

Supplementary Information (SI)

1. Overview of UK Biobank variables

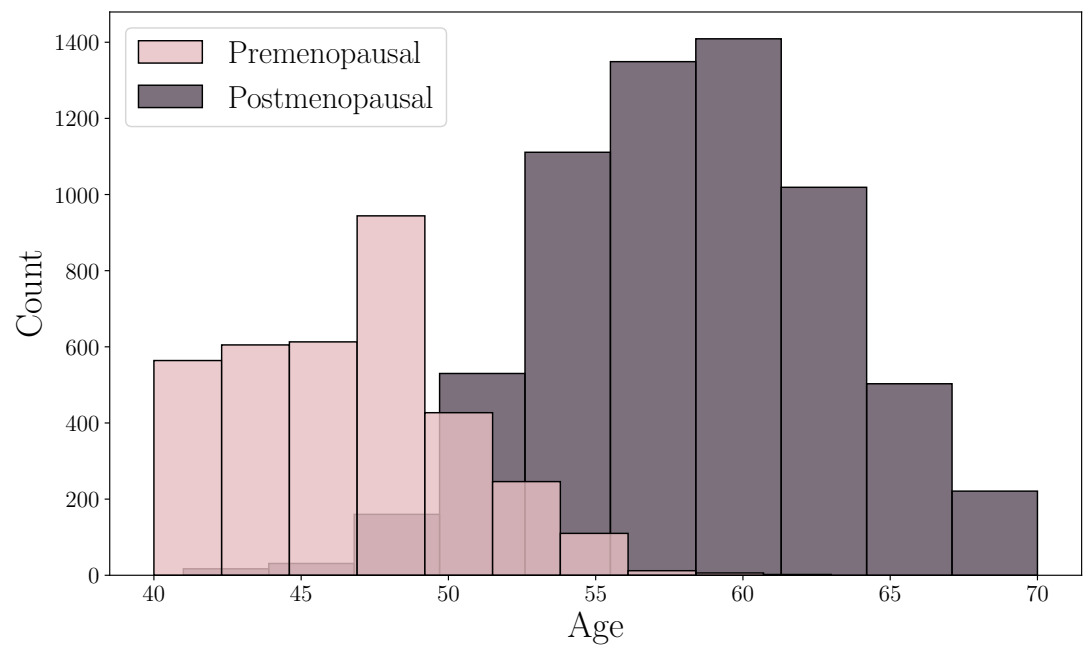
SI Table 1 displays all variables utilised in this study, including the timepoint from which they were employed, and their UK Biobank (UKB) data-field. Waist-to-hip ratio was manually calculated using waist and hip circumference measures, and assessment interval was manually calculated using the date of attending the assessment centre at baseline and timepoint 2.

SI Table 1: Overview of variables utilised in this study, with their respective timepoints and UK Biobank (UKB) data-fields. BL = baseline, TP2 = timepoint 2. BMI = body mass index, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin, WMH volume = white matter hyperintensity volume.

| Variable name | Timepoint | UKB data-field |
|---------------------------------|------------|----------------|
| Menopausal status | BL and TP2 | 2724 |
| Age | BL and TP2 | 21003 |
| Date of assessment | BL and TP2 | 53 |
| BMI | BL and TP2 | 21001 |
| Waist circumference | BL and TP2 | 48 |
| Hip circumference | BL and TP2 | 49 |
| HDL | BL | 30760 |
| LDL | BL | 30780 |
| Triglycerides | BL | 30870 |
| Systolic BP | BL | 4080 |
| Diastolic BP | BL | 4079 |
| HbA1c | BL | 30750 |
| Education | BL | 6138 |
| Ethnic background | BL | 21000 |
| WMH volume | TP2 | 25781 |
| Hysterectomy | TP2 | 3591 |
| Bilateral oophorectomy | TP2 | 2834 |
| Hormone replacement therapy use | TP2 | 2814 |
| Oral contraceptive use | TP2 | 2784 |
| Number of childbirths | TP2 | 2734 |
| Smoking status | TP2 | 20116 |
| Alcohol intake frequency | TP2 | 1558 |
| Diabetes diagnosis | TP2 | 2443 |
| Assessment centre | TP2 | 54 |

7 **2. Age at baseline distributions**

8 SI Figure 1 displays age at baseline distributions in the premenopausal and postmenopausal groups.



SI Figure 1: Distributions of age at baseline in premenopausal ($n = 3,529$) and postmenopausal ($n = 6,353$) females.

