

# Can the Events of Early Life Influence the Development of Rheumatoid Arthritis?



I am often asked the same question by newly diagnosed patients, “Why me? Why did I get rheumatoid arthritis?” The easy response is to trot out an answer that both genes and environmental factors are important. However, it is difficult to provide detail to the sequence of events, and the relative importance of each, needed to induce the chronic inflammation of rheumatoid arthritis (RA).

Genetic factors are clearly important. HLA-DRB1 alleles have repeatedly been shown to be associated with the development of RA. Genome-wide studies have also identified other genes both within and outside the major histocompatibility complex (MHC)<sup>1</sup>. In contrast, advances in our understanding of the role of the environment have often been slower and received less attention. Nevertheless, progress has been made. This is particularly true for exposure to tobacco smoke that has been shown in many studies to be a strong risk factor for the development of RA<sup>2</sup>. Smoking exposure is also a key example of the importance of interactions between genes and environment.

Despite some success there are major challenges to studying the role of environmental factors in the etiology of RA. One of these is the fact that disease commonly starts in middle age. This allows the opportunity for many different exposures throughout life to have had an effect on disease development over many decades. It has become clear that immunological and inflammatory changes begin many years before the onset of joint pain and swelling. The autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP) and a raised C-reactive protein (CRP) are all detectable in serum years before symptoms begin<sup>3</sup>. This has led to the idea that a major block to unraveling the role of environmental factors in RA may be that we are “looking too late”<sup>4</sup>. Perhaps crucial environmental exposures are missed when we don’t look early enough. If this is true then is it biologically plausible that events during neonatal life and childhood could have lifelong effects?

There is now a large body of evidence suggesting that early life events can lead to disease in later life. Work in this

area, initially in relation to cardiovascular disease, led to the hypothesis of the “fetal origins of adult disease” proposed by David Barker<sup>5</sup>. The hypothesis proposes that early life development in adverse circumstances produces a “thrifty phenotype” that prepares the offspring for a more challenging environment. This in turn produces unintended adverse consequences later in life. An example of this is seen in the increased likelihood of hypertension in adults who had low birth weight<sup>6</sup>. Some of these effects may be mediated through a re-setting of hypothalamic-pituitary-adrenal (HPA) and growth hormone/insulin-like growth factor-1 (GH/IGF-1) axes. For example, low birth weight appears to result in the programming of the HPA axis to produce more cortisol<sup>7,8</sup>.

Early life events may effect the development of autoimmune disease in 2 main ways. The first is through the effects of poor fetal and infant growth as described for low birth weight and hypertension and the second through early life exposure to exogenous factors including microorganisms. Early life growth has been shown to have effects on the development of autoimmune thyroid disease, with low birth weight being associated with increased thyroid autoimmunity<sup>9,10</sup>. In contrast, development of type I diabetes has been associated with higher weight at 6 months of age<sup>11</sup>.

In this issue of *The Journal* Simard and colleagues have shown a lack of association between preterm birth or being breastfed and incident RA in women<sup>12</sup>. The study was carried out using a large number of individuals from the Nurses’ Health Study (NHS) and the Nurses’ Health Study II (NHSII). The same group has shown an association between high birth weight and a greater risk of developing adult RA in the NHS. Interestingly, they have also shown that higher birth weight was associated with an increased incidence of developing systemic lupus erythematosus in the same cohort<sup>13</sup>. Other groups have shown associations between high birth weight and development of RA<sup>14</sup>, and low birth weight being protective for the development of

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RA and juvenile idiopathic arthritis (JIA) (a nonsignificant trend)<sup>15</sup>. However, birth weight and infant growth have been shown to have no effect on the development of RF in adults<sup>16</sup>. In general, high birth weight seems to increase the likelihood of RA in later life. The new finding that preterm birth does not affect the likelihood of developing RA does not detract from this.

The new results on breastfeeding are in contrast to previous findings that initiation of early breast feeding is associated with the development of RA<sup>14</sup> and that HLA-DR4-negative individuals who are RF-positive are more likely to have been breastfed<sup>17</sup>. There are differences in the populations studied, and diverse results from different groups may also show the difficulty in studying these effects in RA. However, the most recent study contains the largest number of individuals and has the most detailed information on the degree of exposure to breastfeeding.

One major difficulty with defining associations between environmental factors and a complex disease like RA is its heterogeneity. This may ultimately be addressed by exact phenotyping of patients into different disease subgroups. This subtyping is likely to increase the reliability of future studies including those looking at environmental factors. The importance of this approach has already been highlighted by studies showing that the effect of breastfeeding in the development of RF is dependent on the presence or absence of HLA-DR4<sup>17</sup>.

So does all this work help to answer the patient's question as to why they developed RA? Well, maybe. It suggests that large babies are more likely to develop RA, that being preterm has no effect, and that if breastfeeding is important it is probably less so. Perhaps high birth weight results in the programming of the HPA axis to produce less cortisol and shifts the balance towards chronic inflammation.

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