Red Hair Color Is Associated with Elevated CRP Levels among US Women

**Abbreviations**: NHS, Nurses’ Health Study

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**TO THE EDITOR**

Hair color, especially red hair, is a variable phenotypic trait with high heritability. The *MC1R* gene accounts for 73% of red hair heritability (Morgan et al., 2018). Whereas 92% of red-haired individuals carry two *MC1R* variants, there is incomplete penetrance because most dual *MC1R* variants exhibit blonde or light brown hair (Morgan et al., 2018). Red hair is associated with sunburns, skin cancer, (Scherer and Kumar, 2010), and pain sensitivity (Li et al., 2005). In addition, positive associations between red hair and cardiovascular disease and cancer in women, but not in men, have been reported (Frost et al., 2017). We examined the Nurses’ Health Study (NHS) for associations in women between hair color and CRP, a marker of acute and chronic inflammation and cardiovascular risk (Ridker et al., 1997).

The NHS is a 1976 US cohort study of 121,700 female registered nurses aged 30–55 years who provided written, informed consent. Follow-up details have been described previously (Bao et al., 2016). Between 1989 and 1990, a total of 32,826 women provided blood specimens. There was no difference between these women and those who did not provide blood specimens with respect to demographics, diet, and lifestyle (Bao et al., 2016). Procedures regarding blood collection have been reported previously (Bao et al., 2016). This study was approved by the Brigham and Women’s Hospital (Boston, MA) Institutional Review Board.

Hair color was ascertained in 1982 by asking: “What was the natural color of your hair at age 21?” with responses: “red,” “blonde,” “light brown,” “dark brown,” and “black.” CRP was measured using latex-enhanced immunoturbidimetric (Hang et al., 2019). Because multiple batches assessed CRP levels, lower detection limits and intra-assay coefficients of variation were examined (Supplementary Table S1). We used previously developed methods to account for batch variability (Rosner et al., 2008) and used recalibrated levels (Hang et al., 2019).

In the NHS, demographic factors were collected at baseline and biennially. We included the following covariates: age, fasting status, body mass index, physical activity, smoking, alcohol consumption, Alternate Healthy Eating Index, multivitamin use, aspirin or non-steroidal anti-inflammatory drug use, high blood pressure, elevated cholesterol, menopausal status, hormone replacement therapy use, and average July noon-time erythemal UVR. Average July noon-time erythemal UVR was calculated using previously published methods (VoPham et al., 2016). We calculated cumulative average measurements from baseline to blood draw for continuous covariates, including body mass index, physical activity, alcohol consumption, Alternate Healthy Eating Index score, and UVR. Otherwise, we used covariate status at blood draw, when possible, or carried forward the last available information.

We used the generalized extreme studentized deviate test to exclude outliers (Hang et al., 2019). To improve data normality, we used natural log-transformed CRP levels. Age-adjusted and multivariable-adjusted linear regression analyses were conducted to examine the associations between four hair color groups (red—reference, blonde, light brown, and dark brown and/or black) and CRP levels. The results were presented as percentage differences in CRP versus the reference using the equation: [exp (β-coefficient) − 1] × 100%. Multiplicative interactions between hair color and covariates were tested. We also used multinomial logistic regression to examine for associations between hair color and CRP cardiovascular risk categories: low (<1.0 mg/ml), intermediate (1.0–3.0 mg/l), and high (>3.0 mg/l). Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Two-sided P-values < 0.05 were considered statistically significant.

This study included 11,141 participants with CRP levels (Supplementary Figure S1). We excluded 1,746 participants (15.7%) with outlier CRP concentrations, erroneous records, missing data on hair color, non-white race, or a history of diabetes, cardiovascular disease, and/or cancer at blood draw, leaving 8,994 women (84.3%) remaining, among whom 390 (4.3%) had red hair (Supplementary Table S2). The most common hair color was dark brown and/or black (45.1%). Mean CRP values were higher for women with red hair (3.7 mg/l, SD = 3.9) than for those with blonde (3.3 mg/l, SD = 4.4), light brown (3.0 mg/ml, SD = 4.0), or dark brown and/or black (3.2 mg/l, SD = 4.3) hair.

In age-adjusted and multivariable-adjusted models, women with non-red hair had CRP levels of 14.2–18.1% lower (P ≤ 0.01) and 10.9–14.1% lower (P ≤ 0.04), respectively, than those of red-haired women (Table 1). Interaction tests were nonsignificant for each covariate (P > 0.05). When examining CRP cardiovascular risk categories, we found, as expected, that non-red-haired women were less likely to have high CRP levels (Table 2). Specifically, women with dark brown and/or black hair color had 0.67 lower odds of high CRP levels than red-haired women in both age-adjusted (95% confidence interval = 0.52–0.87) and multivariable-adjusted (95% confidence interval = 0.50–0.90) models.
We found elevated CRP levels in red-haired women in the NHS. This finding could potentially explain a previous report of increased risks of cardiovascular disease and cancer in red-haired women (Frost et al., 2017). Although we observed similar associations in the NHS between red hair and cardiovascular disease and cancer, they were not statistically significant (Supplementary Tables S3 and S4).

