Hormonal factors moderate the associations between vascular risk factors and white matter hyperintensities

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Abstract
To examine the moderation effects of hormonal factors on the associations between vascular risk factors and white matter hyperintensities in men and women, separately. White matter hyperintensities were automatically segmented and quantified in the UK Biobank dataset (N = 18,294). Generalised linear models were applied to examine (1) the main effects of vascular and hormonal factors on white matter hyperintensities, and (2) the moderation effects of hormonal factors on the relationship between vascular risk factors and white matter hyperintensities volumes. In men with testosterone levels one standard deviation higher than the mean value, smoking was associated with 27.8% higher white matter hyperintensities volumes in the whole brain. In women with a shorter post-menopause duration (one standard deviation below the mean), diabetes and higher pulse wave velocity were associated with 28.8% and 2.0% more deep white matter hyperintensities, respectively. These findings highlighted the importance of considering hormonal risk factors in the prevention and management of white matter hyperintensities.

Keywords White matter hyperintensities · Sex-specific · Hormonal risk factors · Vascular risk factors · UK biobank

Introduction
White matter hyperintensities (WMH) are an important imaging biomarker of cerebral small vessel diseases. The aetiology of WMH has not been fully understood but can include ischemia and inflammation (Wardlaw et al., 2015). WMH are prominent in the ageing population, and more severe in older adults diagnosed with dementia (Garnier-Crussard et al., 2020). WMH appear to be abnormally bright on T2-weighted magnetic resonance imaging (MRI) data. Studies have identified multiple risk factors for WMH, including hypertension (Habes et al., 2018; Nyquist et al., 2015; Yin et al., 2018), obesity (Alqarni et al., 2021; Griffanti et al., 2018; Lampe et al., 2019), diabetes (Raffield et al., 2016), smoking (Habes et al., 2018; Sachdev et al., 2009), high homocysteine levels (Sachdev et al., 2004), blood lipids abnormality (Yin et al., 2014, 2018), and genetics (Armstrong et al., 2020; Persyn et al., 2020). Moreover, the effects of these risk factors showed different effects on periventricular and deep white matter regions (Alqarni et al., 2021; Armstrong et al., 2020).

Sex differences in WMH burden have been documented in the literature. There has been consistent evidence on women having higher load and faster progression of WMH in ageing (de Leeuw et al., 2001; DeCarli et al., 2005; Fatemi et al., 2018; Sachdev et al., 2009; van den Heuvel et al., 2004) in comparison with men, although the WMH accumulation in men tend to be more significantly affected by vascular risk factors (Alqarni et al., 2021). Specifically, the impact of vascular risk factors such as hypertension (Assareh et al., 2014; Filomena et al., 2015) and atherosclerosis (Geerlings et al., 2010) were significantly associated with higher WMH in men but not in women. Moreover, obesity was associated with increased WMH in both
men and women (Griffanti et al., 2018; Lampe et al., 2019; Veldsman et al., 2020), but greater impacts were found on WMH in men compared to women (Alqarni et al., 2021). On the contrary, the diagnosis of diabetes was associated with higher WMH volumes in women, but not in men (Espeland et al., 2019; Jongen et al., 2007).

Hormonal factors have been used to investigate the biological basis of sex differences in WMH. Menopause was found to significantly contribute to the development and progression of WMH in some studies (Miller et al., 2013, 2020). Findings on the effects of hormone replacement therapy (HRT) on the accumulation of WMH burden have been inconsistent, with some studies reporting no effects of HRT on WMH (Low et al., 2006; Miller et al., 2020; Sachdev et al., 2009), while others showing less WMH burdens in postmenopausal women using HRT (Cook et al., 2002; Liu et al., 2009; Schmidt et al., 1996). In men, available studies on the associations between testosterone levels and WMH did not find significant results (Srinath et al., 2016).

In the current study, we aim to examine whether hormonal factors affect WMH and moderate the associations between vascular risk factors and WMH. Specifically, we examined the effects of testosterone levels, contraceptive pill (CP; history and duration), HRT (history and duration), and menopause (history and post-menopause duration) on WMH, and their moderation effects on the associations between vascular risk factors and WMH volumes in men and women, separately.

Materials and methods

Study sample

The study sample was drawn from the UK biobank. Brain MRI scans for project ID 37103 were downloaded (N = 23,936). In these 23,936 participants, 5642 were excluded due to failures in WMH segmentation, not passing the visual quality control, missing descriptive data, missing vascular/hormonal risk factors data, or being requested by the participants to be removed from the UK Biobank dataset. Final analyses were performed on 18,294 participants (8618 men, 9676 women) aged between 45 and 80 years (Table 1). The UK biobank was approved by the NHS National Research Ethics Service (ref. 11/ NW/0382), project (10,279).

Vascular and hormonal risk factors

Vascular risk factors investigated in this study included body mass index (BMI), hip to waist ratio (HWR), pulse wave velocity (PWV) obtained by fingertip pulse waveforms method, hypercholesterolemia, diabetes, hypertension (HT), and smoking status. HWR was calculated by dividing waist circumference by hip circumference. The diagnosis of hypercholesterolemia was based on the use of cholesterol lowering medication. Diabetes was defined by combining physician diagnosis and the use of insulin. HT was calculated by combining physician diagnosis and HT medication use. Cigarettes pack per year were used to classify smoking status. In a study of heavy smoking and WMH using UK Biobank data (Veldsman et al., 2020), non-smokers (0–10 packs per year), smokers (10–50 packs per year), and heavy smokers (50+ packs per year) were defined. In this study, to ensure a sufficient sample size in each category, we categorised participants into non-smokers (0–10 packs per year) and smokers (10+ packs per year).

