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(Genetic) Epidemiology of Inflammation, Age-related Pathology and Longevity

Sas, Arthur Alexander

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Summary of the thesis

In a broad perspective, the lifecourse of most organisms is highly comparable. This means birth, followed by a period as a child, adolescent, the reproductive and post-reproductive phase and –ultimately- death. How this endpoint is reached however (e.g., length and timing of the aforementioned phases, diseases organisms develop and –ultimately- cause of death) varies widely between individuals. For humans, these “moderators of lifespan” can be divided into genetic influences (or genetic predisposition) on the one hand, and non-genetic influences (e.g., environmental influences and (risk) behaviours) on the other hand. In order to further clarify these moderators the use of biomarkers for quantifying the status or speed of ageing has been evaluated in an attempt to identify individuals who are more prone to age-related pathology. In this context, it has been demonstrated that ageing is associated with a low-grade elevation of inflammatory markers, attributed to the deregulation of immune and inflammatory pathways with ageing. In accordance with these findings, it has been shown that chronic inflammation predisposes to morbidity and mortality from many chronic, age-related diseases (such as chronic pulmonary and cardiovascular disease).

The synthesis and regulation of serum levels of inflammatory markers has been extensively studied, showing the significance of both environmental and genetic influences in this process. Optimal study designs to assess these influences as well as possible “moderators” are classical twin studies. These types of studies typically use variance component models, also known as structural equation modeling. Twin methodology allows estimation and quantification of the relative contribution of genes and environment to the disease or trait of interest. The classic twin study design is based on the idea that two kinds of twin pairs exist. Monozygotic (MZ) twins are genetically “equal”; any phenotypic differences between them are due to their differential environments. Dizygotic (DZ) twins are genetically no more comparable than siblings (which share on average 50% of their segregating genes). The actual variance component analysis is based on the comparison of the variance-covariance matrices in MZ and DZ twin pairs, and allows separation of the observed phenotypic variance into its genetic and environmental components: additive (A) or dominant (D) genetic components and common (C) and unique (E) environmental components (E also includes measurement error). In general, any greater phenotypic similarity among MZ twins compared with DZ twins reflects the importance of genetic influences, assuming that both types of twins share environmental influences to the same extent.

In **chapter 2**, the relative influence of genetic and environmental factors on four key cytokines involved in the human immune response (IL-1 β , IL-6, IL-10 and TNF- α) was assessed. In addition, the role of age as a possible moderator on these influences was evaluated. The study was conducted in 1,603 females from the Twins UK registry, including 863 monozygotic

and 740 dizygotic twins. Heritabilities on IL-1 β , IL-6, IL-10 and TNF- α were estimated using structural equation and shown to be moderate, ranging from xx to xx.

In addition, twin studies not only provide estimates of the relative contribution of genetic and environmental influences. They also allow exploration of interaction models, for example a gene-age interaction. This model directly incorporates age as a continuous moderator and allows to estimate whether and to what extent the A (or D), C and E components on a trait of interest are modified by age and was also evaluated in chapter 2. For IL-1 β , heritability declined with age due to an increase in unique environmental influences. For TNF- α , heritability increased with age due to a decrease in unique environmental factors. Although longitudinal studies are the gold standard for studying changes in serum cytokine levels and variance components over time, such studies are difficult to conduct as they are time consuming and expensive to establish. By using age as a moderator of genetic and environmental influences, the statistical models allowed us to mimic longitudinal outcomes in a cross-sectional dataset.

In **chapter 3**, we used a “real” longitudinal twin study to estimate heritabilities on CRP, as well as the genetic correlations at different timepoints (visits). This is in contrast to **chapter 2**, where a cross-sectional dataset was used to mimic these longitudinal outcomes. Heritability estimates for CRP were around 50% at all three time points, and thus very stable over time (0.46–0.52). Adjustment for BMI only slightly reduced heritability estimates (0.49–0.51). CRP levels significantly increased from visit 1 to visit 2 and between visit 1 and visit 3, but not between visit 2 and visit 3. The genetic correlations between visits were significantly smaller than one, ranging from 0.66 (visit 1 – visit 3) to 0.85 (visit 2–visit 3). These findings indicated that a large part of the genetic influences over time could be attributed to the same genes. However, partly different genes regulating CRP levels also impact at different time-points in an individual’s life course. Although significant, the environmental correlations between visits were consistently low (0.16 – 0.27) indicating that the environmental influences on CRP were mostly different at the three time points.

The personality trait neuroticism is an important marker of vulnerability for both mental and physical disorders, e.g. anxiety, depression, atopic eczema, cardiovascular disease and (ultimately) mortality, which to a large extent are the same mental and physical disorders as related to inflammatory markers. In chapter 4, the phenotypic and genetic relationship between neuroticism and three commonly used inflammatory markers (CRP, fibrinogen and IgG) is determined. The study was conducted in 125 Dutch female twin pairs. For each participant, four different neuroticism scores and serum levels of the abovementioned inflammatory markers were available.

Heritabilities, phenotypic and genetic correlations were estimated using bivariate structural equation modeling. We tested the hypothesis that, considering their similar effect on health and apparently ageing, phenotypic and genetic correlations must be significant between neuroticism and the aforementioned inflammatory markers.

Heritabilities were fair for neuroticism (0.55), CRP (0.52) and fibrinogen (0.67) and moderate for IgG (0.43). However, no significant phenotypic or genetic correlations were found between neuroticism and the inflammatory markers in these healthy female twins. As no phenotypic or genetic overlap between neuroticism scores and serum cytokine levels were found, higher neuroticism levels are not associated with higher inflammation. One explanation of the observed relationship between neuroticism and inflammation markers as reported in the literature could be that confounding factors such as stressors and risk behavior are associated with higher neuroticism scores as well as higher serum levels of inflammatory markers. This illustrates the importance of testing the influence of potential confounders influencing baseline levels of inflammatory markers. In accordance, in all of the studies in the present thesis the effects of established covariates on the data were assessed and statistically corrected for.

In chapters 5 and 6, it was argued that Gompertz' demographic law on survivorship can be used as a simple and generally applicable "law of ageing", by applying the principle of ergodicity. In this context, a (cross-sectional) population survival curve hypothetically reflects the longitudinal ageing process in a single, average prototypical organism of that population. We demonstrated in these chapters that mathematical formulas describing these data accurately describe survival curves (both human and animal), as well as common age-related pathologies such as colon and prostate cancers. An interesting feature however, is that with these curves we were not able to describe incidence data of external causes of pathology and death as illustrated by (for example) cervix cancer data (caused by an infection of the human papilloma virus (HPV)). This could hypothetically mean, that a cross-sectional population survivorship curve reflects a basic, intrinsic longitudinal biological ageing process in a prototypical individual.

The results of the present thesis indicate a strong genetic component in the regulation (and deregulation) of inflammatory markers with age. Nevertheless, environmental components also play an important role in this. This implies that individuals (and therefore families) at risk of higher inflammatory markers could be a target for future (anti-inflammatory) treatment, to reduce old-age morbidity and mortality.