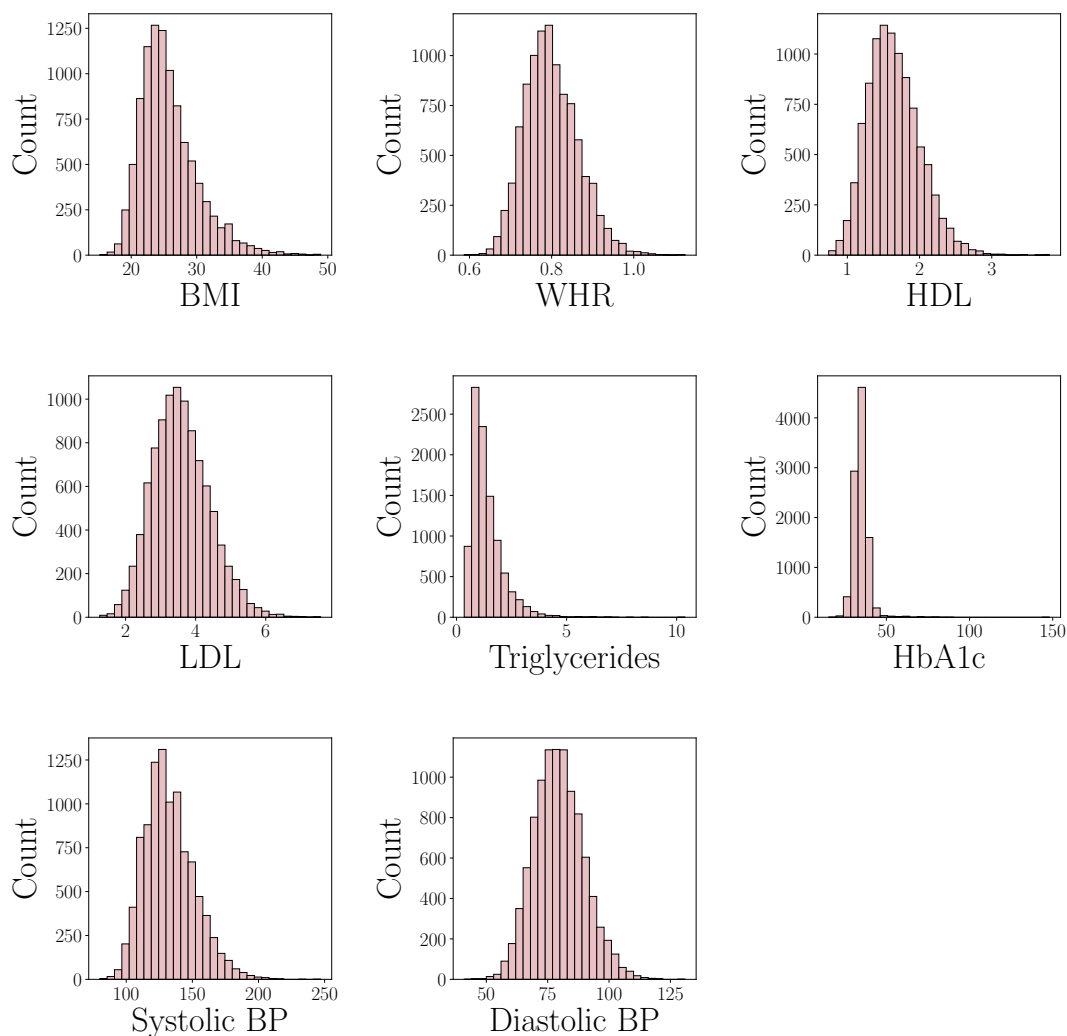
3. Overview of cardiometabolic markers

SI Table 2 provides an overview of the cardiometabolic markers and their respective thresholds considered healthy based on the World Health Organisation (WHO) and the National Cholesterol Education Program Expert Panel (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; World Health Organization, 2011a,b, 2021, 2022). Participants were excluded for sensitivity analyses in SI section 6.3 if their marker values ranged outside these thresholds.

SI Table 2: Descriptions of the cardiometabolic markers utilised in this study, and their respective healthy thresholds, based on the resources specified above.

| Abbreviation | Full name | Summary | Healthy levels |
|---------------|--------------------------|---|----------------|
| BMI | Body mass index | Measures body fat based on height and weight; higher levels indicate obesity | > 30 |
| WHR | Waist-to-hip ratio | Assesses fat distribution; a higher ratio indicates increased abdominal fat | > 0.85 |
| HDL | High density lipoprotein | “Good” cholesterol; higher levels can indicate protective cardiovascular effect | < 1.03 mmol/L |
| LDL | Low density lipoprotein | “Bad” cholesterol; higher levels can indicate increased cardiovascular risk | > 4.13 mmol/L |
| Triglycerides | Triglycerides | Type of fat in blood; higher levels can increase cardiovascular risk | > 2.26 mmol/L |
| Systolic BP | Systolic blood pressure | Pressure in arteries during heartbeats; higher levels can suggest risk of hypertension | > 140 mmHg |
| Diastolic BP | Diastolic blood pressure | Pressure in arteries between heartbeats; higher levels can suggest risk of hypertension | > 90 mmHg |
| HbA1c | Glycated haemoglobin | Average blood glucose over 3 months; higher levels indicate poor control | > 48 mmol/mol |