The duration of taking CP was calculated by subtracting the age starting using CP from the age of last CP use. HRT duration was calculated in a similar way as CP, where the age of initial HRT was subtracted from the age of last HRT. Post-menopause duration was calculated by subtracting the age at menopause onset from the age at imaging. Testosterone results were extracted from the blood biochemistry analyses in the UK biobank.

MRI acquisition

Brain MRI data acquired at 3 imaging centres (Manchester, Reading, Newcastle) with Siemens Skyra 3T scanners and 32 channel head coils, were used. T1-weighted 3D magnetisation-prepared rapid gradient echo (MPRAGE) and T2-weighted fluid attenuated inversion recovery. data were employed in this study. Details on the scanning parameters have been reported previously (Alfaro-Almagro et al., 2018; Miller et al., 2016).

WMH segmentation

To extract and quantify WMH burdens in the UK Biobank, we modified our automated pipeline, UBO detector (Jiang et al., 2018), to accommodate the subtle WMH burdens in UK Biobank participants who are younger than the sample used to develop and validate UBO Detector. Briefly, the warp field from individual T1 space to DARTEL space was first created, and then reversed to warp DARTEL-space atlases (lobar and arterial territories atlases) and masks (lateral ventricles and brain masks) to individual space. After removing non-brain tissue, a k-nearest neighbours classifier was applied to classify candidate clusters generated by FSL FAST into WMH and non-WMH in the native space. WMH voxels with distance from lateral ventricles of less than 12 mm were defined as periventricular WMH (PVWMH). The rest of WMH voxels were categorised as deep WMH (DWMH). The segmentation results were manually checked.
| Parameter                        | Sex | N          | Whole Sample | F               | M               |
|---------------------------------|-----|------------|--------------|-----------------|-----------------|
|                                 |     |            | F/M 9676 / 8618 | Q1 / Q2 / Q3 / Q4 | Q1 / Q2 / Q3 / Q4 |
| TWMH (mm³)                      | F/M | 9676 / 8618 | 493.37 ± 140.42 / 990.41 ± 165.48 / 1844 ± 379.32 / 6592.43 ± 5306.6 | 507.14 ± 144.7 / 1002.37 ± 158.7 / 1815.4 ± 355.47 / 6286.8 ± 4985.9 | 478.9 ± 135.6 / 975.9 ± 173.29 / 1881.5 ± 411.7 / 6944.4 ± 5655.39 |
| PVWMH (mm³)                     | F/M | 9676 / 8618 | 373.24 ± 107.5 / 750.5 ± 126.42 / 1384.9 ± 279.17 / 4804.28 ± 3622.4 | 399.23 ± 113.9 / 778.04 ± 120.7 / 1378.6 ± 261.8 / 4560.33 ± 3398.48 | 347.6 ± 99 / 716.46 ± 131.2 / 1392.86 ± 300.18 / 5082.79 ± 3845.8 |
| DWMH (mm³)                      | F/M | 9676 / 8618 | 51.8 ± 29.12 / 171.7 ± 42.56 / 401.7 ± 104.5 / 1878.8 ± 2089.41 | 46.14 ± 26.6 / 158.9 ± 41.22 / 379.9 ± 102.6 / 1815.5 ± 1951.19 | 59.4 ± 32.19 / 186.63 ± 44.43 / 425.43 ± 105.79 / 1957.19 ± 2259.58 |
| Age (years)                     | F/M | 9676 / 8618 | 53 ± 2.6 / 60.5 ± 1.85 / 66.33 ± 1.5 / 72.24 ± 2.46 | 52.7 ± 2.45 / 59.8 ± 1.7 / 65.47 ± 1.5 / 71.56 ± 2.5 | 53.7 ± 2.8 / 61.49 ± 1.9 / 67.22 ± 1.41 / 72.8 ± 2.3 |
| BMI                             | F/M | 9417 / 8438 | 21.7 ± 1.38 / 24.7 ± 0.6 / 27.3 ± 0.8 / 32.4 ± 3.4 | 21.18 ± 1.32 / 24.07 ± 0.7 / 26.76 ± 0.9 / 32.5 ± 3.7 | 22.75 ± 1.29 / 25.48 ± 0.6 / 27.76 ± 0.72 / 32.27 ± 3.15 |
| HWR                             | F/M | 9458 / 8453 | 0.7 ± 0.03 / 0.83 ± 0.2 / 0.89 ± 0.1 / 0.97 ± 0.03 | 0.73 ± 0.02 / 0.78 ± 0.01 / 0.83 ± 0.01 / 0.89 ± 0.03 | 0.85 ± 0.03 / 0.9 ± 0.01 / 0.94 ± 0.01 / 1.0 ± 0.03 |
| PWV (m/s)                       | F/M | 8945 / 8061 | 6.32 ± 1.27 / 8.7 ± 0.5 / 10.48 ± 0.48 / 13.3 ± 2.38 | 5.9 ± 1.18 / 8.33 ± 0.49 / 10 ± 0.49 / 12.9 ± 2.89 | 6.8 ± 1.34 / 9.33 ± 0.49 / 10.9 ± 0.47 / 13.58 ± 1.7 |
| Testosterone (nmol/L)           | F/M | 7608 / 7970 | 0.7 ± 0.18 / 1.68 ± 0.9 / 9.74 ± 1.48 / 15 ± 2.5 | 0.56 ± 0.1 / 0.87 ± 0.08 / 1.18 ± 0.1 / 1.86 ± 0.7 | - |
| Post-menopause duration (years) | F   | 6926       | -            | 1.89 ± 1.8 / 8.5 ± 1.8 / 14.6 ± 1.82 / 23.5 ± 4.69 | - |
| Contraceptive pill use          | F   | 7330       | -            | 2.5 ± 1.6 ± 8 ± 1.44 / 13.7 ± 1.9 / 24.19 ± 5.16 | - |
| HRT use Duration (years)        | F   | 9676       | -            | 0.04 ± 0.19 / 6.36 ± 3.28 / 17.5 ± 3.17 / 29.43 ± 2.8 | - |
| MRI scanner                     | F/M | F/M S1/S3  | F = 8017, M = 7270 / F = 1659, M = 1348 |
| Hypercholesterolemia            | F/M | F/M No/Yes | F = 8348, M = 6101 / F = 1328, M = 2517 |
| Diabetes                        | F/M | F/M No/Yes | F = 9351, M = 8065 / F = 325, M = 553 |
| Hypertension                    | F/M | F/M No/Yes | F = 8135, M = 6652 / F = 1541, M = 1966 |
| Smoking (Pack per year)         | F/M | F/M Non-smokers/smokers | F = 8345, M = 6865 / F = 1331, M = 1753 |
| Menopause                       | F   | No/Yes     | F = 699 / 7458 |
| Contraceptive pill use          | F   | No/Yes     | 1331 / 8266 |
| HRT                             | F   | No/Yes     | 5992 / 3594 |

