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*Chapter 1*

General introduction



## Features of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease. In general, symmetrically located joints are affected, especially the wrists, and the small joints of hands and feet. Other joints may become involved as well, resulting in pain, radiologically visible damage, and loss of function. People with the disease often have fatigue, stiffness, especially in the morning, occasionally fever, and a general sense of not feeling well.

In healthy people, the inner lining of the joint capsule, called synovium, produces synovial fluid, which lubricates and nourishes the cartilage that covers the meeting bones. In RA, which is considered to be an autoimmune disease, the synovium becomes hypertrophic and edematous and starts eroding the articular cartilage and underlying bone. This is a painful process, which may lead to full destruction of the joint with dislocation of the bones, and serious loss of function. Since synovium is present in tendon sheaths as well, RA often damages the tendons that run in it. Tendons may even rupture, most frequently in the hands.

RA occurs in all races and ethnic groups, the prevalence in Europe and the USA being about 1% (Abdel-Nasser *et al.* 1997). Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults may also become affected. About two to three times more women than men have the disease. The course of the disease varies from a few months mild self limiting disease without causing any noticeable damage to many years of severe disease with ups and downs but active most of the time, resulting in serious joint damage and disability or even death (Rasker & Cosh 1984).

In 1978, the first signs of RA came on myself. In the beginning occasionally, and from September 1979 onward RA is there every day. After a few years in which I got more or less used to having RA, I wondered what might cause the irregular variations in my joint complaints. My rheumatologist, and the literature could not answer my questions. In 1983, 4 years after the onset of the disease, I started to score the joint pain daily on myself. Deprived of any knowledge of RA, I developed my own standardized scoring method. Years later, when I became acquainted with other scoring methods, I continued to use the method I started with, in order to keep the pain scores comparable. Now, 21 years later, I am still scoring my daily joint pain in the same way (see below).

## Monitoring of disease activity in RA

Objective quantification of disease activity in RA might be possible by measuring physical variables of joints, like swelling, temperature, load-bearing capacity, and function. Such measurements will reflect rather precisely the inflammatory state of a joint but can only be applied on superficially located joints. The method is very laborious, and may give a rough indication of the total disease activity. In fact, RA disease activity cannot be measured directly. However, an impression of the disease activity can be obtained by the combined use of objective variables like the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), and subjective variables like pain, and duration of morning stiffness. Daily determination of the former is impracticable due to costs and being a burden to the RA patient, while the latter can be scored daily but, even with highly standardized scoring methods, it remains subjective. Disease activity scoring methods that correlate best with later disease outcome like radiographic damage, apply subjective as well as objective variables (van der Heijde *et al.* 1993; Ward 1993; van Leeuwen *et al.* 1994).

In addition to a reliable quantification method, monitoring of disease activity requires appropriate intervals at which the quantifications are done. In order to study possible effects of the day-to-day variations in the weather, I considered it necessary that daily data are available. In most of the studies described in this thesis, the joint pain was scored daily in the following standardized way.

1. Scoring was done in the morning, immediately after getting up. At this time of the day RA complaints are maximal. Pain scoring in the evening is less reliable since variable daytime circumstances, like tiredness, might influence the scoring more than the in general more stable nighttime period.
2. The pain was scored during the execution of standardized exercises because joint pain strongly depends upon positioning and movements of the joints. The exercises consisted of simple unloaded flexions, extensions, and rotations.
3. Pain was scored for separate joints (e.g. left shoulder) or groups of joints (e.g. all joints of the right hand). Thus 21 pain scores ranging from 0 (no pain) to 9 (very severe pain) were obtained for the hands, wrists, elbows, shoulders, temporomandibular joints, hips, knees, ankles, feet, and the neck, back, and costosternal joints.

With one exception, in all studies described in this thesis, the pain scores were supplemented with the routinely determined laboratory determinations. Figure 1 of *Chapter 11* summarizes all quantifications of RA variables determined on myself. As described in *Chapter 9*, I found a significant positive correlation between my daily joint pain score and routinely determined ESR during 3 years. The correlation was even stronger if a time delay of 10 days between the two variables (ESR preceding pain) was taken into account.

In a majority of patients with RA, rheumatoid factor (RF) is found in their serum. RF indicates a group of antibodies (mostly IgM) with anti-IgG activity. These antibodies were first found in high titers in patients with RA. Although the designation suggests that it would be indicative for the disease activity in RA, the diagnostic value of RF is limited, especially in low titer (Lopez *et al.* 1992). In general, patients with RA who have high titer RF are more likely to have severe disease than other patients. Recent studies reported evidence that RF is indicative for disease activity (Knijff *et al.* 2002) as well as predictor of radiological destruction (Knijff *et al.* 2002; Bukhari *et al.* 2002; van Gaalen *et al.* 2003, Alessandri *et al.* 2004). The study described in *Chapter 8* supports the association between RF and variables of RA.

