducing SBP by 20% if above 140 mmHg            | 10.2 (8.7, 12.2)          | 0.92 (0.75, 1.05)  | -1 (-3.1, 0.6)          | 82.9                 |
| 5  | Quitting smoking                                  | 11 (9.4, 12.7)            | 0.99 (0.94, 1.03)  | -0.1 (-0.6, 0.3)        | 22.8                 |
| 6  | Joint 1 + 5                                       | 10.2 (8, 12.6)            | 0.91 (0.68, 1.08)  | -1 (-3.8, 0.9)          | 98.5                 |
| 7  | Joint 2 + 5                                       | 10 (8.6, 11.8)            | 0.9 (0.8, 1)       | -1.1 (-2.5, 0)          | 88.3                 |
| 8  | Joint 3 + 5                                       | 10 (8.7, 11.8)            | 0.9 (0.77, 1.01)   | -1.1 (-2.8, 0.1)        | 88.2                 |
| 9  | Joint 4 + 5                                       | 10.1 (8.4, 12.3)          | 0.91 (0.73, 1.05)  | -1.1 (-3.4, 0.5)        | 88.2                 |
2.6. Men subgroup
The observed risk at 15 years is \textbf{6.7\%}.

| No | Intervention                        | Absolute Risk (%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|-------------------------------------|-------------------|-------------------|-------------------------|-----------------------|
|    |                                     | CI(95%)           |                   |                         |                       |
| 0  | Natural course                      | 7 (6, 8.9)        | 1 (1, 1)          | 0 (0, 0)                | 0.0                   |
| 1  | Maintaining SBP below 120 mmHg      | 9.5 (7.1, 12.8)   | 1.36 (1.09, 1.66) | 2.5 (0.6, 4.7)          | 98.2                  |
| 2  | Maintaining SBP below 140 mmHg      | 8.1 (6.7, 10.6)   | 1.15 (1.03, 1.33) | 1.1 (0.2, 2.2)          | 83.4                  |
| 3  | Reducing SBP by 10\% if above 140 mmHg | 8.4 (6.7, 11.2) | 1.2 (1.03, 1.37) | 1.4 (0.2, 2.6)          | 83.8                  |
| 4  | Reducing SBP by 20\% if above 140 mmHg | 9.1 (6.8, 11.9) | 1.29 (1.05, 1.51) | 2.1 (0.3, 3.7)          | 83.8                  |
| 5  | Quitting smoking                    | 7.5 (6.4, 9.6)    | 1.08 (1, 1.16)    | 0.6 (0, 1.1)            | 30.5                  |
| 6  | Joint 1 + 5                         | 10.4 (7.3, 14.1)  | 1.48 (1.13, 1.81) | 3.4 (0.9, 5.7)          | 98.7                  |
| 7  | Joint 2 + 5                         | 8.8 (7.1, 11.2)   | 1.26 (1.09, 1.42) | 1.8 (0.7, 3)            | 89.0                  |
| 8  | Joint 3 + 5                         | 9.1 (7, 11.9)     | 1.31 (1.08, 1.49) | 2.1 (0.6, 3.5)          | 89.7                  |
| 9  | Joint 4 + 5                         | 9.8 (7.2, 13)     | 1.4 (1.12, 1.64)  | 2.8 (0.8, 4.5)          | 89.7                  |
### Table e-18

2.7. Without hypertension medication at baseline subgroup
The observed risk at 15 years is **8.6%**.

| No | Intervention                          | Absolute Risk (%) | Risk Ratio CI(95%) | Risk Difference CI(95%) | Total Intervened (%) |
|----|---------------------------------------|-------------------|--------------------|-------------------------|-----------------------|
| 0  | Natural course                        | 8.8 (8, 10.2)     | 1 (1, 1)           | 0 (0, 0)                | 0.0                   |
| 1  | Maintaining SBP below 120 mmHg        | 10 (7.6, 12.3)    | 1.14 (0.93, 1.34)  | 1.2 (-0.6, 3)           | 97.9                  |
| 2  | Maintaining SBP below 140 mmHg        | 9.1 (7.7, 10.9)   | 1.04 (0.95, 1.13)  | 0.3 (-0.5, 1.2)         | 81.7                  |
| 3  | Reducing SBP by 10% if above 140 mmHg | 9.3 (7.7, 11)     | 1.06 (0.94, 1.16)  | 0.5 (-0.5, 1.4)         | 81.5                  |
| 4  | Reducing SBP by 20% if above 140 mmHg | 9.8 (7.8, 11.7)   | 1.11 (0.94, 1.25)  | 1 (-0.5, 2.3)           | 81.5                  |
| 5  | Quitting smoking                      | 8.9 (8, 10.6)     | 1.01 (0.97, 1.06)  | 0.1 (-0.3, 0.5)         | 28.4                  |
| 6  | Joint 1 + 5                           | 10.3 (7.6, 12.6)  | 1.17 (0.94, 1.35)  | 1.5 (-0.5, 3)           | 98.8                  |
| 7  | Joint 2 + 5                           | 9.3 (7.8, 11.1)   | 1.06 (0.94, 1.16)  | 0.5 (-0.6, 1.3)         | 88.1                  |
| 8  | Joint 3 + 5                           | 9.5 (7.8, 11.3)   | 1.07 (0.94, 1.19)  | 0.6 (-0.6, 1.6)         | 88.2                  |
| 9  | Joint 4 + 5                           | 9.9 (7.7, 11.8)   | 1.12 (0.95, 1.27)  | 1.1 (-0.4, 2.4)         | 88.2                  |
2.8. Free of heart disease at baseline subgroup
The observed risk at 15 years is 8.6%.