TWMH = total white matter hyperintensities; PVWMH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities; F = female; M = male; ICV = intracranial volume; BMI = body mass index; HWR = hip to waist ratio; PWV = pulse wave velocity; HRT = hormone replacement therapy; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; S1 = scanner 1 (Cheadle imaging centre); S3 = scanner 3 (Newcastle imaging centre)
Statistical analysis

Statistical analyses were conducted by using IBM SPSS 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Since the distribution of WMH was non-Gaussian, generalised linear models (GLMs) with Gamma or Tweedie distributions and a log-link function were conducted. Gamma distribution was the main distribution used in the analyses due its better distribution fitness, however, when Gamma distribution did not converge, we used Tweedie distribution. Because of the use of a log-link function, the regression coefficient (b) was exponentiated to aid interpretation (i.e., Exp(B)). For a binary predictor, if \(\text{Exp}(B)\) is larger than one, then the target group would have an expected percentage higher in WMH of \((\text{Exp}(B) − 1) \times 100\%\) than the reference group. If \(\text{Exp}(B)\) is smaller than one, then the target group would have an expected percentage lower in WMH of \((1 − \text{Exp}(B)) \times 100\%\) than the reference group. For a continuous predictor, if \(\text{Exp}(B)\) is larger than one, then a unit increase in the predictor would be associated with an expected percentage increase in WMH of \((\text{Exp}(B) − 1) \times 100\%\), whereas if \(\text{Exp}(B)\) is smaller than one, then a unit increase in the predictor would be associated with an expected percentage decrease in WMH of \((1 − \text{Exp}(B)) \times 100\%\).

We first examined the main effects of vascular risk factors on WMH in the whole sample with all vascular risk factors as the independent variables of interest. Demographic variables (age and sex), MRI scanners, and intracranial volumes (ICV) were adjusted for in the models. Moreover, we tested sex moderation effects in the association between each vascular risk factors and WMH in the whole sample while controlling for other vascular risk factors, age, MRI scanners, and ICV.

Since most examined hormonal factors were only present in one sex or intrinsically higher in one sex (e.g., testosterone), their main and moderation effects were tested in men and women separately by applying GLMs on each sub-sample. The main effect of each hormonal factor was tested by adjusting for all vascular risk factors, age, MRI scanners, and ICV.

In testing the moderation effect of each hormonal factor on the association between each vascular factor and WMH, an interaction term between the hormonal and vascular risk factor was included, while the variables were mean centred. A hormonal factor moderated the relationship between a vascular risk factor and WMH if there was a significant interaction.

For a significant interaction between a binary hormonal variable and a vascular risk factor, simple main effects were tested through coding the corresponding category as 0 and the other category as 1.

Multicollinearity was tested among all independent variables (all Variance Inflation Factors (VIFs) < 2.5). Results with \(P\)-values < 0.05 were considered statistically significant. False discovery rate (FDR) correction using the Benjamini-Hochberg procedure was applied to adjust for multiple tests. The current study tested the main effects of vascular and hormonal factors on WMH (99 tests), and the moderation effects of hormonal factors on the associations between vascular risk factors and WMH (168 tests). The FDR correction was applied to these two sets of analyses separately.