### **Arthritis and weather**

For centuries, people have believed that arthritis pain is influenced by the weather. In his book *Airs, Waters, and Places* (translated by Jones 1939) Hippocrates discussed the relationship between the elements and chronic diseases. He points out that a physician should be aware of what effects each season of the year can produce, where he writes:

*"... he will know beforehand the nature of the year that is coming. Through these considerations and by learning the times beforehand, he will have full knowledge of each particular case, will succeed best in securing health, and will achieve the greatest triumphs in the practice of his art. If it be thought that all this belongs to meteorology, he will find out, on second thoughts, that the contribution of astronomy to medicine is not a very small one but a very great one indeed. For with the seasons men's diseases, like their digestive organs, suffer change."*

Up to the present, patients with chronic pain frequently report that their pain and stiffness are influenced by changes in the weather (Hill 1972; Sibley 1985; Rasker *et al.* 1987; Affleck *et al.* 1987; Jamison *et al.* 1991). There are even arthritis patients who claim that the relationship is sufficiently precise that they can predict the weather changes by their symptoms (Hill 1972; Nyberg & Nyberg 1984). In contrast to these widespread opinions, science offers no proof. The vast quantity of publications on effects of weather on RA has not accomplished a great knowledge of these effects. Most reports are anecdotal case studies, other studies had very small sample sizes, and often references were cited erroneously. Therefore, the number of studies that contribute to the understanding of weather effects on arthritis is small. Moreover, the conclusions of these studies are not unanimous. This is likely to be caused by several factors that hamper such studies. As mentioned above, it is difficult to monitor the disease activity, and the used methods differed considerably. In *Chapter 2*, the literature on weather effects in RA is reviewed and evaluated.

### **Weather variables**

Weather variables are routinely, and frequently measured at many places. Therefore, in contrast to RA data, weather data are easily available. Daily means of most weather variables can be obtained from reports of a neighboring meteorological station. Effects of air temperature, relative humidity, and barometric pressure are searched for by almost all studies on weather effects on RA. Less frequent studied variables are wind speed, precipitation and sunshine. Effects of other weather variables have hardly been investigated. Apart from a few studies only separate influences of weather variables were considered.

The range of variation of most weather variables depends on study duration. For instance, a study of one month in the summer can apply only relatively high temperatures with a narrow range. A full-year study will comprise the whole range of yearly temperatures for a particular location.

Two studies tried to overcome the dependence on outdoor weather by using a controlled climate chamber (Edström *et al.* 1948; Hollander & Yeostros 1963). The effects found in some experiments on a few RA patients have never been repeated.

## Relationships between weather variables

There are several mutual relationships between weather variables, e.g. the well known negative relation between barometric pressure and wind speed: depressions are often accompanied by storms while high pressure is associated with quiet weather. Therefore it is important to realize that any association between a weather variable and an RA variable may result from an association of that weather variable with a different weather variable. Understanding of the relationship between air temperature and humidity is very important because this relation is very strong, and as mentioned above, effects of these variables are searched for in almost all reported studies.

As the temperature of air increases it can hold more water, and if water is available for evaporation, it will contain more water in the form of vapor. Figure 1 illustrates the increase of vapor pressure (absolute humidity) with increasing temperature for the marine climate of The Netherlands.

Due to winds from the sea, the relative humidity is in general high (yearly mean about 85%). Wind from the opposite direction is associated with much lower relative humidity and vapor pressure. For instance, on the days marked by the circles below the 50% relative humidity reference line (Figure 1), the wind always came from eastern directions.

Figure 1 shows that cold, wet weather never exists in The Netherlands. Cold air can contain only a small amount of water. Excess water is lost by condensation on cold objects. Even during rain in cold weather, the air between the rain drops is very dry. Although the relative humidity can be about 100%, it is much lower at warm surfaces (e.g. the human skin; compare electrically heated car rear window). For instance, if the outdoor temperature is 0 °C, with a relative humidity of 100%, the relative humidity close to the skin of the human face at a skin temperature of 20 °C, is about 30% (move horizontally from 0 to 20 °C on the 4 g/kg dry air level in Figure 1).

