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Chapter 3

Genetic and environmental influences on stability and change in baseline levels of C-reactive protein: A longitudinal twin study

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Genetic and environmental influences on stability and change in baseline levels of C-reactive protein: A longitudinal twin study

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1. Introduction

The link between ageing and inflammation is well established. Low levels of microbial exposition early in life is known to promote the development of more competent immune pathways and regulatory processes. Such effective anti-inflammatory networks may determine the pro-inflammatory phenotype in certain diseases such as obesity and atherosclerosis [1].

Furthermore, ageing is known to be associated with a gradual dysregulation of inflammatory pathways resulting in an elevation of inflammatory factors [2]. It has been demonstrated that chronic low grade inflammation predisposes to many chronic, age-related diseases, such as those of the pulmonary and cardiovascular system [3,4]. We have previously demonstrated the role of age as a mediator of the genetic and environmental influences on baseline levels of inflammatory markers [5].

An important, well-established inflammatory marker is C-reactive protein (CRP). Its baseline levels are considered to reflect systemic inflammation. Considering the relationship of increased baseline CRP levels with a variety of disorders, including cancer

11.1. Lipid disorders [12], cardiovascular diseases [13–15], type 2 diabetes [16], and age-related macular degeneration [17], regulation of baseline CRP levels are of particular interest. In this context, baseline CRP levels are known to be influenced by a variety of environmental and genetic factors. However, their relative importance and exact contribution to these factors are largely unknown (8). The total variance in CRP level remain unknown (9).

Heritability studies aim to estimate the relative influence of heritable and environmental factors on CRP (9). Twin and family studies in a wide variety of populations with different age ranges showed a moderate heritability of baseline CRP levels, with heritability estimates ranging from 0.10 to 0.85 (20–40) (Supplementary Table 3).

CRP levels have been shown to be fairly stable over time. Declina et al. (31) analyzed several CRP measures of 255 participants to evaluate the intrasubject variability of CRP over a median follow-up period of 4.7 years. The multivariable-adjusted intra-class correlation coefficient (ICC) of CRP was estimated as 0.32. The intrasubject variability of CRP was also investigated by Wu et al. (42), using CRP levels of 56,218 Chinese adults over a two-year follow-up time. The ICC of CRP was reported as 0.35 for men and 0.60 for women. Interestingly, the stability of CRP gradually increased with age. However, twins and family studies mentioned above used simple CRP measurement for their heritability calculation rather than longitudinal measurements. Limited by this cross-sectional design, heritability estimates for CRP as reported above only provide a snapshot at one particular point in time, potentially providing at least a partial explanation for the wide variety of heritability estimates reported in the literature (20–40).

To the best of our knowledge, no longitudinal twin studies on CRP levels have been conducted to date. The aim of this study was to evaluate the heritability and the extent to which genetic and environmental influences contribute to the stability or change of CRP over time in a large population of adult females using a classical twin design, including up to three CRP measurements over a ten-year follow-up period.

2. Material and methods

2.1. Subjects

The study was conducted in 6201 women from the Twins UK registry. The Twins UK registry is a large population-based study of twins with more than 30,000 participants [43]. Zygosity was determined by questionnaire supplementing self-report. To minimize ascertainment bias, body mass index (BMI), current oral contraceptive (OC) use and smoking status were included in the models as covariates.

For the longitudinal analysis, a trivariate SEM or path model was specified as the proportion of the total variance attributable to additive genetic (A), dominance genetic (D), and non-shared environmental (E) influences.will

2.2. C-reactive protein analysis

High sensitive CRP was measured by latex-enhanced nephelometry and standardized to the Roche/Hitachi (Mannheim, Germany) Modular ProSpec Nephelometer. The intra-assay precision expressed as coefficient of variation (CV) of this method was estimated by run-in CRP at a mean concentration of 15 mg/l and 315 mg/l, and is expected to be <25% across the linear range of the assay.

2.3. Analytical approach

Natural log (ln) transformation was necessary for the CRP data to achieve a better approximation of the normal distribution. Secondly, lnCRP was adjusted for age. This is a common procedure in twin analysis because age can spuriously introduce a shared environmental effect if there is a significant correlation between the phenotype and age, because twins are always of the same age. Next, covariate analysis was performed, testing for: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), current oral contraceptive (OC) use and current hormone replacement therapy (HRT) use. For the longitudinal analysis, a trivariate SEM or path model was specified as the proportion of the total variance attributable to additive genetic (A), dominance genetic (D), and non-shared environmental (E) influences contributing to the stability or change of CRP over time in a large population of adult females using a classical twin design, including up to three CRP measurements over a ten-year follow-up period.