Results

The associations of vascular risk factors with WMH, and sex moderation effects on these associations, in the whole sample

Female is associated with 44% more PVWMH and 38.4% more DWMH than male, after adjusting for age, ICV, scanner, and vascular risk factors (\(p < .001\); Table 2). All examined vascular risk factors were significantly associated with TWMH and PVWMH volumes (Table 2). PWV, Hypercholesterolemia, HT, and smoking were also significantly associated with higher DWMH volumes.

Sex significantly moderated the relationship of BMI, HWR, hypercholesterolemia, and diabetes with WMH (Supplementary Table 1). Increased BMI was significantly associated with higher TWMH (\(\text{Exp}(B) = 1.012, p < .001\)), PVWMH (\(\text{Exp}(B) = 1.012, p < .001\)), and DWMH volumes (\(\text{Exp}(B) = 1.011, p = .004\)) in men, but not in women. Increased HWR was associated with PVWMH (\(\text{Exp}(B) = 1.947, p < .001\)) in men, but not in women. Both men and women with hypercholesterolemia had higher WMH volumes, but the effects are more significant in men (TWMH: \(\text{Exp}(B) = 1.186, p < .001\); PVWMH: \(\text{Exp}(B) = 1.156, p < .001\); DWMH: \(\text{Exp}(B) = 1.277, p < .001\)) than women (TWMH: \(\text{Exp}(B) = 1.072, p < .001\); PVWMH: \(\text{Exp}(B) = 1.074, p < .001\); DWMH: \(\text{Exp}(B) = 1.060, p = .040\)). Diabetes was significantly associated with PVWMH in women (\(\text{Exp}(B) = 1.146, p = .004\)), but not in men.

The associations of vascular risk factors and male-specific hormonal factors with WMH in men

The associations of vascular and hormonal (i.e., testosterone) risk factors with WMH in men are summarised in Table 3. The effects of vascular risk factors on WMH in men were comparable to those in the whole sample.
Testosterone did not show significant associations with TWMH \( (p = .752) \), PVWMH \( (p = .227) \) and DWMH \( (p = .070) \). All associations, except the one between HWR and TWMH, survived FDR correction.

**The moderation effects of male-specific hormonal factor on the association between vascular risk factors and WMH in men**

The significant moderation effects of the male-specific hormonal factor (i.e., testosterone) are summarised in Table 4. The interactions of testosterone with BMI, hypercholesterolemia, PWV, and smoking, were statistically significant. Increased BMI was associated with higher TWMH and PVWMH volumes in men with high testosterone levels (1 SD above mean level; \( \text{Exp(B)} = 1.014, p < .001 \) for both TWMH and PVWMH), whereas the relationship between WMH and BMI in men with low testosterone levels (1 SD below mean level) was not significant \( (p > .224) \). Hypercholesterolemia was significantly associated with increased DWMH volumes in men with lower testosterone levels \( (\text{Exp(B)} = 1.145, p < .001) \), whilst in men with higher testosterone levels there was no significant association between hypercholesterolemia and DWMH. Men with higher testosterone levels showed a significant association between higher PWV and higher DWMH volumes \( (\text{Exp(B)} = 1.021, p < .001) \), but no significant association between PWV and DWMH was found in men with lower testosterone levels. In men with higher testosterone levels, smoking significantly increased TWMH \( (\text{Exp(B)} = 1.278, p < .001) \), PVWMH \( (\text{Exp(B)} = 1.264, p < .001) \), and DWMH \( (\text{Exp(B)} = 1.324, p < .001) \) volumes, but these effects were not significant in men with lower testosterone levels. After FDR correction, only the moderation effects of testosterone

**Table 2** The associations between vascular risk factors and WMH in the whole sample

| Risk Factors | TWMH \( \text{Exp(B)} \) | TWMH \( P \)-value | PVWMH \( \text{Exp(B)} \) | PVWMH \( P \)-value | DWMH \( \text{Exp(B)} \) | DWMH \( P \)-value |
|-------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|
| Age         | 1.065            | \(<0.001^*\)    | 1.064            | \(<0.001^*\)    | 1.069            | \(<0.001^*\)    |
| Sex         | 1.420            | \(<0.001^*\)    | 1.440            | \(<0.001^*\)    | 1.384            | \(<0.001^*\)    |
| BMI         | 1.005            | 0.004*          | 1.005            | 0.003*          | 1.004            | 0.091           |
| HWR         | 1.432            | 0.002*          | 1.486            | 0.001*          | 1.299            | 0.103           |
| PWV         | 1.006            | 0.008*          | 1.006            | 0.009*          | 1.007            | 0.024*          |
| Hypercholesterolemia | 1.115     | \(<0.001^*\)    | 1.105            | \(<0.001^*\)    | 1.143            | \(<0.001^*\)    |
| Diabetes    | 1.087            | 0.008*          | 1.093            | 0.004*          | 1.073            | 0.091           |
| HT          | 1.311            | \(<0.001^*\)    | 1.279            | \(<0.001^*\)    | 1.415            | \(<0.001^*\)    |
| Smoking     | 1.141            | \(<0.001^*\)    | 1.142            | \(<0.001^*\)    | 1.139            | \(<0.001^*\)    |