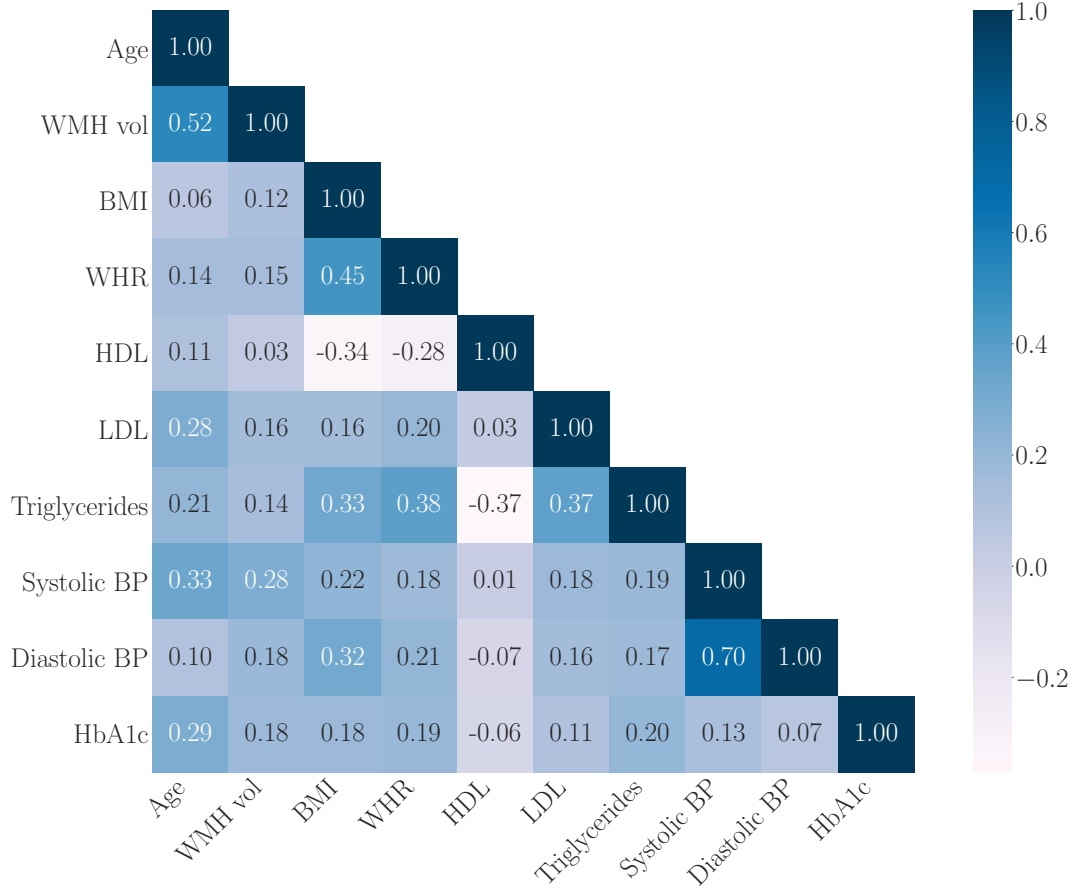
16 SI Figure 2 displays the distribution plots for the baseline cardiometabolic markers. As some vari-
 17 ables did not show a normal distribution, the statistical analyses provided in main manuscript section
 18 2.5 were re-run after log-transforming the variables (see SI section 6.4).



SI Figure 2: Distribution plots of baseline cardiometabolic markers. BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

4. Correlations of the main variables

SI Figure 3 shows the correlation matrix for baseline age, baseline cardiometabolic markers, and white matter hyperintensity (WMH) volume at timepoint 2. The variables were tested for multicollinearity using Variance Inflation Factors (VIFs), where values > 10 can indicate high levels of collinearity (James et al., 2013) (SI Table 3).



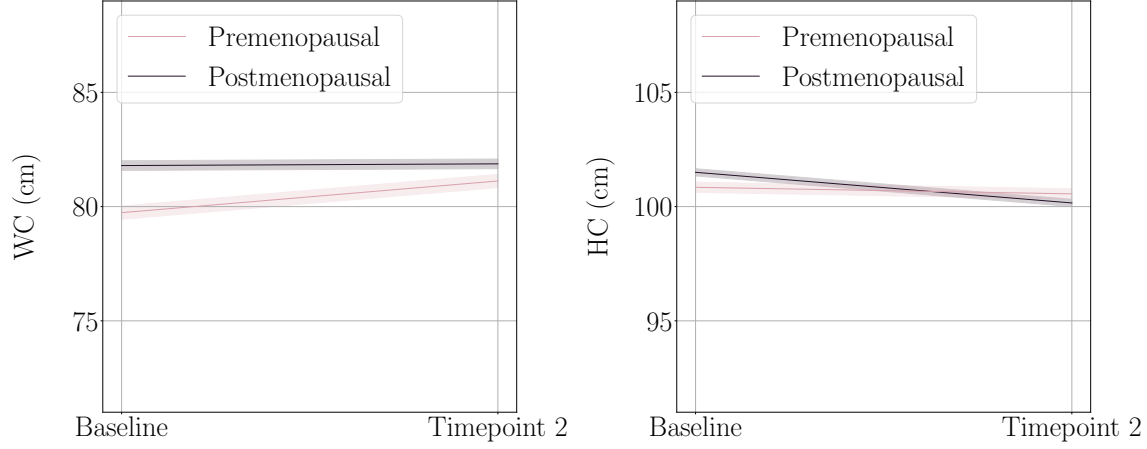
SI Figure 3: Correlation matrix. WMH vol = white matter hyperintensity volume, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

SI Table 3: Variance Inflation Factors (VIF) for baseline cardiometabolic markers. BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin. Values of > 10 can indicate high levels of collinearity.

| | BMI | WHR | HDL | LDL | Triglycerides | Systolic BP | Diastolic BP | HbA1c |
|-----|------|-------|------|------|---------------|-------------|--------------|-------|
| VIF | 52.4 | 123.4 | 23.6 | 24.8 | 6.9 | 102.0 | 123.4 | 57.6 |

5. Change of waist circumference and hip circumference over time

SI Figure 4 shows mean waist circumference (WC) and hip circumference (HC) plotted at both timepoints for each menopause status group. We observed significant main effects of timepoints for WC, and significant interactions with menopause status group for both WC and HC (SI Table 4).



SI Figure 4: Waist circumference (WC) and hip circumference (HC) at baseline and timepoint 2, plotted separately for the premenopausal and postmenopausal groups. The shaded bands indicate 95% confidence intervals. Note that these plots illustrate the raw mean values and are not adjusted for age.