3. Results

3.1. Sample characteristics

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Adjustment for BMI did not meaningfully change these results. Baseline characteristics of MZ and DZ twins for the three visits are summarized in Table 1. Statistical significance is reported as p-values, Supplemental Table 1).

Baseline characteristics of MZ and DZ twins for the three visits are summarized in Table 1. Statistical significance is reported as p-values, Supplemental Table 1).

Table 1

<table>
<thead>
<tr>
<th>Visit</th>
<th>Age (years)</th>
<th>N</th>
<th>MZ Mean (SD)</th>
<th>DZ Mean (SD)</th>
<th>p-value</th>
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<tr>
<td>1</td>
<td>25.6</td>
<td>2365</td>
<td>49.1 (1.2)</td>
<td>49.4 (1.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>25.6</td>
<td>2365</td>
<td>49.1 (1.2)</td>
<td>49.4 (1.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>25.6</td>
<td>2365</td>
<td>49.1 (1.2)</td>
<td>49.4 (1.2)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Even though we optimally made use of the available follow-up mean CRP over a ten-year period, only subsamples of twins returned for the second and third visits. As an additional sensitivity analysis we repeated the trivariate Cholesky modeling using only returning subjects, i.e., twins that participated in all three visits. We did not find evidence for genetic dominance, however, in contrast to some previous cross-sectional twin studies that also had large sample sizes [17,20].

A limitation of the present study, however, is that our conclusions are not generalizable to men, or subjects with diseases since basal levels of CRP are lowest in healthy women. The longitudinal design, with the long follow-up time of up to 10 years, and the relatively large sample size provided more statistical power and methodological opportunities compared to previous smaller, cross-sectional studies. We did not find evidence for genetic dominance, however, in contrast to some previous cross-sectional twin studies that also had large sample sizes [17,20].
Table 2

Genetic correlations (rG, %) are given below the diagonal and environmental parameter estimates (95% CI) of best fitting models above the diagonal. Model 1: adjusted for age and BMI. Model 2: adjusted for age, BMI, and sex.

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (95% CI)</th>
<th>Model 2 (95% CI)</th>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0.46 (0.38-0.54)</td>
<td>0.48 (0.42-0.54)</td>
</tr>
<tr>
<td>3</td>
<td>0.54 (0.46-0.64)</td>
<td>0.58 (0.50-0.65)</td>
</tr>
<tr>
<td>4</td>
<td>0.50 (0.42-0.58)</td>
<td>0.53 (0.45-0.61)</td>
</tr>
</tbody>
</table>

Table 3

Genetic correlations (rG, %) are given below the diagonal and environmental parameter estimates (95% CI) of best fitting models above the diagonal. Model 1: adjusted for age and BMI.

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Important aspects of the study include the following:

1. **Genetic Correlations**
   - Genetic correlations (rG, %) are given below the diagonal and environmental parameter estimates (95% CI) of best fitting models above the diagonal. Model 1: adjusted for age and BMI. Model 2: adjusted for age, BMI, and sex.

2. **Environmental Parameter Estimates**
   - Parameter estimates (95% CI) of best fitting models: A, additive genetic variance component; E, unique environmental variance component.

3. **Conclusion**
   - In conclusion, this study emphasizes the relatively stable role of genetics in regulation of baseline CRP levels, emphasizing its potential as a biomarker of ageing over other, more biologically reactive sub-clinical inflammatory markers.

4. **Supplementary Data**
   - Supplementary data related to this article can be found at [this link](http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.008).

5. **References**
   - For a list of references, please see the article at [this link](http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.008).

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**Appendix A**

**Supplementary Data**

- Supplemental data related to this article can be found at [this link](http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.008).

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**References**


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**Note**

- The above text is a sample representation of the content extracted from the document. It includes key findings, methodologies, and conclusions drawn from the study. The document discusses the role of genetics and environment in the regulation of CRP levels, emphasizing the stability of genetic contributions over time.

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**Appendix A**

**Supplementary Data**

- Supplemental data related to this article can be found at [this link](http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.008).

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**References**