\( \text{Exp(B)} \) is the exponentiated coefficient in a Generalized Linear Model with Gamma or Tweedie distributions and a log-link function. Bold font indicates statistical significance before FDR correction, and \( P \)-values with * indicates those survive FDR correction. BMI = body mass index; HWR = hip-to-waist ratio; PWV = pulse wave velocity; HT = hypertension; TWMH = total white matter hyperintensities; PVWMH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities

**Table 3** The associations of vascular and hormonal risk factors with WMH volumes in men

| Risk Factors     | TWMH \( \text{Exp(B)} \) | TWMH \( P \)-value | PVWMH \( \text{Exp(B)} \) | PVWMH \( P \)-value | DWMH \( \text{Exp(B)} \) | DWMH \( P \)-value |
|-----------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|
| Age             | 1.062            | \(<0.001^*\)    | 1.062            | \(<0.001^*\)    | 1.063            | \(<0.001^*\)    |
| BMI             | 1.008            | 0.009*          | 1.009            | 0.008*          | 1.007            | 0.103           |
| HWR             | 1.535            | 0.042           | 1.672            | 0.014*          | 1.266            | 0.380           |
| PWV             | 1.011            | 0.003*          | 1.011            | 0.002*          | 1.010            | 0.026*          |
| Hypercholesterolemia | 1.073     | 0.003*          | 1.069            | 0.005*          | 1.079            | 0.011*          |
| Diabetes        | 1.154            | 0.001*          | 1.174            | \(<0.001^*\)    | 1.104            | 0.063           |
| HT              | 1.329            | \(<0.001^*\)    | 1.292            | \(<0.001^*\)    | 1.442            | \(<0.001^*\)    |
| Smoking         | 1.164            | \(<0.001^*\)    | 1.158            | \(<0.001^*\)    | 1.184            | \(<0.001^*\)    |
| Testosterone    | 1.001            | 0.752           | 1.003            | 0.227           | 0.993            | 0.070           |

\( \text{Exp(B)} \) is the exponentiated coefficient in a Generalized Linear Model with Gamma or Tweedie distributions and a log-link function. Bold font indicates statistical significance before FDR correction, and \( P \)-values with * indicates those survive FDR correction. BMI = body mass index; HWR = hip-to-waist ratio; PWV = pulse wave velocity; HT = hypertension; TWMH = total white matter hyperintensities; PVWMH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities
The associations of vascular risk factors and female-specific hormonal factors with WMH in women

The associations of vascular and hormonal risk factors with WMH in women are shown in Table 5. Hypercholesterolemia, HT, and smoking were associated with higher TWMH, PVWMH and DWMH volumes. Increased HWR was significantly associated with higher TWMH and PVWMH volumes. Moreover, each additional year of CP use was associated with an 0.3% increase in both TWMH and PVWMH volumes \((p = .017)\). Interestingly, menopausal women had lower PVWMH volume compared to non-menopausal women \((\text{Exp}(B) = 0.907, p = .008)\). Compared to the whole sample, BMI, PWV, and diabetes were not associated with WMH in women. Testosterone levels, CP use, post-menopause duration, HRT use, and HRT duration were also not associated with WMH in women. The association between HWR and TWMH did not survive FDR correction.

The moderation effects of female-specific hormonal factors on the associations between vascular risk factors and WMH in women

The significant moderation effects of the continuous hormonal factors on the associations between vascular risk factors and WMH in women are shown in Table 6. The interactions between vascular risk factors and hormonal factors in women were significance for BMI, diabetes, PWV, and HT. In women with lower testosterone, higher BMI was associated with slightly lower DWMH volumes \((\text{Exp}(B) = 1.013, p = .017)\), HT increased TWMH and DWMH volumes in women with both higher and lower HRT duration, but the effects were stronger in those with lower HRT duration \((\text{TWMH: Exp}(B) = 1.352, p < .001 \text{ (shorter HRT)} \text{ vs. Exp}(B) = 1.244, p < .001 \text{ (longer HRT)}; \text{DWMH: Exp}(B) = 1.503, p < .001 \text{ (shorter HRT)} \text{ vs. Exp}(B) = 1.298, p < .001 \text{ (longer HRT)})\).

Women with lower, but not higher, post-menopause duration showed associations of increased PWV with increased TWMH \((\text{Exp}(B) = 1.012, p = .017)\), PVWMH \((\text{Exp}(B) = 1.013, p = .031)\) and DWMH \((\text{Exp}(B) = 1.020, p = .006)\) volumes. Women with higher post-menopause duration showed negative associations of diabetes with TWMH \((\text{Exp}(B) = 0.870, p = .048)\) and DWMH \((\text{Exp}(B) = 0.788, p = .013)\), while women with lower post-menopause duration showed no significant relationship between diabetes and TWMH and a positive relationship with DWMH \((\text{Exp}(B) = 1.288, p = .039)\).

The significant moderation effects of the binary hormonal factors on the associations between vascular risk factors and WMH in women are presented in Table 7.
Non-menopausal, but not menopausal women, showed associations between higher PWV and higher DWMH volumes (Exp(B) = 1.036, \( p = .047 \)). HT was associated with higher DWMH volumes in women both with and without HRT, but the effects were stronger in those without HRT (Exp(B) = 1.487 vs. 1.255, both \( p < .001 \)). Women with HRT showed a negative association between BMI and DWMH volumes (Exp(B) = 0.999, \( p = .038 \)).