SI Table 4: Results from the mixed linear models for WC (waist circumference) and HC (hip circumference). DV = dependent variable, SE = standard error, TP = timepoint (baseline and timepoint 2), MP status = menopause status.

| DV | Term | β | SE | z | p -value | Adj. p -value |
|----|----------------|---------|-------|-------|------------|-----------------|
| WC | TP | 0.072 | 0.012 | 6.03 | < 0.001 | < 0.001 |
| | TP x MP status | -0.055 | 0.015 | -3.72 | < 0.001 | < 0.001 |
| HC | TP | -0.015 | 0.012 | -1.28 | 0.200 | 0.280 |
| | TP x MP status | -0.057 | 0.015 | -3.88 | < 0.001 | < 0.001 |

6. Sensitivity analyses

6.1. Additional covariates

When adjusting for additional covariates (see main manuscript section 2.7.1), the associations between baseline cardiometabolic markers and WMH volume, as well as change in BMI/WHR and WMH volume, were highly consistent with our main results (SI Table 5 and SI Table 6). When adjusting for all other cardiometabolic markers (SI Table 7), baseline body anthropometrics and BP measures continued to show significant associations with WMH volume, but blood lipids and HbA1c did not. Associations between change in BMI/WHR and WMH volume remained consistent when adjusting for other baseline cardiometabolic markers (SI Table 8). They also remained consistent when adjusting for change in systolic and diastolic BP in a smaller subsample with available data ($n = 8,101$) (SI Table 9.)

SI Table 5: Results from the linear regression models testing associations between baseline cardiometabolic markers and WMH (white matter hyperintensity) volume at timepoint 2, adjusting for smoking status, alcohol use, education, ethnic background, hormone replacement use, oral contraceptive use, and number of childbirths, all reported at timepoint 2, in addition to age and assessment interval. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|---------------|---------|-------|-------|------------|-----------------|
| WMH vol | BMI | 0.089 | 0.008 | 10.64 | < 0.001 | < 0.001 |
| | WHR | 0.074 | 0.008 | 8.97 | < 0.001 | < 0.001 |
| | HDL | -0.025 | 0.009 | -2.94 | 0.003 | 0.006 |
| | LDL | 0.011 | 0.009 | 1.24 | 0.214 | 0.296 |
| | Triglycerides | 0.037 | 0.008 | 4.39 | < 0.001 | < 0.001 |
| | Systolic BP | 0.121 | 0.009 | 14.00 | < 0.001 | < 0.001 |
| | Diastolic BP | 0.128 | 0.008 | 15.66 | < 0.001 | < 0.001 |
| | HbA1c | 0.029 | 0.009 | 3.30 | 0.001 | 0.002 |

SI Table 6: Results from the linear regression models testing associations between BMI (body mass index) or WHR (waist-to-hip ratio) change and WMH (white matter hyperintensity) volume at timepoint 2, adjusted for smoking status, alcohol use, education, ethnic background, hormone replacement use, oral contraceptive use, and number of childbirths, all reported at timepoint 2, in addition to age and assessment interval. DV = dependent variable, SE = standard error.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|------------|---------|-------|------|------------|-----------------|
| WMH vol | BMI change | 0.037 | 0.008 | 4.44 | < 0.001 | < 0.001 |
| | WHR change | 0.045 | 0.008 | 5.47 | < 0.001 | < 0.001 |

SI Table 7: Results from the linear regression models testing associations between baseline cardiometabolic markers and WMH (white matter hyperintensity) volume at timepoint 2, adjusted for all other cardiometabolic markers, in addition to age and assessment interval. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|---------------|---------|-------|-------|------------|-----------------|
| WMH vol | BMI | 0.044 | 0.010 | 4.49 | < 0.001 | < 0.001 |
| | WHR | 0.040 | 0.010 | 4.21 | < 0.001 | < 0.001 |
| | HDL | 0.009 | 0.009 | 0.98 | 0.327 | 0.431 |
| | LDL | -0.018 | 0.009 | -1.93 | 0.054 | 0.084 |
| | Triglycerides | 0.000 | 0.010 | 0.02 | 0.987 | 0.999 |
| | Systolic BP | 0.051 | 0.012 | 4.19 | < 0.001 | < 0.001 |
| | Diastolic BP | 0.075 | 0.012 | 6.21 | < 0.001 | < 0.001 |
| | HbA1c | 0.011 | 0.009 | 1.33 | 0.184 | 0.260 |

SI Table 8: Results from the linear regression models testing associations between BMI (body mass index) or WHR (waist-to-hip ratio) change and WMH (white matter hyperintensity) volume at timepoint 2, adjusted for all other baseline cardiometabolic markers (bar BMI and WHR, respectively), in addition to age and assessment interval. DV = dependent variable, SE = standard error.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|------------|---------|-------|------|------------|-----------------|
| WMH vol | BMI change | 0.041 | 0.008 | 4.94 | < 0.001 | < 0.001 |
| | WHR change | 0.034 | 0.008 | 4.12 | < 0.001 | < 0.001 |

SI Table 9: Results from the linear regression models testing associations between BMI (body mass index) or WHR (waist-to-hip ratio) change and WMH (white matter hyperintensity) volume at timepoint 2, adjusted for systolic and diastolic blood pressure change in a subsample ($n = 8,101$). DV = dependent variable, SE = standard error.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|------------|---------|-------|------|------------|-----------------|
| WMH vol | BMI change | 0.025 | 0.009 | 2.66 | 0.008 | 0.014 |
| | WHR change | 0.039 | 0.009 | 4.23 | < 0.001 | < 0.001 |

6.2. Additional age adjustments

SI Table 10, SI Table 11, and SI Table 12 show group differences for the baseline markers based on models that i) did not include age as an independent variable, ii) included linear age as an independent variable, and iii) included both linear age and age² as independent variables. When not including age, postmenopausal females showed significantly higher levels on all markers compared to premenopausal females. When including age, or age and age², postmenopausal females showed significantly higher values for lipids and HbA1c only.