Likewise, Figure 1 shows that warm, dry air never exists in The Netherlands. At 20 °C, the outdoor vapor pressure is virtually always higher than 60%. About the same circumstances will be present at the skin of the human face, at the level of 10-12 g/kg dry air. Warm, dry air only occurs in dry areas without supply of humid air, and where water is

hardly available for evaporation. As clarified in *Chapter 2*, this is one of the reasons why studies done in different climates reported different conclusions about the influence of the weather on RA patients.

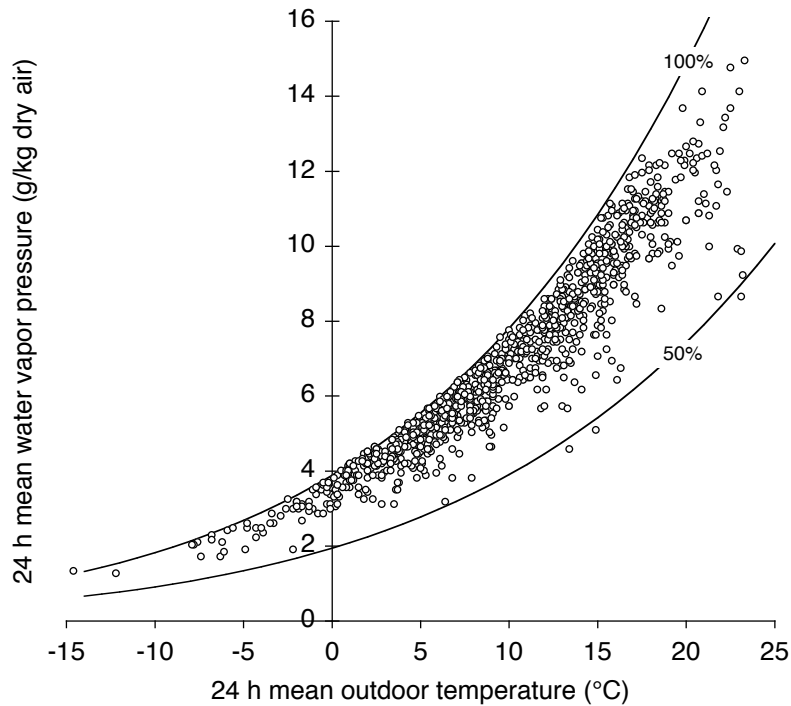


Figure 1 Plot of 24 h mean water vapor pressure against 24 h mean outdoor temperature for a 3-year period (1997-1999) at Groningen Airport, The Netherlands. Reference lines indicate 50 and 100% relative humidity.

Since living (thus heated) human bodies are involved, only vapor pressure (absolute humidity) is used as a measure for humidity in the studies described in this thesis. As mentioned above, relative humidity is not a useful humidity measure of the air because it is temperature dependent. Due to the strong relationship between temperature and vapor pressure in The Netherlands, the outdoor temperature curves throughout this thesis also reflect the outdoor vapor pressure (cf. Figure 1 of Chapter 4).

The relation between two variables can be obscured due to a delay between the variations of one variable with respect to changes in the other, e.g. the yearly variation in temperature lags about one month behind the

variation in sunshine. This is shown in Figure 2 as a broad maximum at a phase shift of about 45 days. Superimposed on this slow yearly variation in temperature, which is governed by the earth's orbit around the sun, there are rapid changes in daily temperature, which are correlated with variations in sunshine due to variations in cloud cover. This is reflected by the narrow positive elevation around a phase shift of 1 day in the correlogram (Figure 2). Although the latter two variables are correlated with barometric pressure, there is no correlation between barometric pressure and temperature. As illustrated in Figure 2, cross correlation is a tool that can reveal immediate, as well as delayed relationships between two variables. Another example of a dual effect shown in a single cross correlogram is given in *Chapter 10*.