In addition to its role in pigmentation, animal models suggest that MC1R may influence inflammation through adaptive and innate immune responses (Nasti and Timares, 2015). However, given the incomplete penetrance of MC1R in hair color, it is unclear whether our findings are due to MC1R, another nearby gene, or other environmental factors. We examined MC1R genotypes and CRP levels among 6,509 participants in the NHS but did not find an association and were limited by statistical power. A recent large GWAS has identified two genes located near MC1R, ZFPM1, and FANCA, which are associated positively with CRP levels (Han et al., 2020). Genetic markers on these two genes have also been linked previously to hair color (Kichaev et al., 2019).

Our study has additional limitations. Hair color was identified by self-report, although in the NHS, self-reported variables have been validated (Colditz and Hankinson, 2005), and hair color GWAS identified known pigmentation genes (Han et al., 2008). The generalizability of our study may be limited because the NHS included predominantly white, female health professionals. Further studies are needed to validate our findings and understand the clinical significance and underlying mechanisms.

Data availability statement
Data will be made available upon request. This study involved human subjects, and to protect the privacy of study participants, data requests will be reviewed by the Nurses’ Health Study Steering Committee. Requests for data

Table 1. Association between Hair Color and Plasma CRP Levels

<table>
<thead>
<tr>
<th>Hair Color</th>
<th>Red (Reference)</th>
<th>Percentage Difference in CRP (95% CI)</th>
<th>P-value</th>
<th>Blonde</th>
<th>Percentage Difference in CRP (95% CI)</th>
<th>P-value</th>
<th>Light Brown</th>
<th>Percentage Difference in CRP (95% CI)</th>
<th>P-value</th>
<th>Dark Brown or Black</th>
<th>Percentage Difference in CRP (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>390</td>
<td>1.095</td>
<td></td>
<td>4.351</td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
<td>0.01</td>
<td>0.006</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Model 1</td>
<td>0 (reference)</td>
<td>−15.2 (−25.5 to −3.2)</td>
<td>0.01</td>
<td>−18.1 (−27.3 to −7.8)</td>
<td>0.001</td>
<td>−14.2 (−23.8 to −3.5)</td>
<td>0.01</td>
<td>−10.9 (−19.9 to −0.75)</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>0 (reference)</td>
<td>−12.7 (−22.5 to −1.7)</td>
<td>0.03</td>
<td>−14.1 (−22.9 to −4.3)</td>
<td>0.006</td>
<td>−10.9 (−19.9 to −0.75)</td>
<td>0.04</td>
<td>−10.9 (−19.9 to −0.75)</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; CI, confidence interval; cig, cigarette; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.

1Model 1 was adjusted for age at blood draw.

2Model 2 was additionally adjusted for the following covariates: fasting status (yes or no), cumulative average levels of BMI (<18.5, 18.5–25, >30 kg/m²), cumulative average physical activity (<5.0, 5.0–11.5, 11.5–22, ≥22 MET hours/week), smoking status (never smoker, past smoker: unknown, past smoker: 1–14 cigs/day, past smoker: 15–34 cigs/day, past smoker: ≥35 cigs/day, current smoker: unknown, current smoker: 1–14 cigs/day, current smoker: 15–34 cigs/day, current smoker: ≥35 cigs/day), cumulative average alcohol consumption (0, <0.15, 0.15–7.5, 7.5–15, ≥15.0 g/day), cumulative average AHEI dietary score (<37.52, 37.52–43.46, 43.46–49.84, ≥49.84), average July noon-time erythemal UVR (quartiles), regular multivitamin use (yes or no), regular aspirin and/or NSAID use (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), menopausal status (premenopause, postmenopause, or dubious menopause), and postmenopausal hormone therapy (never, past, or current use).

Table 2. OR for the Association between CRP Cardiovascular Risk Categories and Hair Color

<table>
<thead>
<tr>
<th>CRP Cardiovascular Risk Category</th>
<th>Hair Color</th>
<th>Low (CRP of &lt;1.0 mg/l)</th>
<th>Intermediate (CRP of 1.0–3.0 mg/l)</th>
<th>High (CRP of &gt;3.0 mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Red (reference)</td>
<td>102</td>
<td>1 (reference)</td>
<td>156</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blonde</td>
<td>349</td>
<td>0.85 (0.63–1.14)</td>
<td>335</td>
<td>0.65 (0.48–0.86)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td>0.83 (0.61–1.13)</td>
<td>0.62 (0.45–0.86)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light brown</td>
<td>1,173</td>
<td>0.80 (0.61–1.04)</td>
<td>1,073</td>
<td>0.60 (0.46–0.78)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td>0.80 (0.60–1.06)</td>
<td>0.60 (0.45–0.80)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark brown or black</td>
<td>1,311</td>
<td>0.85 (0.65–1.12)</td>
<td>1,321</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td>0.86 (0.65–1.14)</td>
<td>0.67 (0.50–0.90)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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CONFICT OF INTEREST
The authors state no conflicts of interest.

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AUTHOR CONTRIBUTIONS
Conceptualization: RIH; Data Curation: HT, DH, MS; Formal Analysis: HT, XL; Investigation: XL; Methodology: RIH; XL; Project Administration: XL; Resources: MS, XL; Supervision: XL; Visualization: RIH, HT; Writing - Original Draft Preparation: RIH; Writing - Review and Editing: HT, MS, HN, XL

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SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.09.015.

REFERENCES

Host-Pathogen Interactions in Human Polyomavirus 7–Associated Pruritic Skin Eruption


TO THE EDITOR
Certain polyomaviruses (PyVs), such as JC and BK, are known to cause severe disease in immunocompromised hosts (Moens et al., 2017). Human PyV

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