SI Table 13, SI Table 14, and SI Table 15 show BMI and WHR changes depending on menopause status group, either not adjusting for age, adjusting for age, or adjusting for age and age², respectively. The results did not differ between models; timepoint was significantly associated with BMI

49 and WHR, while the interaction between menopause status group and timepoint was only significant
50 for BMI across all models.

SI Table 10: Results from the weighted regression models measuring mean differences between premenopausal (n = 3,529) and postmenopausal (n = 6,353) females in cardiometabolic markers at baseline, not adjusting for age. The β values for menopause (MP) status indicate the estimated group difference, with premenopausal status used as the reference group. Adjusted p-values represent FDR-corrected values. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------------|-----------|---------|-------|-------|------------|-----------------|
| BMI | MP Status | 0.116 | 0.020 | 5.75 | < 0.001 | < 0.001 |
| WHR | MP Status | 0.247 | 0.020 | 12.45 | < 0.001 | < 0.001 |
| HDL | MP Status | 0.249 | 0.020 | 12.64 | < 0.001 | < 0.001 |
| LDL | MP Status | 0.592 | 0.019 | 31.23 | < 0.001 | < 0.001 |
| Triglycerides | MP Status | 0.385 | 0.019 | 19.97 | < 0.001 | < 0.001 |
| Systolic BP | MP Status | 0.512 | 0.019 | 26.80 | < 0.001 | < 0.001 |
| Diastolic BP | MP Status | 0.189 | 0.020 | 9.38 | < 0.001 | < 0.001 |
| HbA1c | MP Status | 0.554 | 0.019 | 28.76 | < 0.001 | < 0.001 |

SI Table 11: Results from the weighted regression models measuring mean differences between premenopausal (n = 3,529) and postmenopausal (n = 6,353) females in cardiometabolic markers at baseline, including age as an independent variable. The β values for menopause (MP) status indicate the estimated group difference, with premenopausal status used as the reference group. β values for age show the estimated relation between baseline age and the dependent variable in each model. Adjusted p-values represent FDR-corrected values. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | Term | β | SE | t | p-value | Adj. p-value |
|---------------|-----------|---------|-------|--------|---------|--------------|
| BMI | MP Status | 0.026 | 0.034 | 0.764 | 0.445 | 0.445 |
| | Age | 0.056 | 0.017 | 3.341 | 0.001 | 0.001 |
| WHR | MP Status | 0.037 | 0.033 | 1.119 | 0.263 | 0.281 |
| | Age | 0.129 | 0.016 | 7.928 | < 0.001 | < 0.001 |
| HDL | MP Status | 0.139 | 0.033 | 4.243 | < 0.001 | < 0.001 |
| | Age | 0.067 | 0.016 | 4.149 | < 0.001 | < 0.001 |
| LDL | MP Status | 0.304 | 0.032 | 9.641 | < 0.001 | < 0.001 |
| | Age | 0.178 | 0.016 | 11.431 | < 0.001 | < 0.001 |
| Triglycerides | MP Status | 0.121 | 0.032 | 3.786 | < 0.001 | < 0.001 |
| | Age | 0.163 | 0.016 | 10.259 | < 0.001 | < 0.001 |
| Systolic BP | MP Status | -0.063 | 0.031 | -2.014 | 0.044 | 0.054 |
| | Age | 0.354 | 0.015 | 23.045 | < 0.001 | < 0.001 |
| Diastolic BP | MP Status | 0.044 | 0.034 | 1.298 | 0.194 | 0.222 |
| | Age | 0.089 | 0.017 | 5.389 | < 0.001 | < 0.001 |
| HbA1c | MP Status | 0.239 | 0.032 | 7.470 | < 0.001 | < 0.001 |
| | Age | 0.194 | 0.016 | 12.310 | < 0.001 | < 0.001 |

SI Table 12: Results from the weighted regression models measuring mean differences between premenopausal (n = 3,529) and postmenopausal (n = 6,353) females in cardiometabolic markers at baseline, including age and age² as independent variables. The β values for menopause (MP) status indicate the estimated group difference, with premenopausal status used as the reference group. β values for age and age² show the estimated relation between linear and quadratic baseline age and the dependent variable in each model. Adjusted p-values represent FDR-corrected values. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | Term | β | SE | t | p-value | Adj. p-value |
|---------------|------------------|---------|-------|--------|---------|--------------|
| BMI | MP Status | 0.014 | 0.034 | 0.414 | 0.679 | 0.829 |
| | Age | 0.056 | 0.017 | 3.338 | 0.001 | 0.002 |
| | Age ² | -0.021 | 0.010 | -2.093 | 0.036 | 0.060 |
| WHR | MP Status | 0.037 | 0.033 | 1.101 | 0.271 | 0.371 |
| | Age | 0.129 | 0.016 | 7.927 | < 0.001 | < 0.001 |
| | Age ² | -0.000 | 0.010 | -0.019 | 0.985 | 0.999 |
| HDL | MP Status | 0.113 | 0.033 | 3.405 | 0.001 | 0.001 |
| | Age | 0.067 | 0.016 | 4.146 | < 0.001 | < 0.001 |
| | Age ² | -0.047 | 0.010 | -4.833 | < 0.001 | < 0.001 |
| LDL | MP Status | 0.268 | 0.032 | 8.423 | < 0.001 | < 0.001 |
| | Age | 0.178 | 0.016 | 11.448 | < 0.001 | < 0.001 |
| | Age ² | -0.064 | 0.009 | -6.837 | < 0.001 | < 0.001 |
| Triglycerides | MP Status | 0.120 | 0.033 | 3.693 | < 0.001 | < 0.001 |
| | Age | 0.163 | 0.016 | 10.258 | < 0.001 | < 0.001 |
| | Age ² | -0.002 | 0.010 | -0.260 | 0.795 | 0.926 |
| Systolic BP | MP Status | -0.062 | 0.032 | -1.954 | 0.051 | 0.081 |
| | Age | 0.354 | 0.015 | 23.044 | < 0.001 | < 0.001 |
| | Age ² | 0.002 | 0.009 | 0.201 | 0.840 | 0.965 |
| Diastolic BP | MP Status | 0.018 | 0.034 | 0.5740 | 0.590 | 0.708 |
| | Age | 0.089 | 0.017 | 5.388 | < 0.001 | < 0.001 |
| | Age ² | -0.046 | 0.010 | -4.570 | < 0.001 | < 0.001 |
| HbA1c | MP Status | 0.242 | 0.032 | 7.467 | < 0.001 | < 0.001 |
| | Age | 0.194 | 0.016 | 12.310 | < 0.001 | < 0.001 |
| | Age ² | 0.006 | 0.010 | 0.598 | 0.550 | 0.697 |