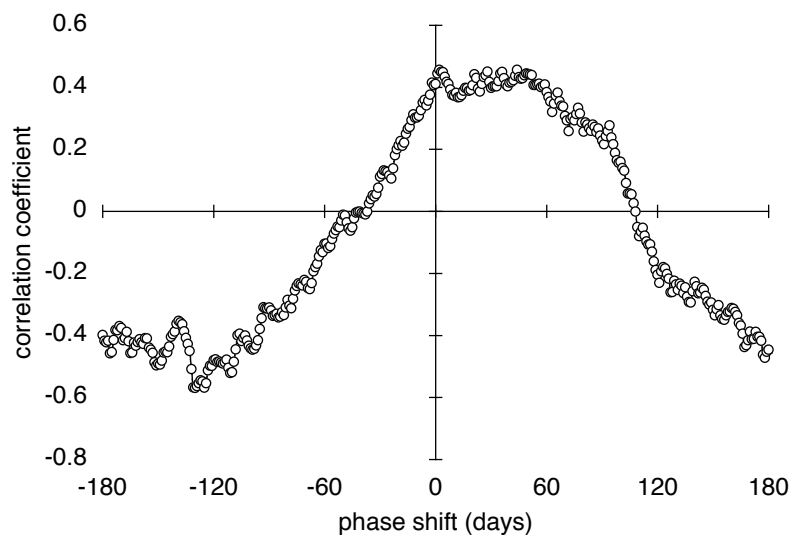


Figure 2 Cross correlation between the 24 h means of duration of sunshine, and temperature in 2001. The correlogram shows a short latency (1 day) maximum superimposed on a broad delayed (about 45 days) maximum.

### Exposure to weather

In studies on effects of weather on patients with RA, the participants were never really exposed to weather during the whole study period. In other words, people were not outdoors naked. Of course not, but it im-

plies that the stimulus in the experiments that were done, is far from well defined. The extent to which studied patients were exposed to weather was virtually never taken into account. Meteorological data are always used in these studies but, except for barometric pressure, the values of meteorological variables are mostly quite different from what is "felt" by the human body. A clear example of this is outdoor frost, which will have little effect on people staying indoors all day.

Weather exposure is dependent on e.g. occupation, habits, housing, clothing, and the weather itself. Two studies, in which a relationship between the time spent outdoors and RA variables was found, are described in *Chapter 7 and 8*. The review described in *Chapter 2* shows that if local circumstances are taken into account, the four most comprehensive studies on weather effects on RA are much more in agreement than they seemed at first sight.

### **The microclimate**

In the end, it is the microclimate, the "weather" close to the human skin that exerts its influence on the body. As is discussed in *Chapter 2*, it is unlikely that effects on the respiratory tract play a role. In general, the skin of the head and hands is most influenced by the weather, especially when being outdoors. Other parts of the skin are often, or almost always, shielded from the weather by clothes. It is obvious that clothing, blankets, housing, etc. can have strong effects on the microclimate. Especially when clothed heavily, the microclimate is strongly influenced by the body itself. In addition to heating, the skin humidifies the air beneath the clothes, even if no sweating occurs. Clothes will hamper the ventilation over the skin, keeping the vapor pressure elevated, while airy clothing brings about the opposite. This is discussed in *Chapter 2*.

### **Historical background and outline of the thesis**

As mentioned above, I started to score my RA joint pain daily in 1983, 4 years after the onset of the disease. Around that time, I became involved in a study done by my rheumatologist on effects of weather on joint pain in 88 RA patients. The participants scored their pain daily during 1 year (1981), and a positive correlation between the daily averaged pain score and the meteorological temperature as well as humidity

was found (*Chapter 6*). Also the daily-determined RA pain score of myself appeared to be positively correlated with the outdoor temperature and vapor pressure. In *Chapter 3* this is described for the period 1983-1985, and in *Chapters 4 and 5* for 1983-1988. Having found that low temperature and low vapor pressure turned out to be beneficial, I took measures to lower the 24 h mean temperature and vapor pressure of the air that surrounded me. Effects of removal of nocturnal barriers for transfer of heat and water vapor, and of staying at higher altitudes are described in *Chapters 3, 4, and 5*.

So far, studies on myself were mainly based on the daily joint pain score. In order to add an objective RA variable to my studies, from 1989 on, the ESR was determined more frequently than before: 1-2 times a month instead of about 3 times a year. In *Chapter 9*, it is shown for the first time that there is a positive correlation between the outdoor temperature and the ESR, i.e. between an objective weather variable and an objective RA variable.

The study in *Chapter 10*, does not deal with weather effects. It describes the delayed worsening effect of alcohol on RA pain. The negative peak in the cross correlation curve between the daily alcohol intake and the pain score is a demonstration of the sensitivity of the analysis: it nicely shows the temporary pain suppression by alcohol.

In addition to the earlier measures for lowering the 24 h mean temperature and vapor pressure of the air that surrounded me, from 1992 on I studied the effect of periods in which I daily spent a long time outdoors, on the joint pain score and the ESR. The effect turned out to be beneficial and is described in *Chapter 7*. Moreover, as described in *Chapter 8*, I recently found that the effect of being outdoors is very pronounced on the RF. The RF level virtually always decreased during periods in which I daily spent a long time outdoors, and increased during short outdoors periods.

Finally, in *Chapter 2* the literature on weather effects in RA is reviewed and evaluated. At first sight there was not much agreement among the findings of the different studies. However, a great deal of the controversies could be explained by intimate relationships between weather variables, and by differences in local circumstances.

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