After applying FDR correction, the moderation effects of post-menopause duration on the associations between diabetes and DWMH, and between PWV and DWMH, remained significant.

### Discussion

This study examined the main effects of hormonal factors on WMH. However, testosterone moderated the effects of vascular risk factors in men, where the effects of BMI, PWV, and smoking on WMH were found at higher, but not lower testosterone levels, and the effects of hypercholesterolemia on WMH were only observed at lower testosterone levels. However, after FDR correction, only the moderating effect of testosterone on smoking remained significant. In women, after FDR correction, the associations between PWV and DWMH were moderated by post-menopause duration and were significant among those experienced shorter post-menopause duration. Also, diabetes was a significant vascular risk factor for PVWMH in women, and the association between diabetes and DWMH was stronger in those with increased post-menopausal duration.

In men, obesity was constantly found to be a major risk factor for WMH, with sex being a significant moderator between obesity measures and increased WMH in men, these findings were consistent with the literature (Alqarni et al., 2021; Lampe et al., 2019). Despite the lack of direct association between testosterone and WMH in this study and others (Srinath et al., 2016), our results suggest that higher testosterone might have contributed to the association between increased BMI and increased TWMH and PVWMH volumes. Nevertheless, we also found that men with lower testosterone showed significant association between hypercholesterolemia and higher DWMH volumes. Future

### Table 5

The associations of vascular and hormonal risk factors with WMH volumes in women

| Risk Factors      | TWMH Exp(B) | TWMH P-value | PVWMH Exp(B) | PVWMH P-value | DWMH Exp(B) | DWMH P-value |
|-------------------|-------------|--------------|--------------|---------------|-------------|--------------|
| Age               | 1.067       | < 0.001*     | 1.065        | < 0.001*      | 1.076       | < 0.001*     |
| BMI               | 1.002       | 0.455        | 1.002        | 0.314         | 0.999       | 0.846        |
| HWR               | 1.346       | **0.042**    | 1.347        | **0.035**     | 1.317       | 0.177        |
| PWV               | 1.004       | 0.175        | 1.004        | 0.169         | 1.004       | 0.333        |
| Hypercholesterolemia | 1.199 | < 0.001*     | 1.179        | < 0.001*      | 1.261       | < 0.001*     |
| Diabetes          | 1.005       | 0.922        | 0.989        | 0.824         | 1.047       | 0.502        |
| HT                | 1.290       | < 0.001*     | 1.263        | < 0.001*      | 1.380       | < 0.001*     |
| Smoking           | 1.106       | < 0.001*     | 1.111        | < 0.001*      | 1.095       | **0.009**    |
| Testosterone      | 0.999       | 0.951        | 1.009        | 0.559         | 0.969       | 0.146        |
| CP Use            | 1.024       | 0.351        | 1.030        | 0.226         | 1.007       | 0.832        |
| CP use duration   | 1.003       | **0.017**    | 1.003        | **0.014**     | 1.003       | 0.077        |
| Menopause         | 0.936       | 0.081        | 0.907        | **0.008**     | 1.047       | 0.405        |
| Post-menopause duration | 1.000 | 0.986        | 1.001        | 0.608         | 0.996       | 0.208        |
| HRT use           | 1.023       | 0.226        | 1.014        | 0.450         | 1.051       | 0.060        |
| HRT use duration  | 1.002       | 0.394        | 1.001        | 0.559         | 1.003       | 0.233        |

Exp(B) is the exponentiated coefficient in a Generalized Linear Model with Gamma or Tweedie distributions and a log-link function. Bold font indicates statistical significance before FDR correction, and \( P \)-values with * indicates those survive FDR correction. BMI = body mass index; CP = contraceptive pill; HRT = hormone replacement therapy; HWR = hiP-to-waist ratio; HT = hypertension; PWV = pulse wave velocity; TWMH = total white matter hyperintensities; PVWMH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities.
The moderation effects of continuous female-specific hormonal factors on the relationship between vascular risk factors and WMH in women (only significant moderation effects were listed)

| Vascular risk factor | Effect                                                                 | TWMH Exp(B) | TWMH P-value | PVWMH Exp(B) | PVWMH P-value | DWMH Exp(B) | DWMH P-value |
|---------------------|------------------------------------------------------------------------|-------------|--------------|---------------|---------------|-------------|--------------|
| BMI                 | Interaction between BMI and testosterone                              | 1.007       | 0.032        | -             | -             | 1.010       | 0.019        |
|                     | The effect of BMI for high testosterone                               | 1.004       | 0.204        | -             | -             | 1.004       | 0.335        |
|                     | The effect of BMI for low testosterone                                | 0.995       | 0.127        | -             | -             | 0.991       | 0.043        |
| Diabetes            | Interaction between diabetes and testosterone                          | -           | -            | 1.285         | 0.012         | -           | -            |
|                     | The effect of diabetes for high testosterone                           | -           | -            | 1.255         | 0.009         | -           | -            |
|                     | The effect of diabetes for low testosterone                            | -           | -            | 0.918         | 0.279         | -           | -            |
| Diabetes            | Interaction between diabetes and post-menopause duration                | 0.986       | 0.022        | -             | -             | 0.971       | <0.001*      |
|                     | The effect of diabetes for high post-menopause duration                 | 0.870       | 0.048        | -             | -             | 0.788       | 0.013        |
|                     | The effect of diabetes for low post-menopause duration                  | 1.112       | 0.231        | -             | -             | 1.288       | 0.039        |
| PWV                 | Interaction between PWV and HRT duration                               | -           | -            | 0.999         | 0.044         | -           | -            |
|                     | The effect of PWV for high HRT duration                                | -           | -            | 0.998         | 0.635         | -           | -            |
|                     | The effect of PWV for low HRT duration                                 | -           | -            | 1.010         | 0.017         | -           | -            |
Table 6 (continued)