SI Table 13: Results from the mixed linear models for BMI (body mass index) and WHR (waist-to-hip ratio), not adjusting for age. DV = dependent variable, SE = standard error, TP = timepoint (baseline and timepoint 2), MP status = menopause status.

| DV | Term | β | SE | z | p -value | Adj. p -value |
|-----|----------------|---------|-------|-------|------------|-----------------|
| BMI | TP | 0.048 | 0.012 | 4.01 | < 0.001 | < 0.001 |
| | TP x MP status | -0.076 | 0.015 | -5.09 | < 0.001 | < 0.001 |
| WHR | TP | 0.135 | 0.012 | 11.44 | < 0.001 | < 0.001 |
| | TP x MP status | -0.028 | 0.015 | -1.92 | 0.054 | 0.084 |

SI Table 14: Results from the mixed linear models for BMI (body mass index) and WHR (waist-to-hip ratio), including age as an independent variable. β values for age show the estimated relation between baseline age and the dependent variable in each model. DV = dependent variable, SE = standard error, TP = timepoint (baseline and timepoint 2), MP status = menopause status.

| DV | Term | β | SE | z | p -value | Adj. p -value |
|-----|----------------|---------|-------|-------|------------|-----------------|
| BMI | TP | 0.048 | 0.012 | 4.00 | < 0.001 | < 0.001 |
| | TP x MP status | -0.075 | 0.015 | -5.08 | < 0.001 | < 0.001 |
| | Age | 0.011 | 0.011 | 0.99 | 0.323 | 0.323 |
| WHR | TP | 0.133 | 0.012 | 11.33 | < 0.001 | < 0.001 |
| | TP x MP status | -0.025 | 0.015 | -1.73 | 0.084 | 0.084 |
| | Age | 0.139 | 0.011 | 12.76 | < 0.001 | < 0.001 |

SI Table 15: Results from the mixed linear models for BMI (body mass index) and WHR (waist-to-hip ratio), including age and age² as independent variables. β values for age and age² show the estimated relation between linear and quadratic baseline age and the dependent variable in each model. DV = dependent variable, SE = standard error, TP = timepoint (baseline and timepoint 2), MP status = menopause status.

| DV | Term | β | SE | z | p -value | Adj. p -value |
|-----|------------------|---------|-------|-------|------------|-----------------|
| BMI | TP | 0.047 | 0.012 | 3.99 | < 0.001 | < 0.001 |
| | TP x MP status | -0.075 | 0.015 | -5.07 | < 0.001 | < 0.001 |
| | Age | 0.015 | 0.011 | 1.28 | 0.200 | 0.280 |
| | Age ² | -0.011 | 0.007 | -1.49 | 0.137 | 0.201 |
| WHR | TP | 0.133 | 0.012 | 11.33 | < 0.001 | < 0.001 |
| | TP x MP status | -0.025 | 0.015 | -1.73 | 0.083 | 0.124 |
| | Age | 0.138 | 0.011 | 12.36 | < 0.001 | < 0.001 |
| | Age ² | 0.004 | 0.007 | 0.51 | 0.607 | 0.759 |

6.3. Exclusion of participants with values of cardiometabolic markers above healthy levels

Following exclusion of participants whose values for the cardiometabolic markers exceeded established healthy thresholds, BMI, WHR, and systolic and diastolic BP continued to show significant associations with WMH volume, while lipids and HbA1c did not (SI Table 16).

SI Table 16: Results from the linear regression models testing associations between baseline cardiometabolic markers and WMH (white matter hyperintensity) volume at timepoint 2 in a subsample excluding participants with values of cardiometabolic markers above healthy levels (n in subsample = 3,863). DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|---------------|---------|-------|-------|------------|-----------------|
| WMH vol | BMI | 0.043 | 0.013 | 3.37 | 0.001 | 0.001 |
| | WHR | 0.042 | 0.013 | 3.31 | 0.001 | 0.002 |
| | HDL | -0.009 | 0.013 | -0.69 | 0.488 | 0.0625 |
| | LDL | -0.011 | 0.013 | -0.80 | 0.423 | 0.548 |
| | Triglycerides | 0.023 | 0.013 | 1.76 | 0.079 | 0.118 |
| | Systolic | 0.064 | 0.013 | 4.97 | < 0.001 | < 0.001 |
| | Diastolic | 0.069 | 0.013 | 5.45 | < 0.001 | < 0.001 |
| | HbA1c | -0.005 | 0.014 | -0.34 | 0.731 | 0.878 |