| No | Intervention                                      | Absolute Risk (%) Cl(95%) | Risk Ratio Cl(95%) | Risk Difference Cl(95%) | Total Intervened (%) |
|----|---------------------------------------------------|---------------------------|--------------------|-------------------------|----------------------|
| 0  | Natural course                                    | 8.8 (8, 10)               | 1 (1, 1)           | 0 (0, 0)                | 0.0                  |
| 1  | Maintaining SBP below 120 mmHg                   | 9.3 (7.4, 11.3)           | 1.06 (0.88, 1.21)  | 0.5 (-1, 1.8)           | 98.0                 |
| 2  | Maintaining SBP below 140 mmHg                   | 8.9 (7.6, 10.5)           | 1.02 (0.91, 1.09)  | 0.1 (-0.8, 0.9)         | 83.7                 |
| 3  | Reducing SBP by 10% if above 140 mmHg            | 8.9 (7.6, 10.5)           | 1.01 (0.9, 1.12)   | 0.1 (-0.9, 1.1)         | 83.2                 |
| 4  | Reducing SBP by 20% if above 140 mmHg            | 9.1 (7.6, 11)             | 1.04 (0.89, 1.16)  | 0.3 (-0.9, 1.4)         | 83.2                 |
| 5  | Quitting smoking                                  | 8.8 (7.8, 10)             | 1 (0.96, 1.04)     | 0 (-0.4, 0.4)           | 26.3                 |
| 6  | Joint 1 + 5                                       | 9.4 (7.6, 11.3)           | 1.07 (0.89, 1.23)  | 0.6 (-1, 1.9)           | 98.9                 |
| 7  | Joint 2 + 5                                       | 9 (7.7, 10.4)             | 1.02 (0.9, 1.11)   | 0.2 (-0.9, 1)           | 88.7                 |
| 8  | Joint 3 + 5                                       | 9 (7.6, 10.7)             | 1.02 (0.91, 1.13)  | 0.2 (-0.8, 1.2)         | 88.8                 |
| 9  | Joint 4 + 5                                       | 9.2 (7.6, 11.1)           | 1.05 (0.9, 1.16)   | 0.4 (-0.9, 1.6)         | 88.8                 |
## STROBE Statement

Checklist of items that should be included in reports of cohort studies

| Item No | Recommendation                                                                 | Page No |
|---------|---------------------------------------------------------------------------------|---------|
| **Title and abstract** | **1** | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 3       |
|         | **1** | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3       |
| **Introduction** | **2** | Explain the scientific background and rationale for the investigation being reported | 4       |
| **Objectives** | **3** | State specific objectives, including any prespecified hypotheses | 5       |
| **Methods** | **4** | Present key elements of study design early in the paper | 5 – 7   |
| **Study design** | **4** | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 – 7   |
| **Setting** | **5** | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5 – 7   |
| **Participants** | **6** | (b) For matched studies, give matching criteria and number of exposed and unexposed | -       |
| **Variables** | **7** | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5 – 8   |
| **Data sources/measurement** | **8** | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7 OR*:3 |
| **Bias** | **9** | Describe any efforts to address potential sources of bias | 9       |
| **Study size** | **10** | Explain how the study size was arrived at | Figure 1 |
| **Quantitative variables** | **11** | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | OR: 1   |
| **Statistical methods** | **12** | (a) Describe all statistical methods, including those used to control for confounding | 7 – 9   |
|         | **12** | (b) Describe any methods used to examine subgroups and interactions | 7 – 9   |
|         | **12** | (c) Explain how missing data were addressed | OR: 4   |
|         | **12** | (d) If applicable, explain how loss to follow-up was addressed | 7 – 9   |
|         | **12** | (e) Describe any sensitivity analyses | 9       |
| **Results** | **13** | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| **Participants** | **13** | (b) Give reasons for non-participation at each stage | Figure 1 |
|                | (c) Consider use of a flow diagram | Figure 1 |
|----------------|-----------------------------------|----------|
| Descriptive data | 14*                              | Table 1  |
|                 | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |          |
|                 | (b) Indicate number of participants with missing data for each variable of interest | Table 1  |
|                 | (c) Summarise follow-up time (eg, average and total amount) | 9        |
| Outcome data    | 15*                              | 9, 10    |
|                 | Report numbers of outcome events or summary measures over time |          |

*OR: Online resources