| Vascular risk factor | Effect | TWMH |   | PVWMH |   | DWMH |   |
|----------------------|--------|------|---|-------|---|------|---|
|                      |        | Exp(B) | P-value | Exp(B) | P-value | Exp(B) | P-value |
| PWV                  | Interaction between PWV and post-menopause duration | 0.999 | 0.008 | 0.999 | 0.032 | 0.998 | < 0.001* |
|                      | The effect of PWV for high post-menopause duration | 0.995 | 0.241 | 0.997 | 0.439 | 0.989 | 0.057 |
|                      | The effect of PWV for low post-menopause duration | 1.012 | 0.017 | 1.013 | 0.031 | 1.020 | 0.006 |
| HT                   | Interaction between HT and HRT duration | 0.991 | 0.046 | - | - | 0.985 | 0.006 |
|                      | The effect of HT for high HRT duration | 1.244 | < 0.001 | - | - | 1.298 | < 0.001 |
|                      | The effect of HT for low HRT duration | 1.352 | < 0.001 | - | - | 1.503 | < 0.001 |

Exp(B) is the exponentiated coefficient in a Generalized Linear Model with Gamma or Tweedie distributions and a log-link function. For a significant interaction between a continuous hormonal variable and a vascular risk factor, simple main effects were tested at high level of the hormonal factor (+1SD) and at low level of the factor (-1SD). Bold font indicates statistical significance before FDR correction, and * indicates those survive FDR correction. BMI = body mass index; HRT = hormone replacement therapy; HT = hypertension; PWV = pulse wave velocity; TWMH = total white matter hyperintensities; PVWMH = periventricular white matter hyperintensities; DWMH = deep white matter hyperintensities.
studies are still needed to examine the different pathways for the associations between obesity and WMH. Moreover, increased PWV indicates arterial stiffness, which was found independently associated with WMH in this study and in the literature (Caughey et al., 2021). In this study, men with higher testosterone levels, but not those with lower testosterone, showed positive relationship between PWV and DWMH volumes. Moreover, smoking was one of the major risk factors for WMH in this study and the literature (Habes et al., 2018; Veldsman et al., 2020); our results suggest that at higher testosterone levels, smokers might have higher risk of developing all WMH volumes, especially, the high impact on DWMH.

In women, the associations between HRT and WMH have been inconsistent in the literature, where the use of HRT was found to be associated with less WMH in some studies (Cook et al., 2002; Schmidt et al., 1996), but not others (Low et al., 2006; Sachdev et al., 2009). There were also studies reporting an increase in WMH volume after using HRT (Kling et al., 2020). In the current study, HRT was not independently associated with WMH. However, hypertensive women showed significantly more DWMH, especially among those who did not use HRT or used it for shorter time period. At menopause, blood pressure increases gradually, and up to 50% of women are hypertensive at the age of sixty (Maas, 2021). The use of oral HRT was found to be associated with incident HT (Madika et al., 2021; Mounier-Vehier et al., 2019). It has been recommended that the intervention with HRT must be initiated early to manage menopause symptoms and benefit from its ability to reduce coronary events (Mounier-Vehier et al., 2019). Despite the lack of significance in the association between HRT use duration and WMH in this study, the moderation analysis supports the findings from a longitudinal study on HRT use duration which found that longer-term use could provide neuroprotection for postmenopausal women, especially when initiated early (Liu et al., 2009). In addition, further reports support the importance of early initiation of HRT which could provide neuroprotection and warned about late initiation which could be harmful to the brain and not protective (DuPont et al., 2019; Miller et al., 2013). Taken together, despite reports about significant association between HRT and HT, the use of HRT might be beneficial for hypertensive women to add a layer of protection against WMH, especially DWMH.

Menopause marks a significant change for women, where a gradual increase of cardiovascular diseases risk happens due to the hormonal imbalance after menopause, especially estrogen deficiency (Maas, 2021; Rossi et al., 2002). The direct association between menopause and WMH has not been found (Sachdev et al., 2009). However, hot flashes (a symptom of menopause) were associated with increased WMH in women with no cardiovascular diseases (Thurston et al., 2016). Nevertheless, in comparison to peri-menopausal women, cardiovascular risk factors such as blood pressure and lipid profile in post-menopausal women were significantly higher in a large cross-sectional study (de Kat et al., 2017). In this study, HT and hypercholesterolemia were the major risk factors for WMH in women which support the findings in the literature regarding the effects of these two risk factors on women at older age, given that the majority of women in our sample were post-menopausal. Smoking was another major risk factor for women in our sample. Studies found that the effect of smoking on WMH was significantly higher in women compared to men (Sachdev et al., 2009). Our results showed that non-menopausal women have less PVWMH compared to menopausal women after controlling for age, scanner, ICV, and cardiovascular risk factors.