6.4. Utilising log-transformed cardiometabolic markers

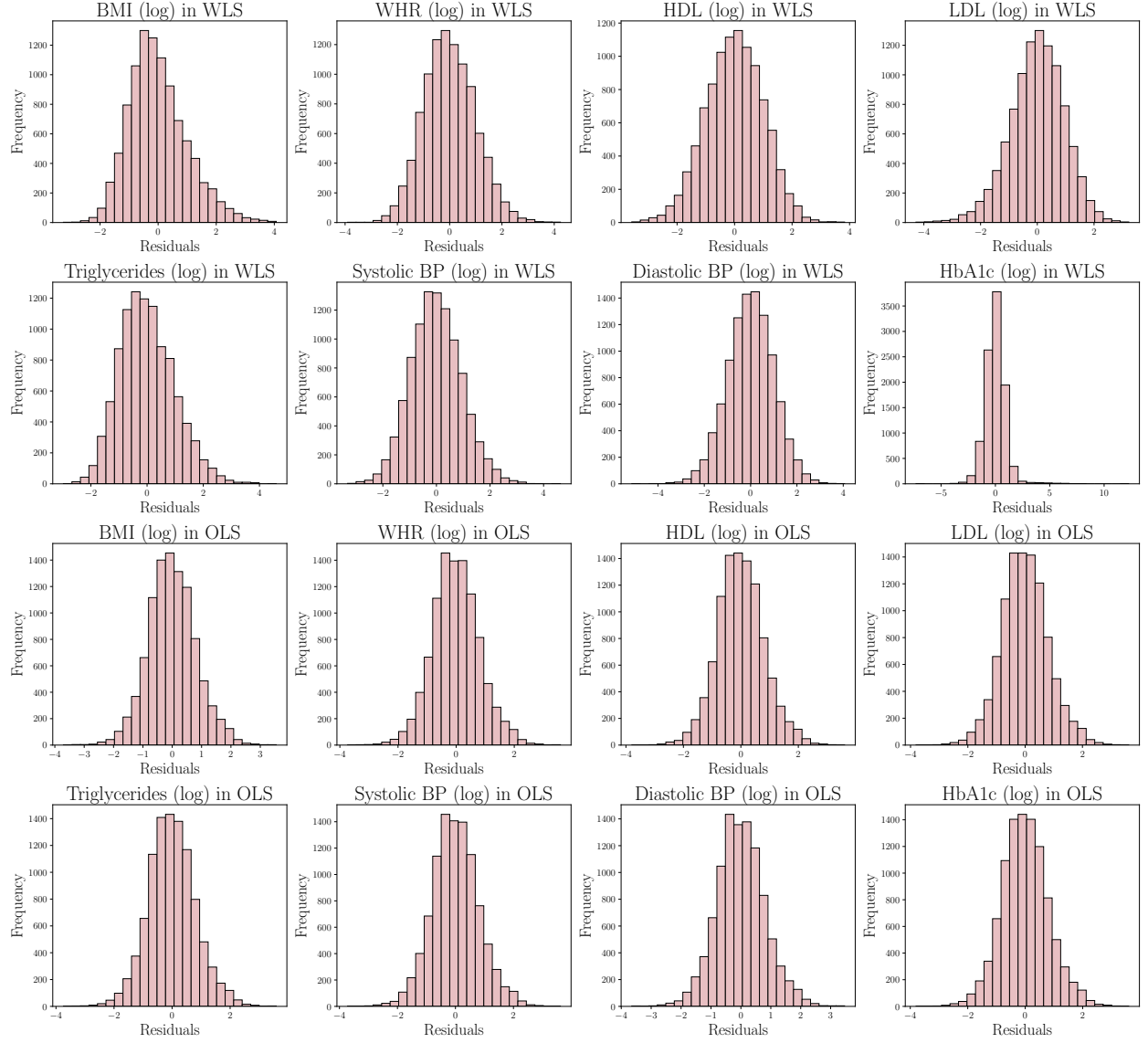
When re-running the main analyses with log-transformed baseline cardiometabolic markers, the results were consistent with our main findings (SI Table 17 and SI Table 18). See SI Figure 5 for the residual distributions of the log-transformed markers in these analyses.

SI Table 17: Results from the weighted regression models measuring group differences in log-transformed baseline cardiometabolic factors by menopause status (n premenopausal = 3,529, n postmenopausal = 6,353). The β values indicate the estimated group difference, with premenopausal status used as the reference group. Adjusted p-values represent FDR-corrected values. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

| DV | β | SE | t | p -value | Adj. p -value |
|---------------|---------|-------|--------|------------|-----------------|
| BMI | 0.027 | 0.034 | 0.800 | 0.424 | 0.529 |
| WHR | 0.035 | 0.033 | 1.063 | 0.228 | 0.379 |
| HDL | 0.132 | 0.033 | 9.636 | < 0.001 | < 0.001 |
| LDL | 0.309 | 0.032 | 9.641 | < 0.001 | < 0.001 |
| Triglycerides | 0.152 | 0.032 | 4.672 | < 0.001 | < 0.001 |
| Systolic BP | -0.060 | 0.031 | -1.898 | 0.058 | 0.085 |
| Diastolic BP | 0.054 | 0.034 | 1.616 | 0.106 | 0.151 |
| HbA1c | 0.277 | 0.032 | 8.671 | < 0.001 | < 0.001 |

SI Table 18: Results from the linear regression models testing associations between log-transformed baseline cardiometabolic markers and WMH (white matter hyperintensity) volume at timepoint 2. DV = dependent variable, SE = standard error, BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

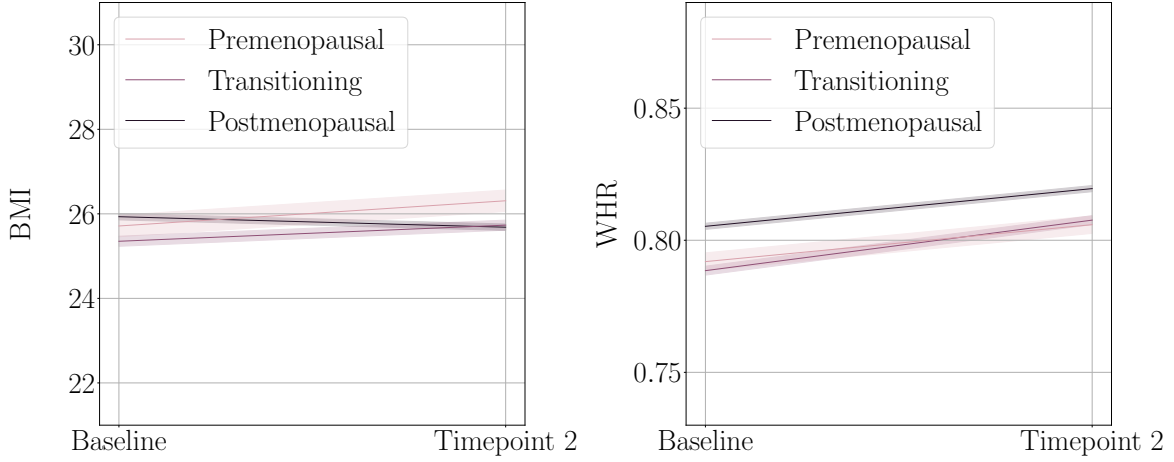
| DV | Term | β | SE | t | p -value | Adj. p -value |
|---------|---------------|---------|-------|-------|------------|-----------------|
| WMH vol | BMI | 0.091 | 0.008 | 11.09 | < 0.001 | < 0.001 |
| | WHR | 0.078 | 0.008 | 9.38 | < 0.001 | < 0.001 |
| | HDL | -0.030 | 0.008 | -3.61 | < 0.001 | 0.001 |
| | LDL | 0.011 | 0.009 | 1.26 | 0.206 | 0.276 |
| | Triglycerides | 0.044 | 0.008 | 5.19 | < 0.001 | < 0.001 |
| | Systolic BP | 0.123 | 0.009 | 14.19 | < 0.001 | < 0.001 |
| | Diastolic BP | 0.127 | 0.008 | 15.58 | < 0.001 | < 0.001 |
| | HbA1c | 0.026 | 0.009 | 2.95 | 0.003 | 0.005 |



SI Figure 5: Distributions of residuals for the log-transformed cardiometabolic markers in the weighted linear regression (WLS) testing for menopause group differences in these markers, and linear regression (OLS) testing for association between these markers and WMH volume. BMI = body mass index, WHR = waist-to-hip ratio, HDL = high density lipoprotein, LDL = low density lipoprotein, BP = blood pressure, HbA1c = glycated haemoglobin.

6.5. Separating premenopausal from transitioning females

SI Figure 6 shows mean BMI and WHR plotted at both timepoints for females who remained premenopausal across timepoints, females who transitioned to menopause between timepoints, and those who were postmenopausal across timepoints. We found significant main effects of time for BMI and WHR, and significant group differences between premenopausal and postmenopausal females for BMI (SI Table 19). There were no significant group differences between premenopausal and transitioning females.



SI Figure 6: Body mass index (BMI) and waist-to-hip ratio (WHR) at baseline and timepoint 2, plotted separately for the premenopausal, transitioning, and postmenopausal groups. The shaded bands indicate 95% confidence intervals. Note that these plots illustrate the raw mean values and are not adjusted for age.

SI Table 19: Results from the mixed linear models for BMI (body mass index) and WHR (waist-to-hip ratio). DV = dependent variable, SE = standard error, TP = timepoint (baseline and timepoint 2). Menopause status is indicated by 0 = premenopausal, 1 = transitioning, 2 = postmenopausal. For the group comparisons, the premenopausal group (0) served as the reference group in the fit. The final comparison between groups 1 and 2 is given by the subtraction of the common reference group 0. This results in the difference between groups 2 and 1 only, as the reference group 0 cancels out in the expression (group 2 - group 0) - (group 1 - group 0).

| DV | Term | β | SE | z | p-value | Adj. p-value |
|-----|-------------------------|---------|-------|-------|---------|--------------|
| BMI | TP | 0.068 | 0.026 | 2.60 | 0.009 | 0.016 |
| | TP group diff (1 vs. 0) | -0.026 | 0.029 | -0.88 | 0.379 | 0.493 |
| | TP group diff (2 vs. 0) | -0.095 | 0.028 | -3.47 | 0.001 | 0.001 |
| | TP group diff (2 vs. 1) | -0.070 | 0.040 | -1.73 | 0.083 | 0.166 |
| WHR | TP | 0.111 | 0.026 | 4.33 | < 0.001 | < 0.001 |
| | TP group diff (1 vs. 0) | 0.027 | 0.029 | 0.94 | 0.348 | 0.457 |
| | TP group diff (2 vs. 0) | -0.004 | 0.027 | -0.13 | 0.894 | 0.998 |
| | TP group diff (2 vs. 1) | -0.031 | 0.040 | -0.78 | 0.438 | 0.501 |

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