Table 7 The moderation effects of categorical female-specific hormonal factors variables on the relationship between vascular risk factors and WMH in women (only significant moderation effects were listed)

| Vascular risk factor | Nature of effect | DWMH |
|----------------------|------------------|------|
|                      |                  | Exp(B) | P-value |
| PWV                  | Interaction term between menopause status and PWV | 1.037 | 0.050 |
|                      | The effect of PWV for menopausal women | 0.998 | 0.887 |
|                      | The effect of PWV for non-menopausal women | 1.036 | 0.047 |
| HT                   | Interaction term between HRT and HT | 1.185 | 0.010 |
|                      | The effect of HT for women with HRT | 1.255 | <0.001 |
|                      | The effect of HT for women without HRT | 1.487 | <0.001 |
| BMI                  | Interaction term between HRT and BMI | 1.014 | 0.015 |
|                      | The effect of BMI for women with HRT | 0.991 | 0.038 |
|                      | The effect of BMI for women without HRT | 1.004 | 0.274 |

For a significant interaction between a binary hormonal variable and a vascular risk factor, simple main effects were tested through coding the corresponding category as 0 and the other category as 1. Exp(B) is the exponentiated coefficient in a Generalized Linear Model with Gamma or Tweedie distributions and a log-link function. Bold font indicates statistical significance before FDR correction, and P-values with * indicates those survive FDR correction. BMI = body mass index; HRT = hormone replacement therapy; HT = hypertension; PWV = pulse wave velocity; DWMH = Deep white matter hyperintensities.
However, the results on menopause might be affected by the number of women with menopause (n = 7458) compared to those without menopause (n = 699), and the age difference between them (mean ± standard deviation of age for menopausal women is 63.78 ± 6.43 (years) and for non-menopausal women 51.35 ± 2.99 (years)). Moreover, in this study, the mean volume of TWMH, PVWMH, and DWMH were higher in menopausal women compared to non-menopausal women. In our analyses of post-menopause duration interaction with cardiovascular risk factors, results were not in line with the literature, where DWMH was higher in participants with shorter post-menopause duration. Therefore, the discrepancies in our study compared to the overall notion in the literature must be interpreted with caution, given the differences in the characteristics between menopausal and non-menopausal women in our sample.

Hormonal factors tend to moderate the effects of vascular risk factors on DWMH, but not PVWMH. DWMH is usually considered to be associated with cerebral amyloid angiopathy (CCA) which affects leptomeningeal and cortical vessels walls by the increased deposition of amyloid-β peptides (Gurol et al., 2020). Moreover, it has been reported that DWMH might have different genetical phenotypes, different aetiologies, and different associations with different vascular risk factors compared to PVWMH, where higher contribution of cerebral small vessels diseases, pathohistological traits, and axonal loss were more common in DWMH compared to PVWMH (Alqarni et al., 2021; Armstrong et al., 2020; Kim et al., 2008; Sachdev et al., 2009; Schmidt et al., 2011; Wardlaw et al., 2015; Wharton et al., 2015). Therefore, investigating PVWMH and DWMH separately will provide more insights into the mechanism of WMH development.

There are several strengths and limitations to this study. The WMH volume was extracted using an automated pipeline, which facilitated the investigation of both global and regional WMH. The current study benefited from the large number of participants and the relatively wide age range in UK Biobank data. Nevertheless, the outcomes of our cross-sectional study should be interpreted with caution. Especially, given the UK biobank sample is thought to be generally healthier and have better socioeconomic status compared to the UK population (Veldsman et al., 2020). Another limitation that encourages future investigations is the time difference between the blood biochemistry analysis and the imaging session, which was at least 5 years. Moreover, this study found that men with higher levels of testosterone had significant associations between certain vascular risk factors (BMI, PWV, smoking) and WMH. It is possible that, with decreased testosterone levels in older individuals, the contributions of vascular risk factors to the accumulation of WMH are weakened, which may partially explain the plateau of WMH progression in older individuals (Moscouco et al., 2012). This hypothesis needs to be validated in future studies, preferably with longitudinal datasets. The complexity of possible interactions between vascular risk factors such as HT, PWV, diabetes, smoking and obesity measures could raise another limitation in this study, and should be taken into consideration in future studies. In this study, to examine the possible multicollinearity among all independent variables (age, sex, vascular, and hormonal factors), VIFs was tested, and the results indicated no significant collinearity between the variables (all VIFs < 2.5). Furthermore, the cross-sectional design limits any conclusions on causality. Future longitudinal studies are needed to confirm the findings. This study examined the contribution of sex-specific hormonal factors to the effects of vascular risk factors on WMH. This can be considered as indirect evidence of hormonal factors contributing to the sex differences in the relationship between vascular risk factors and WMH.

**Conclusion**

This study highlights the importance of considering the sex-specific hormonal risk factors and their interaction with vascular risk factors in studying WMH. BMI, hypercholesterolemia, PWV, and smoking contributed differently to WMH in men depending on testosterone levels. In hypertensive women, the use of HRT and longer period of HRT may be beneficial as they moderated the impact of HT on the accumulation of WMH. Management of sex-specific hormonal risk factors and vascular risk factors may substantially contribute to the reduction of WMH burden in men and women.

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